CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 020667

TRADE NAME: Mirapex .125 mg, .25 mg, 1 mg, 1. 25 mg and 1.5 mg Tablets

GENERIC NAME: Pramipexole dihydrochloride

SPONSOR: Pharmacia and Upjohn, Inc.

APPROVAL DATE: 07/01/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Registered Mail
Return Receipt Requested

NDA 20-667

JUL 1 1997

Pharmacia & Upjohn, Inc.
Attention: Ms. Julianna Stewart
Regulatory Affairs Department
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Ms. Stewart:

Please refer to your new drug application dated December 26, 1995, and your January 7, 1997 resubmission received January 10, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirapex, (pramipexole dihydrochloride), tablets, 0.125 mg, 0.25 mg, 1.0 mg, 1.25 mg, and 1.5 mg.

We also refer to an Agency Approvable letter dated December 23, 1996, and we acknowledge receipt of your submissions dated:

January 6, 1997	January 8, 1997	January 10, 1997
January 24, 1997	January 27, 1997	February 5, 1997
February 10, 1997	February 11, 1997	March 6, 1997
June 12, 1997	June 17, 1997	

The User Fee goal date for this application is July 10, 1997.

This new drug application provides for the treatment of the signs and symptoms of idiopathic Parkinson's Disease.

We have completed the review of this application, as amended, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-667. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Registered Mail
Return Receipt Requested

DEC 23 1996

NDA 20-667

Pharmacia & Upjohn, Inc.
Attention: Ms. Julianna Stewart
Regulatory Affairs Department
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Ms. Stewart:

Please refer to your December 26, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mirapex (pramipexole) Tablets 0.125mg, 0.25 mg, 1.0 mg, 1.25 mg, and 1.5 mg.

We also acknowledge receipt of the following correspondence and amendments:

February 9, 12; March 5, 6, 7, 20, 27; April 8, 16, 23, 24, 25; May 15; June 4, 5, 6, 10, 24; July 19; August 1, 8, 16, 21, 22, 23; September 6, 19, 24, 25, 27; October 7, 9, 18, 28, 29, 30, 31; November 1, 2, 6, 12, 22, 1996.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to adopt as labeling the draft package insert attached to this letter, modified as requested (i.e., as per this letter and the notes embedded within the text of the attached package insert).

Please submit final printed labeling (FPL) identical in content to the enclosed marked-up draft labeling. Please submit sixteen copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of that FPL may be required.

Biopharmaceutics:

Please adopt the following dissolution methodology and specification for all strengths of pramipexole tablets:

Apparatus:	USP Dissolution Apparatus 2 (paddle)
Speed:	50 rpm
Media:	Citrate/Phosphate Buffer, pH 6.8
Volume:	500 mL
Sampling time:	30 Minutes
Specification:	Not less than (Q)

In vitro studies to determine the absence of phase I oxidative metabolism should be performed. Even in the absence of a P450 pathway, inhibition studies should be performed to evaluate potential drug-drug interactions.

Safety Update:

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

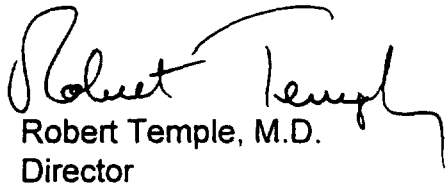
Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact Ms. Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2777.

Sincerely yours,



Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

PRAMIPEXOLE TABLETS NDA 20-667

XIII. PATENT INFORMATION

PATENT CERTIFICATION

1.	Active Ingredient	Pramipexole
2.	Strength(s)	0.125, 0.25, 1.0, 1.25 and 1.5 mg
3.	Trade Name	To be determined
4.	a. Dosage Form	Compressed Tablets
	b. Route of Administration	Oral
5.	Applicant Firm Name	The Upjohn Company
6.	NDA Number	20-667
7.	NDA Approval Date	To be determined
8.	Exclusivity - Date first ANDA could be approved and length of exclusivity period	Five (5) years after date of NDA approval / December 12, 2006 / or date of any patent extension -- whichever date occurs last.
9.	Applicable patent numbers and expiration date of each	4,886,812 - compound patent Expiration date - December 12, 2006 4,843,086 - use in Parkinson's disease Expiration date - June 27, 2006

This is to certify that the above information is correct to the best of my knowledge.

Hendrik J. deKoning Gans, M.D.
Regulatory Liaison

EXCLUSIVITY SUMMARY for NDA # 20-667 SUPPL # ____

Trade Name Mirapex® Generic Name Pramipexole Tablets 0.125; 0.25; 1.0; 1.25; & 1.5 mg.

Applicant Name Pharmacia & Upjohn HFD- 120

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /_X_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X_/

   If yes, what type? (SE1, SE2, etc.) ___

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_X_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /__X_/ NO /__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

____5_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #_____ YES /___/ ! NO /___/ Explain: ___

! _____

Investigation #2

IND #_____ YES /___/ ! NO /___/ Explain: ___

! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

! _____ ! _____

Investigation #2

YES /___/ Explain _____

_____

_____

NO /___/ Explain _____

_____

_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Donald G Grilley 11/20/96
Signature Date
Title: CMO

Signature of Division Director Date 7/1/97

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA # 20-667 Supplement # ___Circle one: SE1, SE2, SE3, SE4, SE5, SE6

HFD-120 Trade (generic) name/dosage form: Mirapex (Pramipexole) Tablets Action: AP AE NA

Applicant Pharmacia & Upjohn Therapeutic Class 1S

Indication(s) previously approved: None

Pediatric labeling of approved indication(s) is adequate ✓ inadequate ___ This is intended

Indication in this application: largely for elderly population; no use yet in pediatric population.

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- ___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- ___ b. The applicant has committed to doing such stuilies as will be required.
  - ___ (1) Studies are ongoing.
  - ___ (2) Protocols were submitted and approved.
  - ___ (3) Protocols were submitted and are under review.
  - ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.
- ___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Robert Temple, Dir ODE I — 7/1/97

Signature of Preparer and Title (PM, CSO, MD, other) **Date**

cc:Orig NDA
HFD-120/Div File
NDA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.
3/96

DEBARMENT CERTIFICATION FOR NDA 20-667

Pramipexole Tablets

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, to the best of its knowledge and belief, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

Ann L. Buckley
Executive Director,
Worldwide Regulatory Compliance

18 Dec 95
Date

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 6, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 20-667, Mirapex, [pramipexole]

TO: File NDA 20-667
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my endorsement of the review team's unanimous recommendation that Pharmacia-Upjohn's **NDA 20-667 for Mirapex™** be declared **approvable.**

The sponsor's NDA provides results of 8 completed, adequate and well controlled, clinical investigations that speak to pramipexole's capacity to ameliorate the signs and symptoms of Parkinson's Disease. A review of the reports of these studies has led the team to conclude that the sponsor has provided substantial evidence of Mirapex's effectiveness as a treatment of the "signs and symptoms of idiopathic Parkinson's Disease." Specifically, reports to the NDA document the beneficial effects of Mirapex™ in patients with both early Parkinson's Disease (basically, in patients not receiving concomitant treatment with l-dopa and a decarboxylase inhibitor[1]) and in those with advanced disease(i.e., those who had once, but were no longer responding satisfactorily, to treatment with maximally tolerable doses of l-dopa/carbidopa[2]).

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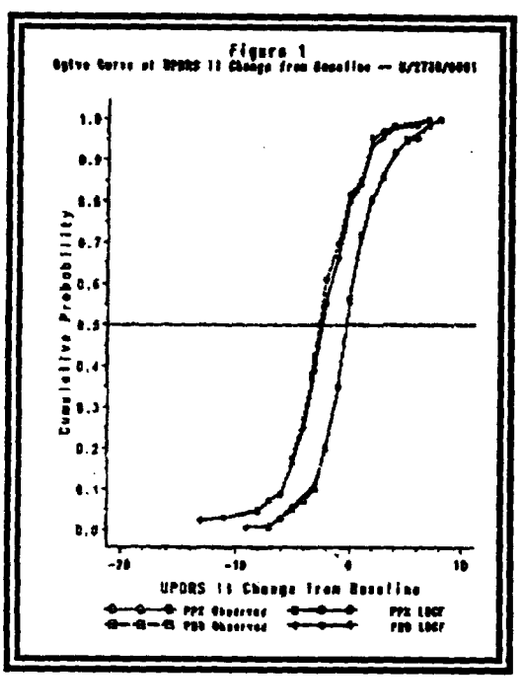
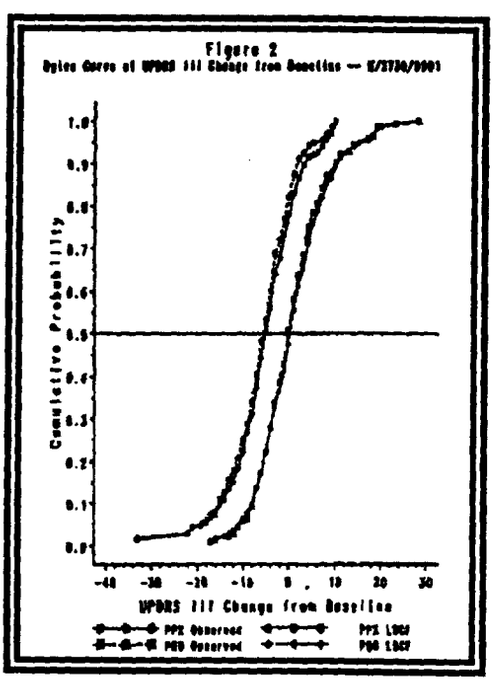
[1] Among the 4 clinical trials (#'s 1,4,17 and 21), Studies 1 and 4 are deemed most persuasive and are the primary basis of our affirmative conclusions in this subpopulation.

[2] Among the 4 completed trials that apply to this subset of the population, Study 10 provides the most compelling results. Studies 19 and 22 are also sources of statistically significant findings supporting the sponsor's claims.

I will not review the effectiveness data here because, as the reviews conducted by Dr. Feeney (9/13/96) and Dr. Hoberman (10/24/96) comprehensively document, the results of the completed trials, including even those that we have not enumerated as sources of substantial evidence, provide robust support for the effectiveness of Mirapex™. The graphics that follow provide a visual insight into the consistency of the evidence of efficacy.

Study 1, Item 2 and 3 on UPDRS





The left shift of the ogive for improvement on UPDRS virtually says it all[3]. Exploratory analyses of the effect of age, sex and medication (other than l-dopa/carbidopa) did not find a treatment by concomitant treatment interaction. This is a strong positive study.

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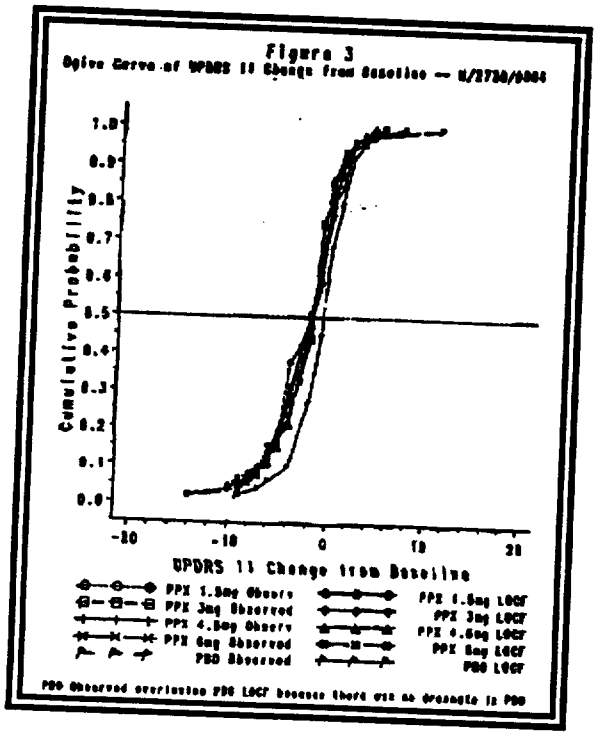
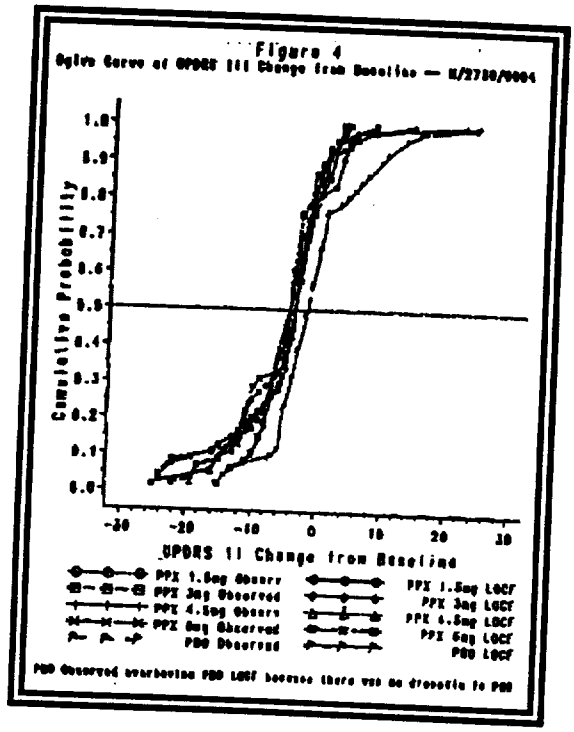
[3] These are extracted verbatim from pages 22 and 25 of Dr. Feeney's review; the imported text on the figures is too small to read, but the consistent left shift of both the LOCF and OC data for pramipexole assigned patients (greater improvement from baseline for Mirapex™ assigned subjects) on both items of the UPDRS are obvious, a finding reflected in the very small 'p' value for the likelihood of the data given the null being true (no treatment effect).

To be clear, the evidence provided in the NDA is not without limitations. The results of Study 4, provided below, reveal, the sponsor has been unable to find a link between dose the magnitude of Mirapex's therapeutic effects.

Study 4, Fixed Dose comparison of 4 pramipexole vs. placebo (pages 45, 46 of Dr. Feeney's review.





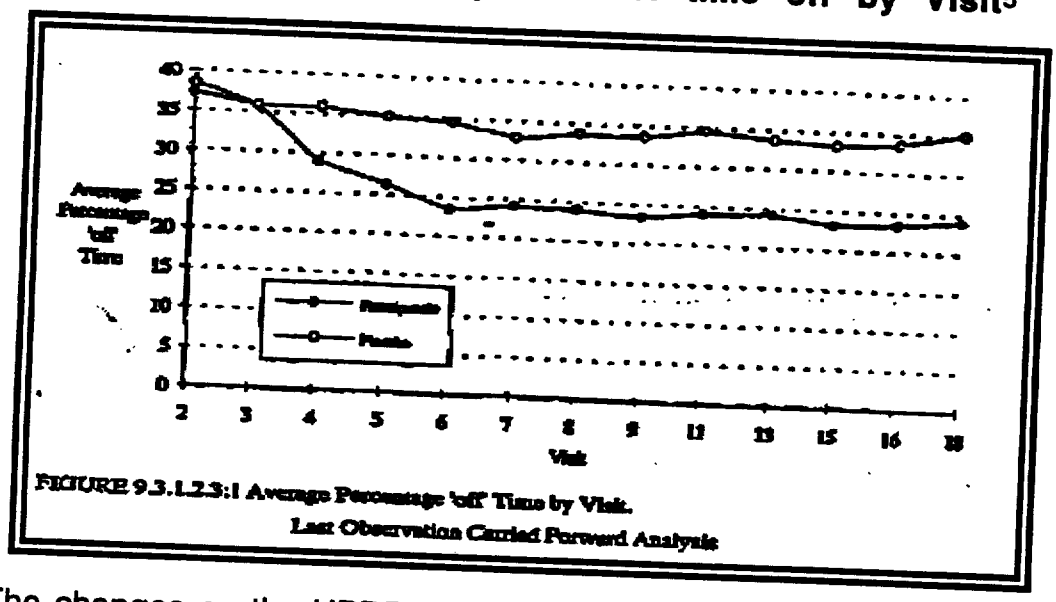
Among the 4 completed trials evaluating Mirapex as an adjunctive treatment, 3 can be deemed to provide support for its efficacy. Among the positive trials (i.e., Studies 10, 19 and 22), **Study 10** is critical to our affirmative conclusions regarding pramipexole's efficacy in this subpopulation.

Study 10

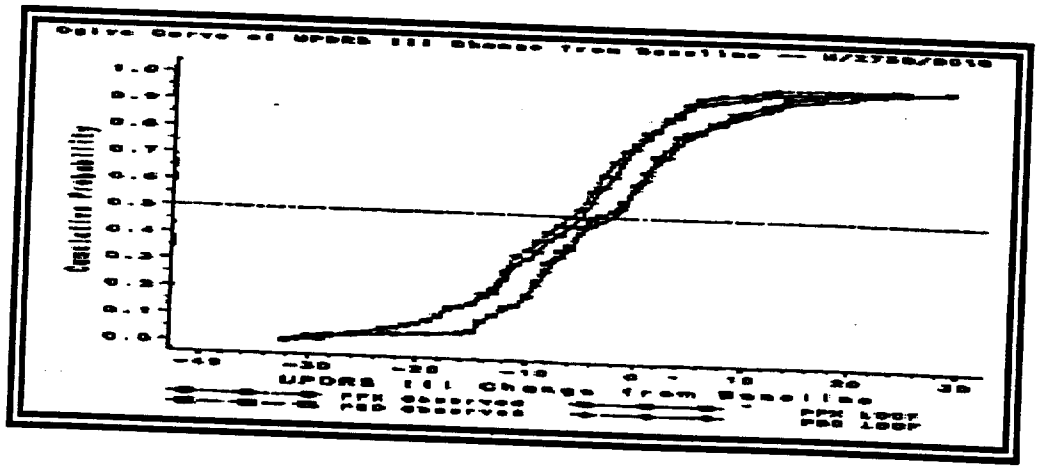
This is a strongly positive study. The graph that follows on the next page illustrates the clinical value of pramipexole in terms of the fraction of time awake that an advanced stage patient, being treated with maximally

tolerated doses of l-dopa, spends in an 'off[4]' state.

Study 10, Average percent of time off by Visit[5]



The changes on the UPDRS for both OC and LOCF data sets in this study are consistent as the cdf ogive for changes in its motor component document displayed below documents. (Feeney page 95).



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[4] The "off" time refers to all time when an awake PD patient is immobilized and/or substantively impaired. Off is contrasted with "on" periods where the patient has some relief from the signs and symptoms of the disease.

[5] taken from page 83 of Dr. Feeney's review

In sum, the NDA provides robust support for the sponsor's claim that Mirapex is an effective treatment for idiopathic Parkinson's Disease.

Safety in use

The evidence collected and reported to the NDA is sufficient to support a conclusion that Mirapex™ will be "safe for use" under the conditions of use enumerated and recommended in the draft product labeling developed by the Division. This conclusion is accompanied by a number of caveats, however.

To begin, a regulatory determination that a drug is "safe for use" is not a finding of fact, but an opinion. The opinion, importantly, is not really about safety, per se, but about the balance of risks and benefits associated with the use of the drug. Thus, when a regulator concludes that a drug has been shown to be safe for use, he is asserting only that the risks known to be associated with the use of the drug are, in his professional opinion, reasonably outweighed by the expected benefits of its use.

It should also be recognized that the basis for the opinion offered rests on imperfect knowledge. The measures of treatment effect obtained in clinical experiments that assess treatment effects on rating scales are, for example, not easily understood in terms of meaningful clinical benefit. Moreover, the risks associated with the use of a drug at the time a decision is made about its "safety for use," are invariably fewer than its actual risks because 1) too few patients are ordinarily exposed to a drug during its commercial development to capture adverse drug induced phenomena that occur at low incidence and 2) the typical clinical cohort in which a new drug is tested is not likely to be as vulnerable to the adverse effects/actions of the drug as is the population of patients for which the drug will be prescribed once marketed.

Both of these limitations affect our assessment of Mirapex's safety for use.

First, the total number of patients treated with pramipexole is small; as of the safety cutoff date (January 1995), only 1231 PD patients in toto

had been exposed to pramipexole. Among these, only 520 or so have been exposed to the maximum recommended dose of 4.5 mg/d for at least 12 weeks. While this number is probably sufficient to identify most of the common adverse events that are likely[6] to be associated with pramipexole's use, the extent of exposure is clearly marginal insofar as its capacity to detect even one case of events that occur at a crude risk of 5 events/1000 patients exposed or less. While the later crude incidence may be deemed reasonably remote from the perspective of the individual patient, it is rather high from a societal viewpoint, especially if any of the risks not detected are serious ones[7].

Also tending to undercut the basis for a conclusion that pramipexole is safe for use is the fact that the patients entered into the development cohort were selected so as to be free of the more serious illnesses (e.g., active heart disease) that are common among patients in the age range in which Parkinson's Disease is prevalent. This gives pause because it means that the risk of pramipexole caused events that arise uniquely or at increased incidence among older patients (either because of their age, per se, or the presence of age related co-existing disease or the treatments used to control the latter), have not been reliably assessed.

These limitations of pramipexole's clinical testing are not, under current interpretations of the Act's requirements, sufficient to bar its approval for marketing. Nevertheless, they are important because they do affect the nature of the extrapolations reasonably drawn from the relatively uneventful clinical experience reported during pramipexole's clinical

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[6] Dopamine agonists have been used in the management of PD since the early to mid 1970s. The common acute adverse events reported for the two approved products, bromocriptine and pergolide, are quite similar including hypotension, nausea, and vomiting. Typically, with dose incrementation, hallucinations and dyskinesias appear.

[7] To illustrate, the use of bromocriptine is believed to be causally related to the occurrence of pleuropulmonary effusion and fibrosis. While I have no reliable basis to estimate the true incidence of this rare complication, which by now is widely attributed to dopamine agonist therapy in general, the incidence is likely to be well below that which would be reliably detected in a drug development cohort of the size used to assess pramipexole.

testing and development. Specifically, given the selected nature of the patients recruited in the Mirapex development cohort, it is prudent to be cautious in regard to inferences concerning the product's capacity to induce orthostatic hypotension (see below).

The limitations enumerated notwithstanding, it is fair to state that in regard to the events that have been reported, Mirapex appears to present no new serious risks of use not already known to be associated with the use of dopamine agonists in the treatment of Parkinson's disease. A review of the causes (hallucinations, dizziness, nausea, somnolence, headache and confusion) for premature discontinuations from studies of pramipexole supports this assertion.

As to more serious morbidities and fatalities associated with the use of pramipexole, clinical experience raises no substantive concerns. I note, however, that a case of rhabdomyolysis following exercise that was associated with CPK elevations has raised some concern among staff about the mean elevation of CPK results seen in the safety database. Given the numerous potential causes for CPK elevation, I see no reason to do more than describe the case (e.g., in the Precautions section) and the CPK findings in labeling.

As to fatalities, only 12 occurred among pramipexole recipients. As a consequence, any estimates of the incidence within subgroups of the sample studied are likely to be unstable. We did, nonetheless, elect to examine fatality rates separately among early and advanced cases of PD because the patients in these two groups were deemed likely to be different in terms of their inherent risk of mortality, an assumption, incidentally, that is not supported by the point estimates of the fatality risk among placebo recipients in these groups. In any case, the rate per 100 patient years is approximately the same among early patients regardless of treatment (0.72 vs 0.9 favoring pramipexole). Among patients with advanced disease, however, the data provide a relative risk estimate of almost 3. (2.52 vs 0.88 deaths per 100 patient years). While unfavorable to Pramipexole, the difference in the estimates is due to a difference of 2 deaths. Accordingly, I am not persuaded the finding represents a signal worthy of pursuit.

Labeling Considerations.

In general, in developing labeling, we sought to maintain some degree of consistency with that of dopamine agonist products already marketed with anti-PD indications (Parlodel[bromocriptine] and Permax [pergolide]). This proved somewhat difficult given the long interval that has elapsed since the initial approval of those products.

We have acted as if certain findings are generalizable to all dopamine agonist treatments. Perhaps the most controversial consequence of this strategy is the warning statement we propose about the risk of hypotension associated with dopamine agonist use. Actually, hypotensive events for Mirapex were not reported to occur at an incidence greater than that seen among placebo patients, a point acknowledged in the warnings statement. As noted earlier, however, we are not fully reassured by the absence of a differential risk because of the highly selected nature of the population. Moreover, we are also concerned that the sponsor's classification system may have obscured the risk (i.e., the sponsor combined dizziness and hypotension, an act that may have caused a differential risk of orthostatic events to be missed).

Dosing

The sponsors fixed dose study failed to establish the shape of pramipexole's dose response surface. Directions for the product's use, therefore, reflect experience gained in the clinical development program.

Conclusions and Recommendations

Mirapex has been shown, within the meaning of the Act, to be effective in use and safe for use under the directions for use provided in the draft labeling developed by the Division. Accordingly, the NDA ~~should~~ be deemed approvable.

Paul Leber, M.D.
December 6, 1996

cc NDA 20-667
HFD 101
Temple
HFD-120
Katz
Feeney
Burkhart
Balian
Knudsen
Steele
Fitzgerald
HFD -710
Hoberman
Grilley
Wheelous

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: June 23, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 20-667, Mirapex, [pramipexole]

TO: File NDA 20-667
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my formal recommendation that the NDA for Mirapex be approved. This recommendation reflects the Division's review team's conclusion that the firm has satisfactorily met the requests and conditions upon which final approval of the application was conditioned (see the agency's action letter of 12/23/96).

In memoranda to the file, Dr. Katz (6/16/97) and Dr. Burkhart (5/13/97) summarize the findings and evidence that led them each to recommend that the application be approved. Although I fully concur with their recommendations, I have a number of comments for the administrative file.

Safety Update [SU]

With the submission of the SU, the clinical data base for the Mirapex NDA now includes a total of some 2150 subjects (there were 1400 in the original NDA) who provide approximately 1925 patient-years of exposure experience.

<u>No previously unrecognized risks of use have been identified.</u>

Although Dr. Balian (2/27/97) concludes that the experience reported upon provides no finding that would cause the agency to reverse its conclusion that Mirapex has been shown to be safe for use, it bears note that a

sizeable fraction of the new information presented does not derive from experience gained with pramipexole in patients with PD, but from reports of studies of the drug in patients with depression or schizophrenia.

The relationship between dose and common ADRs has not been characterized

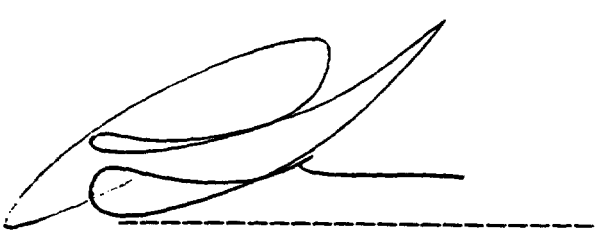
The firm has been unable to develop the information necessary to determine whether or not there is a linkage between ADR incidence and pramipexole dose. The review team is persuaded that their inability to do so is a consequence of 1) the fact that pramipexole dose was advanced by titration (i.e., thus, dose and time are confounded), and, 2) the small numbers of untoward events falling within any of the categories that would be created by an arbitrary partition of the dose and time continuum.

Labeling

The sponsor has persuaded the agency review team that a draft of product labeling differing in a number of ways from the labeling put forth in the approvable action is acceptable. The areas of labeling affected by these changes are identified in Dr. Katz's 6/16/97 memorandum.

Recommendation

The application should be approved.



Paul Leber, M.D.
June 23, 1997

cc NDA 20-667
HFD 101
Temple
HFD-120
Katz
Feeney
Burkhart
Balian
Knudsen
Steele
Fitzgerald
HFD -710
Hoberman
Grilley
Wheelous

MEMORANDUM

DATE: December 2, 1996

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-667

SUBJECT: Supervisory Review of NDA 20-667 for the use of Pramipexole in patients with Parkinson's Disease

BACKGROUND

NDA 20-667, for the use of pramipexole, a D2 receptor agonist (with greatest affinity for the D_3 receptor sub-type), in patients with idiopathic Parkinson's Disease (PD), was submitted by Pharmacia and Upjohn on December 28, 1996. The NDA includes reports of 9 controlled trials; 4 of the trials enrolled patients with relatively early PD who were not receiving concomitant dopaminergic therapy. In the remaining 5 trials, patients with later stage PD were enrolled, and these patients were receiving concomitant dopaminergic therapy.

The effectiveness data were reviewed by Dr. John Feeney (and Dr. James Sherry) of the Division, in a review dated 9/13/96, and a detailed statistical review of 3 of the controlled trials was performed by Dr. David Hoberman of Biometrics in a review dated 10/24/96. The safety database was reviewed by Drs. John Balian and James Knudsen of the Division in a review dated 11/13/96. In this memo, I will briefly review the efficacy and safety data, and offer my recommendation for action on the NDA.

EFFECTIVENESS

EARLY PD

As noted above, the sponsor has submitted the results of 4 controlled trials in patients with early PD; Studies 1, 4, 17, and 21. Study 21 was small, and Study 17 was single-blind. They will be discussed very briefly

here, but I will focus on the results of Studies 1 and 4.

Study 1

This was a multi-center, randomized, placebo controlled, parallel group trial in which patients with PD Stage I-III Hoehn and Yahr who were not receiving concomitant l-dopa therapy were enrolled. The Hoehn and Yahr scale is a frequently used PD staging instrument, in which I=minimal unilateral disease and V=confined to bed or wheelchair. Stage III=Mild to moderate bilateral disease with some postural instability but physically independent.

Patients were permitted to have received l-dopa in the past, but not for greater than 6 months and not for at least 60 days prior to randomization. Treatment was to be initiated at 0.125 mg TID (total daily dose of 0.375 mg), and weekly dose increments were to be carried out, to the patient's maximally tolerated dose or a maximum dose of 1.5 mg TID (total daily dose of 4.5 mg). This titration phase could last up to 7 weeks.

After the titration phase, patients entered a 6 month maintenance phase, which was followed by a 1 week dose reduction phase.

The protocol stated primary outcomes were change from baseline in the score of the Unified Parkinson's Disease Rating Scale (UPDRS) for the Activities of Daily Living (ADL) and Motor Score sub-scales.

The UPDRS is a frequently used multi-item scale which is designed to assess various aspects of the severity of PD. It consists of 42 items, grouped into 4 parts: Mentation, ADL, Motor Exam, Complications of Therapy. Part II (ADL) consists of 13 items, and Part III (Motor Exam) consists of 14 items, each of which are rated from 0-Normal to 4-maximum impairment. Scores for Part II can range from 0-Normal to 42 Maximal Disability. Scores for Part III can range from 0-Normal to 46-Maximal Disability. The items constituting the ADL are assessed for the previous week (both during "on" periods-during which the patient is functioning well, and during"off" periods-periods when the patient is relatively immobile), and the items for the Motor Score are assessed by the examiner during a study visit. These latter items consist of, for

example, assessment of tremor, rigidity, facial expression, speech quality, bradykinesia, posture, gait, etc.

A total of 300 patients were planned to be enrolled at 24 U.S. and Canadian centers.

RESULTS

A total of 335 patients were randomized (pramipexole 164, placebo 171) at 26 centers in the U.S. A total of 28 pramipexole and 34 placebo patients did not complete the trial, and 163 pramipexole and 170 placebo patients were included in the intent-to-treat, last observation carried forward (LOCF) analyses.

The following results were obtained for the primary analysis of UPDRS Parts II and III:

Part II (ADL)

	Change From Baseline	P-value
Pramipexole (N=163)	-1.9	
Placebo (N=170)	+0.4	<0.0001

Similar P-values were obtained for between treatment differences at weeks 0, 4, 8, 12, and 16 (week 0 is the end of titration). The magnitude of the between treatment differences seen at these times was approximately the same as is displayed. Likewise, an analysis of an Area Under the Curve (AUC) analysis for the entire Maintenance Phase yielded values of -57 and -5 for pramipexole and placebo, respectively, with a corresponding p-value of <0.0001. Cumulative Distribution Functions for this outcome are reproduced in Dr. Feeney's review, page 22.

Part III (Motor Score)

	Change From Baseline	P-value
Pramipexole	-5	
Placebo	+0.8	<0.0001

Again, similar p-values were obtained at each assessment week during the Maintenance Phase, including at the end of titration, although the magnitude of the between treatment differences were slightly less than for the LOCF analysis displayed above. Further, an AUC analysis yielded values of -127 and -11 for pramipexole and placebo, respectively, a difference that was highly significant (P<0.0001). Cumulative Distribution Functions for this outcome are reproduced in Dr. Feeney's review on page 25.

As Dr. Hoberman notes in his review (page 3), on average, the patients the LOCF change from baseline for patients discontinuing pramipexole was better than that of dropouts from placebo. Finally, a time to failure analysis yielded a p-value (logrank test) of 0.0015 in favor of pramipexole.

Study 4

This was a multi-center, randomized, double-blind, parallel group study in which patients with idiopathic PD (Hoehn and Yahr I-III) were randomized to one of 3 fixed doses of pramipexole or placebo. Patients were not permitted to have received l-dopa within 3 months prior to the study.

Patients were titrated to their fixed dose over a maximum of 6 weeks. The maximum doses to be achieved were either 0.5 mg TID (1.5 mg/day), 1.5 mg TID (total daily dose of 4.5 mg), 2.0 mg TID (6.0 mg/day), or placebo. Patients not tolerating a given dose could be dropped back to their previous dose, and were not to receive higher doses. After the dose titration, patients entered a 4 week Maintenance Phase, followed by a 1 week Dose Reduction Phase.

Patients were seen every 2 weeks after randomization, at which time the

UPDRS, Parts I-III were assessed. At the final visit, Hoehn and Yahr staging was performed and several quality of life questionnaires were administered.

The primary outcome in this study was change from baseline of the sum of UPDRS Parts I-III. Analyses examining the dose to which patients were randomized as well as the dose actually received were planned.

RESULTS

A total of 264 patients were randomized at 20 centers in the U.S. and Canada. The following table displays the disposition of patients:

	Pr 1.5	Pr 3.0	Pr 4.5	Pr 6.0	Pbo
Randomized	54	50	54	55	51
Completed	44	48	50	46	50

The following table displays the results of analyses of the primary outcome for the doses to which patients were randomized.

	Pr 1.5	Pr 3.0	Pr 4.5	Pr 6.0	Pbo
Baseline	28.5	28.3	27.3	32.9	28.7
Mean Change	-6.1	-5.8	-6.6	-7.1	-1.2

All individual dose-placebo pairwise contrasts yielded p-values of <0.006, (significant in the face of Bonferroni correction) with an overall p-value of 0.0022. Similar changes were seen when the results were analyzed according to the dose actually achieved (in this latter analysis, it is not clear in which group patients not achieving the dose to which they were randomized were counted, although it is true that most of the steps in the titration algorithms would yield one of the 4 "goal" doses).

The sponsor acknowledges that there was no dose response seen, although with placebo included in a regression analysis, a linear dose response was seen (P-value 0.03) for the analysis in which patients were counted in the

group to which they were randomized.

Although between treatment differences of about 1.5 were seen for the individual dose-placebo contrasts for UPDRS Part II (Motor Scale), the overall p-value was 0.06, while the overall p-value for Part III (ADL) was 0.005.

In general, results of the Quality of Life questionnaires did not achieve statistical significance.

Study 17

This was a single blind, randomized, placebo controlled, parallel group trial in PD patients who had not received l-dopa within 3 months. A total of 48 patients were to be enrolled. The trial had a 7 week titration phase, with a maximum dose of 4.5 mg/day. Following titration, there was a 3 week Maintenance Phase, followed by a 1 week dose reduction phase. The primary outcome was mean change from baseline on Parts II and II of the UPDRS.

RESULTS

A total of 56 patients were randomized, with 55 included in the ITT population analyzed. Analysis of observed cases performed by the sponsor yielded a p-value of 0.002 for the pramipexole (N=28)-placebo (N=24) contrast for UPDRS Part II, and a p-value of 0.10 for the between treatment contrast for UPDRS III.

Study 21

This was a double-blind, placebo controlled, randomized, parallel group study of patients with PD who had received no more than 1 week of l-dopa in the past. Patients were to be titrated to a maximally tolerated dose, up to 4.5 mg/day; the titration phase was to last a maximum of 9 weeks, after which they were to enter a 2 week maintenance phase, followed by a 1 week dose reduction phase. A total of 72 patients were to be randomized, to yield 52 completers.

The primary outcome was to be change from baseline in UPDRS, Part III.

RESULTS

Only 24 patients were enrolled. The sponsor performed an analysis excluding 2 of these patients, which they assert yielded a p-value of 0.02.

LATE PD

Study 10

This was a multi-center, randomized, parallel group, placebo controlled trial in which patients with idiopathic PD (Hoehn and Yahr Stages II-IV) who are not adequately controlled on maximally tolerated l-dopa (as well as other anti-PD medications) were randomized to receive adjunctive pramipexole or placebo.

Patients initially entered a titration phase, beginning with a dose of 0.25 mg TID (total daily dose of 0.375 mg) to be followed by weekly dosing increments to a maximum dose of 1.5 mg TID (to be achieved in 7 weeks) or to a lower maximally tolerated dose.

After titration, patients entered a 6 month maintenance phase, and then a 1 week dose reduction phase. During this maintenance phase, the dose of l-dopa could be reduced for control of dopaminergic adverse events. The l-dopa dose could then be increased, but was not to exceed the baseline dose. Other anti-PD medications were to be held constant during the study.

At monthly intervals, patients were assessed with the following measures:

1) UPDRS; the Motor Score was to be assessed during an "on" period.
2) Modified Schwab-England Disability Scale; this is an ADL scale.
3) Timed Walking Test
4) Hoehn and Yahr
5) Parkinson's Dyskinesia Scale

Patients were instructed to record a daily diary for at least 2 full days prior to clinic visits. On this diary, patients were to record the total time awake, as well as the total time spent "off", and the severity of the "off" periods (1-4 scale). Part II of the UPDRS, as well as the Schwab-England and Hoehn and Yahr Scales were to be rated for both "on" and "off" periods.

The primary outcomes were to be change from baseline in Parts II and III. The protocol specified that both outcomes would have to reach significance independently in order for the trial to be considered "positive".

A total of 300 patients were to be enrolled at 24 U.S. and Canadian centers.

RESULTS

A total of 360 patients (pramipexole 181, placebo 179) were enrolled at 26 U.S. And Canadian centers. A total of 351 patients (pramipexole 179, placebo 172) were included in the ITT population.

A total of 30/181 (16.6%) of pramipexole patients and 39/179 (22%) of placebo patients discontinued treatment prior to completing the trial.

The following table presents the results for the protocol specified primary outcomes:

Change From Baseline in UPDRS Part II

	LOCF Change	LOCF AUC for Maintenance
Pramipexole (N=179)	-2.7	-57
Placebo (N=171)	-0.5	-18
P-value	<0.0001	<0.0001

Statistically significant differences were seen for the between treatment change from baseline in Part II at all visits during the Maintenance Phase starting at visit 5. (Scores for Part II are averages of scores for "on" and

"off" times). Cumulative Distribution Functions for this outcome are reproduced in Dr. Feeney's review, page 90.

Change From Baseline in UPDRS Part III

	LOCF Change	LOCF AUC for Maintenance
Pramipexole (N=179)	-5.6	-114
Placebo (N=171)	-2.8	-64
P-value	0.01	0.01

A total of 7/12 between treatment differences were significant during the Maintenance phase (see Dr. Hoberman's review, Figure 2). Cumulative Distribution Functions for this outcome are reproduced in Dr. Feeney's review, page 95.

As Dr. Hoberman notes, the consistency of the results over time suggest that there was little effect of dropouts on the LOCF analysis.

Dr. Feeney suggests in his review that Percent of Awake Time Spent "off" is a useful measure of effectiveness (this was a protocol specified secondary outcome) because, among other reasons, UPDRS Part II was to be an average of scores during "on" and "off" times, but did not take into account time spent in either of these states (theoretically, scores could have improved, but a patient might have spent more time "off", a clearly undesirable outcome). In addition, Part III was to be assessed during an "on" period, also thereby not taking into account a potential increase in "off" time. Finally, he notes that Parts II and III appear to be independent, whereas total "off" time is, in his view, a more global measure of effectiveness.

The following table displays the results for Average Percent of Awake time spent "Off":

	Baseline	Final	Change	P-value
Pramipexole (N=173)	37.2	24	-13	
Placebo (N=172)	38.3	35	-3	0.0006

The difference between treatments emerged by visit 4, increased until visit 6, then remained essentially constant throughout the Maintenance phase (see Dr. Hoberman's review, Figure 5).

Little difference was seen on the Schwab-England ADL scale or the Hoehn and Yahr scale.

The pramipexole group was able to tolerate a decrease in l-dopa dose of about 25% compared to a 6% reduction in the placebo groups (P<0.0001).

Study 19

This was a 7 center randomized, double blind, placebo controlled, parallel group trial in patients with poorly controlled PD (Hoehn and Yahr II-IV) being treated concomitantly with l-dopa at a maximally tolerated dose. Patients were titrated over a maximum of 7 weeks to a maximum daily dose of 5 mg (presumably 1.25 mg QID), after which they entered a 4 week maintenance phase and then a 1 week dose discontinuation phase.

The primary outcome was change from baseline in total UPDRS score.

RESULTS

A total of 78 (pramipexole 34, placebo 44) were treated. According to the sponsor, the following results for the primary measure were obtained:

	Baseline UPDRS	Final UPDRS	P-value
Pramipexole	53.7	33.6	
Placebo	50.2	44.4	0.0002

Study 22

This trial was essentially identical to Study 19. It was performed at 9 centers in Denmark.

RESULTS

A total of 69 patients (pramipexole 36, placebo 33) were enrolled. According to the sponsor, the following results were obtained:

	Baseline UPDRS	Final UPDRS	P-value
Pramipexole	51.9	35.0	
Placebo	56.7	47.7	0.018

Study 18

This was a single blind, placebo controlled, parallel group, randomized trial in patients with motor fluctuations on maximally tolerated l-dopa. A total of 48 patients were to be enrolled.

Patients were entered into a 7 week titration phase designed to reach a maximum dose of 4.5 mg/day. Following the titration phase, patients entered a 3 week maintenance phase, followed by a 1 week dose reduction phase.

The primary outcome was Mean Change from Baseline on UPDRS, Part II, and percentage of "off" time; both were to be significant independently in order for the study to be considered to demonstrate effectiveness.

RESULTS

A total of 50 patients (pramipexole 26, placebo 24) were enrolled at 6 U.S. Centers.

According to the sponsor, there were no significant between treatment differences seen in the change from baseline on Part II when examined during "on" and "off" times individually, nor were there significant between treatment differences on the percent of "off" time.

Study 20

This was to be randomized, s=double blind, parallel group, placebo

controlled trial of advanced PD patients. However, only 19 patients were enrolled, and the trial was not analyzable.

SAFETY

A total of 879 unique patients have been exposed to pramipexole in completed Phase 2/3 controlled trials. Of this total, 702 have been patients with Parkinson's Disease (416 have been patients not receiving concomitant l-dopa [early PD] and 286 were receiving concomitant l-dopa [late PD]); the remaining 177 have been patients with schizophrenia. An additional 260 subjects have been enrolled in Phase 1 trials, resulting in a total of 1139 patients/subjects enrolled in completed trials. However,the NDA contains reports of experience in a total of 1408 patients in Phase 2/3 trials and 253 Phase 1 subjects exposed to pramipexole, including those enrolled in extension trials at the time of the NDA cut-off date (1/95). Of these 1408 patients, 1231 were patients with PD.

Of the 1231 PD patients, 178 have been exposed for greater than 1 year (59 for greater than 2 years), and 365 have been exposed for between 6 months and 1 year. A total of 552/1231 (45%) of PD patients have received the maximum proposed dose of 4.5 mg/day for at least 12 weeks, and 981/1231 (80%) have received at least 1 day of this maximum dose. Of the 702 PD patients in controlled trials, 349 (50%) received an average dose of between 3-4.5 mg/day. Of this group, 207 received this average dose for between 24-36 weeks (this included extension trials).

DEATHS

A total of 17 deaths had occurred in the course of pramipexole's development as of 1/95; of these 17, 15 deaths (or the event leading to death) occurred within 30 days of the last dose of study drug. A total of 12 of the deaths occurred in pramipexole treated patients. In the controlled trials, the following comparisons are made:

	Deaths	Rate/100 patient-years	Relative Risk
Early patients			
Pramipexole (N=416)	1	0.72	0.80
Placebo (N=262)	1	0.90	
Late Patients			
Pramipexole (N=286)	3	2.52	2.87
Placebo (N=289)	1	0.88	

For the entire pramipexole treated PD population, the early patients mortality dropped to 0.11 deaths/100 patient years, while the late patients mortality dropped to 1.83 deaths/100 patient years.

Of the pramipexole deaths, the reviewers considered 8 to be potentially cardiovascular in nature.

Of these 8, there were several documented or presumed MI or heart failures, mostly in patients with past history of severe cardiac disease. One patient had no history of cardiac disease, but had an MI during Study 10 (late PD), presumably sometime towards the middle to late portion of the Maintenance Phase. He died shortly thereafter.

Another patient with no real cardiac history died on day 61 of study 1 (early PD) from a presumed pulmonary embolus. A third patient with a past history of mild cardiac insufficiency and bronchitis suffered multiple episodes of dyspnea and syncope. He died after an episode of syncope, but no autopsy was performed.

DISCONTINUATIONS

Early PD

In controlled trials of early PD patients, the total dropout rate in

pramipexole patients was 14.4%, compared to16.2% in placebo patients. The rate of dropouts secondary to adverse events was 12% for pramipexole patients, compared to 11% for placebo patients. The rates of discontinuations were variable in these studies, with the largest difference between drug and placebo occurring in Study 4; 12% and 2%, respectively. Most of these dropouts occurred secondary to adverse events at the highest dose (6 mg/day). The most common adverse events associated with discontinuation that were greater than 1% and also greater than the placebo rate were: hallucinations (3%), dizziness, nausea (2%), somnolence (1.55%), headache (1.3%), and confusion (1%).

Of the discontinuations due to adverse events, 8/388 (2.1%) of the pramipexole and 3/235 (1.3%) of the placebo patients had events considered serious. Of the 8 pramipexole patients, 1 died secondary to a cardiovascular event, and the remaining 7 included 1 case each of drowsiness, decreased platelets, abdominal pain, somnolence, paranoid psychosis, sensory hallucinations, and confusion/hallucination.

Late PD

In controlled trials in late PD patients, the overall discontinuation rate was 15.4% in pramipexole patients and 20.4% in placebo patients. In these studies, the dropout rate due to adverse events was 11.5% for pramipexole patients and 15.8% for placebo patients. The most common adverse events associated with discontinuation that were greater than 1% and also greater than the placebo rate were: hallucinations (2.7%), postural hypotension (2.3%), dyskinesia (1.9%), confusion, dizziness (1.2%).

Of the discontinuations due to adverse events, 8/259 (3.1%) of the pramipexole and 6/266 (2.3%) of the placebo patients had adverse events considered serious. Of these 8 pramipexole patients, 2 had cardiovascular events and died.

Other Serious Adverse Events in Controlled Trials

Early PD

Of the 388 pramipexole treated patients in controlled trials, 20 (5%) had adverse events deemed serious, while 5.5% of placebo patients had such events. Of the 20 serious adverse events in the pramipexole patients, 7 were cardiovascular. One of these was discussed in the section on Deaths, and the other 6 were 2 MIs, 2 angina, and 1 case each of pulmonary embolism, and LV dysfunction.

Of the remaining 13, 7 have been discussed in the section on serious adverse events leading to discontinuation; the other 6 consisted of 2 cases of prostate cancer, and 1 case each of fractured hip, thyroid nodule, basal cell carcinoma, and rectal cancer.

Late PD

Of the 259 pramipexole treated patients in controlled trials,18 (7%) had serious adverse events, compared to 7.5% of the placebo patients. Of the 18 serious adverse events in pramipexole patients, 3 were cardiovascular; 2 resulted in death, and one had angina. The other 15 consisted of the following: pneumonia, dyskinesia, fractures, somnolence, bladder cancer, paranoia, nausea, neck pain, CPK elevation, increase of periods, back pain, abdominal pain, confusion, and multiple myeloma.

Other serious events

It is difficult to tell from the documents available what the incidence of serious adverse events is in the entire PD database. However, Drs. Balian and Knudsen have highlighted several of the events as being worthy of note.

Cardiovascular

A 72 year old man experienced severe orthostatic hypotension after a single 0.125 mg dose of pramipexole. He was on multiple medications

(including treatment for prostatic CA). One hour after the dose, his supine BP was 130/80, but on standing his BP was essentially 0. He could not stand for about 3.5 hours after dosing. Apparently, his EKG was normal (time after dosing unknown to me).

Hematologic

A 72 year old man receiving pramipexole 4.5 mg/day (as well as nifedipine for about 260 days) was documented to have a platelet count of 72,000/mm^3 after 40 days of treatment (baseline count was 148,000). Three days later the platelet count was 58,000. On day 47, pramipexole was discontinued; at the time, the count was 55,000. A bone marrow aspiration was not consistent with marrow suppression, and no further information is available.

Respiratory

A 77 year old man with a history of cardiac disease and LV dysfunction experienced dyspnea on day 32 of treatment with pramipexole (at the time his dose was 3 mg/day). Four days later, at a dose of 4.5 mg/day, he was hospitalized for dyspnea and was determined to have LV dysfunction and pulmonary congestion. His treatment was discontinued and underwent cardiac bypass surgery shortly thereafter.

Laboratory abnormalities

A 49 year old man experienced a marked increase in CPK (about 11,000 IU/L) after 1 month of treatment. Medication was discontinued, and CPK began to decrease. The patient was admitted to the hospital and treated for rhabdomyolysis.

Other Adverse Events

Early PD

The following adverse events were seen in at least 5% of the 388 pramipexole treated patients in controlled trials and at least twice as frequently as in the placebo patients:

Somnolence-22%
Constipation-14%
Hallucination-9%
Other adverse events seen at a greater incidence than placebo included confusion, anorexia, amnesia, hypesthesia, vision abnormality, dysphagia, weight loss, akathisia, thinking abnormal, decreased libido, myoclonus, and fever.

Late PD

The following adverse events were seen in at least 5% of 260 pramipexole treated patients in controlled trials and at least twice as frequently as in the placebo patients:

Hallucination-16.5%
Dry Mouth-6.5%
Urinary Frequency-5.8%

Other adverse events seen at a greater incidence than placebo included dyskinesia (47% compared to a placebo rate of 32%), chest pain, vision abnormality, rhinitis, twitching, peripheral edema, pneumonia, paranoid reaction, bursitis, CPK increase, myasthenia, delusions, sleep disorder, and diplopia.

Dose Response

Only Study 4 (early PD) was designed as a fixed dose study. In this study, nausea, and somnolence and insomnia were seen to be dose related. In both early and late controlled trials, the greatest risk for several adverse events was observed in the titration phases.

Abnormal Lab Values

In general, pramipexole produced no systematic abnormalities in routine laboratory tests.

However, in the combined controlled trial database (Studies 1, 4, and 10), 19 (3.5%) of the pramipexole treated patients and 9 (2.3%) of the placebo patients had CPK levels exceeding normal limits; this difference was not statistically significant. The number of patients with significant elevations is unclear, although it appears to be a relatively small proportion of the 19.

In other controlled trials, 2/76 (2.6%) of pramipexole treated patients experienced elevated CPK levels, compared to 0/83 (0%) of placebo patients. One of the patients had a CPK at day 48 of 3498 IU/L, resulting in discontinuation of treatment. CPK returned to normal after drug discontinuation.

There was one case diagnosed as rhabdomyolysis; this case has been discussed.

LFTs

In the 3 controlled trials (Studies 1, 4, and 10), a total of 15/553 (2.7%) of pramipexole patients experienced elevations of LFTs (ALT, AST, and/or GGT) greater than 2.5 X ULN. A total of 5/394 (1.3%) of placebo patients had similar elevations. Most of the elevations in the pramipexole patients occurred in Study 10, in which there were 10 such patients (5.7%), compared to 2 (1.2%) placebo patients.

Of the 15 pramipexole treated patients with elevations, 8 had elevations of GGT only; 7 of these 8 had elevations of GGT prior to treatment with pramipexole. Of these 7, 3 had baseline elevations at least 2.5 X ULN; of the remaining 4 with baseline elevations, most had elevations close to 2-2.5 X ULN, and the elevations noted on treatment for most of the 7 with baseline elevations were similar in degree to the pre-treatment elevations.

Most of the other LFT elevations were relatively mild (in most of these patients, the maximum value of either AST or ALT obtained was in the range of 200-250; 1 patient had one ALT of 304). It is difficult to tell, from the reviews, the ultimate disposition of these patients. However, it appears that, for many of these patients, the elevations either stabilized or returned towards normal with continued treatment (for several other cases, alternative explanations for the elevations were available).

One patient (a 67 year old man) in Study 10 experienced a GGT of 1552 U/L (ULN=65 U/L) on day 50 of treatment; this was associated with an ALT of 206. Treatment was discontinued and LFTs returned to normal within 30 days. Throughout, his bilirubin was normal.

Orthostatic Hypotension/Syncope

In animal studies, pramipexole lowers blood pressure and pulse, presumably related to its D2 and alpha$_2$ agonism.

In Phase 1 studies, pramipexole was seen to cause dose related orthostatic hypotension, first seen after single doses of 0.2 mg. In some subjects, syncope occurred upon standing. In controlled trials in early PD patients, there were 5 episodes of syncope in pramipexole patients (1.3%), and 2 such episodes in placebo patients (1.0%).

In controlled trials of late PD patients, there were 4 episodes of syncope in pramipexole patients (2.2%), and 7 in placebo patients (3.4%).

In neither population was there a significant difference between drug and placebo patients in the rate of discontinuations for serious or non-serious adverse events.

Regarding orthostatic hypotension, this was reported at a frequency of 7.7% in early PD patients compared to 8.9% in early placebo patients. In late PD patients, 53% of pramipexole and 48% of placebo patients were reported to have experienced at least 1 episode of orthostatic hypotension. Few of these episodes were symptomatic, and a total of 7 pramipexole and 3 placebo patients discontinued from controlled trials

(combined early and late patients) because of orthostatic hypotension.

SUMMARY

The 3 randomized controlled trials (Studies 1, 4, and 10) described in this memo clearly demonstrate the effectiveness of pramipexole as a symptomatic treatment for patients with Parkinson's Disease. This conclusion applies to patients with relatively mild disease not receiving concomitant dopaminergic therapy, as well as to patients with more advanced disease who are receiving concomitant l-dopa.

The safety experience contained in the NDA provides no signal that pramipexole will be unacceptably dangerous when used according to appropriate labelling, although the safety database is not as large as we might hope. For example, we know that 552 patients have received this dose for at least 12 weeks, but we do not know how many have received this dose for longer durations. It would be useful for the sponsor to explicitly display the number of patients who received 4.5 mg/day for specific durations.

The panoply of adverse events seen are typical for D2 agonists, and there is some reassurance that the incidence of syncope/orthostatic hypotension appears not to have been greater than that seen in placebo patients in the controlled trials (again, given the limitations imposed by the relatively small number of patients in controlled trials). It is of some note that the mortality (deaths/100 patient years) in the late PD patients was 2.52 in pramipexole patients compared to 0.88 in placebo patients (relative risk of 2.9). However, this represents, in reality, 3 deaths in the drug treated group compared to 1 death in a placebo patient, with 95% CIs of (0.3, 27). Examination of the causes of death did not reveal any obvious, specific pramipexole relationship.

RECOMMENDATIONS

For the reasons stated above, I recommend that the attached Approvable letter be sent to the sponsor.

Russell Katz, M.D.

Cc:
NDA 20-667
HFD-120
HFD-120/Leber/Katz/Feeney/Sherry
HFD-120/Burkhart/Balian/Knudsen/Grilley
HFD-710/Hoberman

MEMORANDUM

DATE: June 16, 1997

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: Director
Office of Drug Evaluation I/HFD-101

SUBJECT: Review of Sponsor's Response to Approvable Letter for Pramipexole, NDA 20-667

On December 23, 1996, the Agency sent an Approvable letter to Pharmacia & Upjohn, Inc. for NDA 20-667, Pramipexole in patients with Parkinson's Disease. The letter asked only for the sponsor to accept specific dissolution specifications and methodology as well as submit a safety update. In addition,of course, there were multiple questions embedded in the draft labeling that accompanied the letter.

The sponsor responded to the letter in a submission dated 1/7/97. In that response, the sponsor 1) made a number of changes to the proposed draft labeling, 2) responded to the questions and requests embedded in the draft, 3) submitted a safety update, and 4) agreed to the dissolution specifications and methodology described in the letter.

The sponsor's response has been reviewed by Drs. Balian and Burkhart of this Division, in reviews dated 2/27/97 and 5/13/97, respectively, and by Dr. Baweja of OCPB, in a review dated 4/30/97. No new safety issues emerged. Of note, however, Dr. Burkhart concluded that a reliable analysis of dose response of ADRs could not be performed because 1) dose and time were confounded (due to the fact that the studies used a titration design), and 2) there were too few events of interest in any dose group. This conclusion is important because we asked the sponsor to include in labeling a description of those ADRs, if any, that were dose related. Based on Dr. Burkhart's review, no such statements will be included (see below).

The division reviewed the sponsor's draft labeling, and had a number of areas of disagreement with the firm. The division constructed revised draft labeling, and "faxed" this revised version to the sponsor on 5/28/97. The company informed us of their continued disagreement with some of our proposed language and, as a result, these residual issues were discussed

in a telephone call on 6/10/97.

At this meeting, the Agency and sponsor came to agreement on essentially all issues (minor wording in a few areas was left to the firm to draft). A revised draft of labeling was sent to the Division on 6/12/97. This draft is acceptable with a few minor changes. This most recent draft (again, which we find acceptable) differs from the draft label accompanying the Approvable letter in several important ways:

1) **CLINICAL PHARMACOLOGY**: The sponsor has proposed a sentence at the end of the 1st paragraph that describes relative binding affinities at D_3, D_2, and D_4 receptor sub-types, but that describes (at the Division's urging) the relevance of this binding for Parkinson's Disease as being unknown.

Also, they have removed the last sentence of this section, which discussed the effects of pramipexole on neuronal dopamine metabolism in animals.

2) **CLINICAL STUDIES**: The sponsor corrected the number of placebo controlled double blind trials described to 7, not 8, as had been originally (and incorrectly) stated.

3) **WARNINGS**: We asked the sponsor to re-calculate the comparative incidence of objective orthostatic events (we were concerned with misclassification of events that they included as being manifestations of orthostasis). No additional language was added to that proposed in the draft that accompanied the Approvable letter.

4) **PRECAUTIONS**: The language in the sub-section called **Retinotoxicity in Albino Rats** has been changed to be somewhat more detailed and to include a statement about the potential relevance to humans. The sub-section itself has been re-named; it is now called **Retinal pathology in albino rats**.

5) **ADVERSE EVENTS**: In the draft labeling accompanying the Approvable letter, we asked the sponsor to draft statements about the dose relatedness of ADRs for both early and late PD patients. Upon review of this data, we realized that it was impossible to determine which ADRs might be dose related, because the studies all used a titration design, and dose and time were confounded. Hence, we removed any statements designed to list those ADRs which were dose related, and instead included a statement about this confounding after the first paragraph in this section (before the sub-section **"Early" Parkinson's Disease**).

6) **DOSAGE AND ADMINISTRATION**: In this section, we included a table of dosing adjustments necessary for patients with renal impairment. In this table, for the last category of patients (those with severe impairment), we had written WARNING in the space for the proposed dosing. Upon further reflection, we decided that this was cryptic, at best. The revised version now reads "The use of MIRAPEX has not been adequately studied in this group of patients".

In addition to these changes, the sponsor has adequately responded to all the questions we asked in the body of the draft labeling.

RECOMMENDATIONS

The application should be approved and the attached Approval letter should be sent to the sponsor.

Russell Katz, M.D.

Cc:
NDA 20-667
HFD-120
HFD-120/Leber/Katz/Burkhart/Feeney/Fitzgerald/Steele/Wheelous
HFD-860/Baweja

CLINICAL REVIEW AND EVALUATION OF EFFICACY

NDA 20-667

Mirapex (pramipexole)

Reviewer:	John Feeney, M.D. James Sherry, M.D., Ph.D. (Studies 19 & 22)
Date:	September 13, 1996
Sponsor:	Pharmacia & Upjohn
Indication:	Parkinson's Disease
NDA Submission Date:	December 28, 1995

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Introduction:

Overview of Studies Pertinent to Efficacy

There have been 9 completed controlled trials addressing the efficacy of pramipexole in Parkinson's Disease.

Four of the 9 were conducted in patients with early PD and did not allow concomitant L-dopa therapy: Studies 1,4,17, and 21.

Five of the 9 were conducted in patients with advanced PD, including patients on concomitant L-dopa therapy: Studies 10,18,19,20, and 22.

Early disease was defined as Hoehn and Yahr stages 1-3. Patients in these studies could not be on concomitant L-dopa, but could take some other drugs use to treat symptoms, including amantadine, deprenyl, and anticholinergics. Advanced PD was defined as Hoehn and Yahr stages 2-4, requiring concomitant L-dopa and experiencing some of the adverse events associated with longterm use of L-dopa, including "on-off" periods and dyskinesias.

Studies 1,4, and 10 are the most recent studies (completed around January 1995) and the largest. The sponsor considers these 3 studies the "pivotal" studies. However, **Studies 19 and 22** (both in advanced PD) are not small. Study 19 randomized 78 patients to 2 groups and Study 22 randomized 69 patients to 2 groups. These 2 studies are reviewed by Dr. James Sherry, incorporated into this document.

Study 20 is a very small, double-blind, placebo-controlled trial in advanced PD. It showed no difference between groups, but it really is too small to lead to any generalizations. It stopped enrollment prematurely.

Study 21 is a very small, double-blind, placebo-controlled trial in early PD. It showed a difference in favor of pramipexole. It stopped enrollment prematurely.

Studies 17 and 18 were both single-blind studies, but seem capable by design of demonstrating a difference in favor of the active agent, pramipexole. However, Study 18 in advanced PD showed no difference

MODIFIED HOEHN AND YAHR SCALE RATER'S INITIALS (3): ____ ____ ____

Indicate the patient's Parkinson stage for both 'on' and 'off' periods by checking one box for 'on' and one box for 'off' below.

STAGE	ON	OFF	
0	☐	☐	No signs of disease
1	☐	☐	Unilateral disease
1.5	☐	☐	Unilateral plus axial involvement
2	☐	☐	Bilateral disease, without impairment of balance
2.5	☐	☐	Mild bilateral disease, with recovery on pull test
3	☐	☐	Mild to moderate bilateral disease; some postural instability; physically independent
4	☐	☐	Severe disability; still able to walk or stand unassisted
5	☐	☐	Wheelchair bound or bedridden unless aided

Pramipexole			
Study No.	Study Description	Number of Centers	Number of Patients Studied (Pramipexole / Placebo)
Completed Studies in Parkinson's Disease			
Adequate and Well-Controlled Studies			
1	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	26	335 (164 / 171)
4	Multicenter, Dose response, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	20	264 (213 / 51)
10	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	25	360 (181 / 179)
Other Double-Blind Controlled Studies			
19	Multicenter, Ascending dose, Prospective, Randomized, Double-blind, Placebo-controlled Study	9	77 (43 / 34)
20	Randomized, Double-blind, Placebo-controlled, Parallel-group Study	1	19 (9 / 10)
21	Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	6	24 (11 / 13)
22	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	9	69 (36 / 33)
Single-Blind Controlled Studies			
17	Multicenter, Ascending dose, Prospective, Randomized, Single-blind, Placebo-controlled, Parallel-group Study	4	55 (28 / 27)
18	Multicenter, Ascending dose, Prospective, Randomized, Single-blind, Placebo-controlled, Parallel-group Study	6	50 (26 / 24)

Pramipexole			
Study No.	Study Description	Number of Centers	Number of Patients Studied (Pramipexole / Placebo)
Ongoing Studies in Parkinson's Disease			
Controlled Studies			
M/2730/0005	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	33	176 (1/31/95)
M/2730/0012	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	52	236 (1/31/95)
M/2730/0036	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	36	124 (1/31/95)
M/2730/0055	Randomized, Double-blind, Placebo-controlled, Parallel-group Study	1	6 (1/31/95)
Uncontrolled Studies			
M/2730/0002	Open-label extension of 1	26	281 (1/31/95)
M/2730/0006	Open-label extension of M/2730/0005	33	41 (1/31/95)
M/2730/0011	Open-label, Ascending-dose Study Extension of 10	25	305 (1/31/95)
M/2730/0013	Open-label, Ascending-dose Study Extension of M/2730/0012	52	88 (1/31/95)
M/2730/0014	Open-label, long-term, safety Study Extension of 19, 20, 22	19	89 (1/31/95)
M/2730/0016	Multi-center, Open-labeled, Non-comparative, Safety Study	19	22 (1/31/95)

between drug and placebo, despite a reasonable enrollment. Study 17 in early PD did demonstrate a difference in favor of pramipexole.

The sponsor maintains that all 4 studies conducted in **early PD** showed a difference between pramipexole and placebo. Study 4, a dose-comparison trial, showed no benefit of doses greater than 1.5 mg/day.

Of the 5 studies in **advanced PD**, the sponsor maintains that 3 demonstrate a difference in favor of pramipexole, 1 demonstrates no difference between pramipexole and placebo, and 1 study stopped enrollment so early as to preclude any meaningful interpretation of the results.

Reviews of the individual studies follow.

Unified Parkinson's Disease Rating Scale (UPDRS)

All the studies in this NDA specified the UPDRS (or components) as primary outcome assessments. Studies 1 and 10 required a dual outcome, a positive effect on Part II and a positive effect on Part III of the UPDRS. Study 4 used the sum of Parts I-III as a primary outcome assessment.

A copy of the scale is attached. Part I rates mentation, mood, and behavior. Part II rates ADLs during the past week. Part III is a motor exam. Part IV rates complications of therapy, including dyskinesias.

Part II has 13 items scored from 0 (best) to 4 (worst) for a worst total score of 52. In advanced Parkinson's Disease where unpredictable shifts from states of good functioning to states of poor functioning occur throughout the day, Part II is scored twice, once for the so-called "on" state and once for the so-called "off" state. The total score on Part II then becomes the average of the "on" score and the "off" score. (This will be discussed in more detail in my review of Study 10.) In early Parkinson's Disease, where the "on-off" phenomenon is not occurring, Part II is scored only once and this averaging technique does not apply.

Part III has 14 items scored from 0-4, but some of the items are scored several times for different body regions (right body vs left body; right arm, left arm, right leg, vs left leg) so that the worst total score is 108. Part III is scored only once in both early and advanced Parkinson's Disease.

UNIFIED PARKINSON'S DISEASE RATING SCALE Pramipexole 00679A – M2730/0010

PATIENT INITIALS (3)	DATE OF VISIT (month/day/year)	VISIT	INVEST NO	SHEET NO	PATIENT NO	PAGE
		2			1001	14

The same person should conduct a given part of this evaluation throughout the trial.

When completing this section, indicate the patient's best level of function during the past week.

PART I. MENTATION, BEHAVIOR AND MOOD RATER'S INITIALS (3): ___ ___ ___

The worsening of a patient's disease symptom(s) will be recorded on the Adverse Event Report form only if their frequency has increased and/or severity has worsened since baseline or if, in the opinion of the investigator, they do not represent the patient's usual clinical state prior to study entry.

1. Intellectual Impairment:
- ☐ 0 = None
- ☐ 1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
- ☐ 2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
- ☐ 3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
- ☐ 4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought disorder (DUE TO DEMENTIA OR DRUG INTOXICATION):
- ☐ 0 = None.
- ☐ 1 = Vivid dreaming.
- ☐ 2 = "Benign" hallucinations with insight retained.
- ☐ 3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
- ☐ 4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression:
- ☐ 0 = Not present.
- ☐ 1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
- ☐ 2 = Sustained depression (1 week or more).
- ☐ 3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
- ☐ 4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative:
- ☐ 0 = Normal.
- ☐ 1 = Less assertive than usual; more passive.
- ☐ 2 = Loss of initiative or disinterest in elective (nonroutine) activities.
- ☐ 3 = Loss of initiative or disinterest in day-to-day (routine) activities.
- ☐ 4 = Withdrawn, complete loss of motivation.

PART II. ACTIVITIES OF DAILY LIVING DURING THE PAST WEEK
(score for both 'on' and 'off' periods)

RATER'S INITIALS (3): ___ ___ ___

5. Speech:

ON	OFF	
☐	☐	0 = Normal.
☐	☐	1 = Mildly affected. No difficulty being understood.
☐	☐	2 = Moderately affected. Sometimes asked to repeat statements.
☐	☐	3 = Severely affected. Frequently asked to repeat statements.
☐	☐	4 = Unintelligible most of the time.

6. Salivation:

ON	OFF	
☐	☐	0 = Normal.
☐	☐	1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
☐	☐	2 = Moderately excessive saliva; may have minimal drooling.
☐	☐	3 = Marked excess of saliva with some drooling.
☐	☐	4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

ON	OFF	
☐	☐	0 = Normal
☐	☐	1 = Rare choking.
☐	☐	2 = Occasional choking
☐	☐	3 = Requires soft food.
☐	☐	4 = Requires NG tube or gastrotomy feeding.

8. Handwriting:

ON	OFF	
☐	☐	0 = Normal.
☐	☐	1 = Slightly slow and small.
☐	☐	2 = Moderately slow or small; all words are legible.
☐	☐	3 = Severely affected; not all words are legible.
☐	☐	4 = The majority of words are not legible.

(Continued on next page.)

WHITE COPY:
CANARY COPY: INVESTIGATOR

UPDRS (CONT.)

Pramipexole 00679A – M2730/0010

PATIENT INITIALS (3)	VISIT	INVEST NO	SHEET NO	PATIENT NO	PAGE
	2			1001	15

PART II. – (Continued)

9. Cutting food and handling utensils:

ON OFF
- ☐ ☐ 0= Normal.
- ☐ ☐ 1= Somewhat slow and clumsy, but no help needed.
- ☐ ☐ 2= Can cut most foods, although clumsy and slow; some help needed.
- ☐ ☐ 3= Food must be cut by someone, but can still feed slowly.
- ☐ ☐ 4= Needs to be fed.

10. Dressing

ON OFF
- ☐ ☐ 0= Normal.
- ☐ ☐ 1= Somewhat slow, but no help needed.
- ☐ ☐ 2= Occasional assistance with buttoning, getting arms in sleeves.
- ☐ ☐ 3= Considerable help required, but can do some things alone.
- ☐ ☐ 4= Helpless.

11. Hygiene:

ON OFF
- ☐ ☐ 0= Normal.
- ☐ ☐ 1= Somewhat slow, but no help needed.
- ☐ ☐ 2= Needs help to shower or bathe; or very slow in hygienic care.
- ☐ ☐ 3= Requires assistance for washing; brushing teeth, combing hair, going to bathroom.
- ☐ ☐ 4= Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bedclothes.

ON OFF
- ☐ ☐ 0= Normal.
- ☐ ☐ 1= Somewhat slow and clumsy, but no help needed.
- ☐ ☐ 2= Can turn alone or adjust sheets, but with great difficulty.
- ☐ ☐ 3= Can initiate, but not turn or adjust sheets alone.
- ☐ ☐ 4= Helpless.

13. Falling (unrelated to freezing):

ON OFF
- ☐ ☐ 0= None.
- ☐ ☐ 1= Rare falling.
- ☐ ☐ 2= Occasionally falls, less than once per day.
- ☐ ☐ 3= Falls an average of once daily.
- ☐ ☐ 4= Falls more than once daily.

14. Freezing when walking:

ON OFF
- ☐ ☐ 0= None.
- ☐ ☐ 1= Rare freezing when walking; may have start-hesitation.
- ☐ ☐ 2= Occasional freezing when walking.
- ☐ ☐ 3= Frequent freezing. Occasionally falls from freezing.
- ☐ ☐ 4= Frequent falls from freezing.

15. Walking:

ON OFF
- ☐ ☐ 0= Normal.
- ☐ ☐ 1= Mild difficulty. May not swing arms or may tend to drag leg.
- ☐ ☐ 2= Moderate difficulty, but requires little or no assistance.
- ☐ ☐ 3= Severe disturbance of walking, requiring assistance.
- ☐ ☐ 4= Cannot walk at all, even with assistance.

16. Tremor:

ON OFF
- ☐ ☐ 0= Absent.
- ☐ ☐ 1= Slight and infrequently present.
- ☐ ☐ 2= Moderate; bothersome to patient.
- ☐ ☐ 3= Severe; interferes with many activities.
- ☐ ☐ 4= Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism:

ON OFF
- ☐ ☐ 0= None.
- ☐ ☐ 1= Occasionally has numbness, tingling, or mild aching.
- ☐ ☐ 2= Frequently has numbness, tingling, or aching, not distressing.
- ☐ ☐ 3= Frequent painful sensations.
- ☐ ☐ 4= Excruciating pain.

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UPDRS (CONT.)					Pramipexole 00679A – M2730/0010	
PATIENT INITIALS (3)		VISIT	INVEST NO	SHEET NO	PATIENT NO	PAGE
		2			1001	16

PART III. – MOTOR EXAMINATION (This exam MUST be completed when the patient is in an 'on' period)
This examination should be completed approximately two to three hours following a dose of decarboxylase inhibitor / levodopa therapy but prior to the initial dose of trial drug.

TIME OF EXAMINATION: ____:____ (24-hour clocktime) RATER'S INITIALS (3): ____ ____ ____

18. Speech:
- ☐ 0 = Normal.
- ☐ 1 = Slight loss of expression, diction, and/or volume.
- ☐ 2 = Monotone, slurred but understandable; moderately impaired.
- ☐ 3 = Marked impairment, difficult to understand.
- ☐ 4 = Unintelligible.

19. Facial expression:
- ☐ 0 = Normal.
- ☐ 1 = Minimal hypomimia, could be normal 'Poker Face'.
- ☐ 2 = Slight but definitely abnormal diminution of facial expression.
- ☐ 3 = Moderate hypomimia: lips parted some of the time.
- ☐ 4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted ¼ inch or more.

20. Tremor at rest: (F = Face, LH = Left Hand, RH = Right Hand, LF = Left Foot, RF = Right Foot)

F	LH	RH	LF	RF	
☐	☐	☐	☐	☐	0 = Absent.
☐	☐	☐	☐	☐	1 = Slight and infrequently present.
☐	☐	☐	☐	☐	2 = Mild in amplitude and persistent, or moderate in amplitude, but only intermittently present.
☐	☐	☐	☐	☐	3 = Moderate in amplitude and present all the time.
☐	☐	☐	☐	☐	4 = Marked in amplitude and present most of the time.

21. Action or postural tremor of hands:

L	R	
☐	☐	0 = Absent.
☐	☐	1 = Slight; present with action.
☐	☐	2 = Moderate in amplitude, present with action.
☐	☐	3 = Moderate in amplitude, with posture holding as well as action.
☐	☐	4 = Marked in amplitude, interferes with feeding.

22. Rigidity (judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

LUE = Left upper extremities, RUE = Right Upper extremities
LLE = Left lower extremities, RLE = Right lower extremities

Neck	LUE	RUE	LLE	RLE	
☐	☐	☐	☐	☐	0 = Absent
☐	☐	☐	☐	☐	1 = Slight or detectable only when activated by mirror or other movements.
☐	☐	☐	☐	☐	2 = Mild to moderate.
☐	☐	☐	☐	☐	3 = Marked, but full range of motion easily achieved.
☐	☐	☐	☐	☐	4 = Severe, range of motion achieved with difficulty.

23. Finger taps (Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.):

L	R	
☐	☐	0 = Normal.
☐	☐	1 = Mild slowing and or reduction in amplitude.
☐	☐	2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
☐	☐	3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
☐	☐	4 = Can barely perform the task.

24. Hand movements (Patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately.):

L	R	
☐	☐	0 = Normal.
☐	☐	1 = Mild slowing and/or reduction in amplitude.
☐	☐	2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
☐	☐	3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
☐	☐	4 = Can barely perform the task.

25. Rapid alternating movements of hands (Pronation–supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously.):

L	R	
☐	☐	0 = Normal.
☐	☐	1 = Mild slowing and/or reduction in amplitude.
☐	☐	2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
☐	☐	3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
☐	☐	4 = Can barely perform the task.

(Continued on next page.)

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UPDRS (CONT.) — Pramipexole 00679A – M2730/0010

PATIENT INITIALS (3)	VISIT	INVEST NO	SHEET NO	PATIENT NO	PAGE
	2			1001	17

PART III. – (continued)

26. Leg agility (Patient taps heel on ground in rapid succession, picking up entire leg. Amplitude should be about 3 inches.):

L R
- ☐ ☐ 0 = Normal.
- ☐ ☐ 1 = Mild slowing and/or reduction in amplitude.
- ☐ ☐ 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- ☐ ☐ 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- ☐ ☐ 4 = Can barely perform the task.

27. Arising from chair (Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.):

- ☐ 0 = Normal.
- ☐ 1 = Slow; or may need more than one attempt.
- ☐ 2 = Pushes self up from arms of seat.
- ☐ 3 = Tends to fall back and may have to try more than one time, but can get up without help.
- ☐ 4 = Unable to arise without help.

28. Posture:

- ☐ 0 = Normal erect.
- ☐ 1 = Not quite erect, slightly stooped posture; could be normal for older person.
- ☐ 2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
- ☐ 3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
- ☐ 4 = Marked flexion with extreme abnormality of posture.

29. Gait:

- ☐ 0 = Normal.
- ☐ 1 = Walks slowly, may shuffle with short steps; but no festination or propulsion.
- ☐ 2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
- ☐ 3 = Severe disturbance of gait, requiring assistance.
- ☐ 4 = Cannot walk at all, even with assistance.

30. Postural stability (Response to sudden posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.):

- ☐ 0 = Normal.
- ☐ 1 = Retropulsion, but recovers unaided.
- ☐ 2 = Absence of postural response; would fall if not caught by examiner.
- ☐ 3 = Very unstable, tends to lose balance spontaneously.
- ☐ 4 = Unable to stand without assistance.

31. Body bradykinesia and hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude and poverty of movement in general.):

- ☐ 0 = None.
- ☐ 1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
- ☐ 2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
- ☐ 3 = Moderate slowness, poverty or small amplitude of movement.
- ☐ 4 = Marked slowness, poverty or small amplitude of movement.

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UPDRS (CONT.) — Pramipexole 00679A – M2730/0010

PATIENT INITIALS (3)	VISIT	INVEST NO	SHEET NO	PATIENT NO	PAGE
	2			1001	18

PART IV. - COMPLICATIONS OF THERAPY* (during the past week).

A. DYSKINESIAS*

RATER'S INITIALS (3): ____

32. Duration: What proportion of the waking day are dyskinesias present? (historical information):
- ☐ 0 = None.
- ☐ 1 = 1–25% of day.
- ☐ 2 = 26–50% of day.
- ☐ 3 = 51–75% of day.
- ☐ 4 = 76–100% of day.

33. Disability: How disabling are dyskinesias? (historical information; may be modified by office examination.):
- ☐ 0 = Not disabling.
- ☐ 1 = Mildly disabling.
- ☐ 2 = Moderately disabling.
- ☐ 3 = Severely disabling.
- ☐ 4 = Completely disabled.

34. Painful dyskinesias: How painful are the dyskinesias?
- ☐ 0 = No painful dyskinesias.
- ☐ 1 = Slight.
- ☐ 2 = Moderate.
- ☐ 3 = Severe.
- ☐ 4 = Marked.

35. Presence of early morning dystonia: (historical information):
- ☐ 0 = No.
- ☐ 1 = Yes.

B. CLINICAL FLUCTUATIONS

36. Are any 'off' periods predictable as to timing after a dose of medication?
- ☐ 0 = No.
- ☐ 1 = Yes.

37. Are any 'off' periods unpredictable as to timing after a dose of medication?
- ☐ 0 = No.
- ☐ 1 = Yes.

38. Do any of the 'off' periods come on suddenly, e.g., over a few seconds?
- ☐ 0 = No.
- ☐ 1 = Yes.

39. What proportion of the waking day is the patient 'off' on average?
- ☐ 0 = None.
- ☐ 1 = 1–25% of day.
- ☐ 2 = 26–50% of day.
- ☐ 3 = 51–75% of day.
- ☐ 4 = 76–100% of day.

C. OTHER COMPLICATIONS*

40. Does the patient have anorexia, nausea, or vomiting?
- ☐ 0 = No.
- ☐ 1 = Yes. If yes, check appropriate box(es) below:

1 ☐ Anorexia 2 ☐ Nausea 3 ☐ Vomiting

41. Does the patient have any sleep disturbances, e.g., insomnia?
- ☐ 0 = No.
- ☐ 1 = Yes. Describe: _____

42. Does the patient have symptomatic orthostasis?
- ☐ 0 = No.
- ☐ 1 = Yes. List symptoms: _____

* The worsening of a patient's disease symptom(s) will be recorded on the Adverse Event Report form only if their frequency has increased and/or severity has worsened since baseline or if, in the opinion of the investigator, they do not represent the patient's usual clinical state prior to study entry.

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Study 1

A. Study Design

This was a multicenter, randomized, double-blind, placebo-controlled parallel group study of pramipexole vs. placebo. Randomization was stratified for concurrent l-deprenyl use. The treatment periods were designed to be at least 6 months in duration.

300 patients were to be entered, 150 per treatment group. A total of 24 centers in the U.S. and Canada were planned with up to 30 patients per center.

Inclusion criteria were:

1. Patients with early, symptomatic, idiopathic Parkinson's disease, Hoehn and Yahr Scale scores of I-III, age 25 years and older. Patients could not be taking L-dopa currently.

Exclusion criteria were:

1. Previous treatment with L-dopa for more than 180 days (6 months) and/or within 60 days of Visit 2.

2. Previous treatment with amantadine within 21 days of Visit 2.

3. Previous treatment with direct-acting dopamine receptor agonists.

4. Atypical parkinsonian syndromes, to include drug-induced parkinsonian syndromes.

5. Dementia or active psychosis.

6. Second or third degree AV block or sick sinus syndrome; resting heart rate below 50; CHF Class III or IV; MI within 6 months; other clinically significant heart conditions.

7. Occurrence of a seizure within 2 years.

8. Renal or hepatic impairment. Neoplastic disease.

9. Surgery within 6 months which the investigator believes could impact patient's participation.

10. History of stereotactic brain surgery.

11. SBP less than 100 or a symptomatic drop in SBP of 20 or greater upon standing.

12. Neuroleptics within 60 days; alpha-methyl dopa within 60 days; metoclopramide within 60 days; flunarizine, cinnarizine, parenteral ergots, MAO inhibitors other than deprenyl, methylphenidate, amphetamine, beta blockers if used to treat tremor, or reserpine within 30 days.

13. Adequate contraception and a negative pregnancy test for all women of childbearing potential.

14. Electroconvulsive therapy within 90 days.

Note that the Inclusion/Exclusion criteria do not specifically address the issue of prior or current use of anticholinergic drugs, but the protocol (p11) states that patients may be treated with one concurrent anticholinergic medication at a fixed daily dose.

The schedule of time and events is attached. Patients were seen for a single **screening visit** within 2 weeks of randomization. At the next visit, if they continued to meet the inclusion/exclusion criteria, patients were **randomized** to receive the first dose of study medication. An **ascending-dose phase** followed and could last as long as 7 weeks. If patients experienced dose-limiting toxicity prior to reaching the maximal dose, they entered the **maintenance phase** at that point (prior to 7 weeks). A patient who moved into the maintenance phase after only 1 or 2 weeks of the ascending-dose phase was considered to have missing data for the additional 5-6 weeks of the ascending-dose phase, resuming entries with visit 9. The maintenance phase was 6 months in duration and was followed by a 1 week **dose reduction phase.**

PRAMIPEXOLE PHASE III TRIAL IN EARLY PARKINSON'S DISEASE
PROTOCOL SUMMARY - PART I (Double-Blind, Placebo-Controlled)

	S	Ascending-Dose Interval[1]							Maintenance-Dose Interval[2]									
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18[5]
Days since the last visit		1-14	5-9	5-9	5-9	5-9	5-9	5-9	5-9	10-16	10-16	10-16	10-16	10-16	10-16	25-35	26-35	25-35
Dose Level		1	2	3	4	5	6	7	M[3]	M	M	M	M	M	M	M	M	M
History	x																	
Physical Examination[4]	x																	
Laboratory Tests[4]	x				x				x				x			x		x
Chest X-ray	x																	
12-Lead ECG[4]	x				x				x				x			x		x
Disability Ratings[3,4]	x	x	x	x	x	x	x	x	x		x		x		x	x		x
Adverse Events[4] and Concomitant Meds[4]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization to Treatment		x																
Dispense Study Medication		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs[4]	x	x	x	x	x	x	x	x	x		x		x		x	x		x
Medication Compliance			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

1. Duration of the ascending-dose interval varies depending upon the optimal daily dose of study medication that is achieved. The optimal daily dose is defined as the tolerated dose of study medication associated with stable improvement (i.e. lack of further improvement despite up to two additional dose increases). The degree of improvement is based upon the clinical judgement of the investigator without examination of previous scores on various rating scales used in the trial.
2. Maintenance dose (M) is either the maximally tolerated dose or the optimal dose if adverse events do not prevent dose escalation during the ascending dose interval.
3. UPDRS Part II (activities of daily living) and Part III (motor examination) start at Visit 2. The motor examination is to be done 2 to 3 hours after study medication is administered except for Visit 2 (done prior to the dose of study medication administered in the clinic). Modified Hoehn and Yahr Scale at Visit 1 only.
4. Vital signs (supine and 1 minute standing blood pressure and pulse rate) are taken at Visit 1 in triplicate per protocol, prior to study medication at Visit 2 only and at 2 hours post-dose of study medication at all Visits beyond Visit 1 as noted above.
5. Dose-reduction interval starts with Visit 18 and ends at Visit 19, the final visit in Part 1. See Protocol Summary Part II for specific procedures to be completed for Visit 19.

* Required for patients who drop from the trial

S = Screening

The ascending dose schedule is attached. Study medication was to be taken 1 hour before or 2 hours after meals. There were 7 possible fixed dose regimens, ranging from a total daily dose of 0.375 mg to 4.5 mg. The dose was to be raised until dose-limiting toxicity was reached, the maximum dose was reached, or there was a lack of further clinical improvement in the judgment of the investigator despite up to two additional increases in the dose of study medication.

The protocol does not have instructions for dose adjustments of study medications if patients developed AEs during the maintenance phase. That is, if a patient developed nausea during the maintenance phase, it is not clear if the dose of study drug could be lowered.

The protocol **does state** (p16) that patients receiving anticholinergic medication should not have dose adjustments. Patients on l-deprenyl were allowed to have dose adjustments.

Patient visits occurred every week during the ascending dose phase. Patient visits occurred every 2 weeks for the first 3 months of the maintenance phase and every month for the last 3 months of the maintenance phase.

Monthly, during the maintenance phase, the investigator completed Parts II (activities of daily living) and III (motor exam) of the UPDRS.

Note that during the ascending-dose phase, patients assigned to the pramipexole group received both pramipexole and placebo tablets; patients assigned to the placebo group were not exposed to pramipexole.

Two primary outcome variables were stated in the protocol: Part II of the UPDRS (ADL) and Part III of the UPDRS (motor exam).

The analysis plan stated that "the primary efficacy endpoint for each of these parts of the UPDRS is the change in the score between baseline and maintenance where the maintenance score is the last available score prior to the dose-reduction interval." The primary analysis plan was not clearly specified in the protocol. In order for the study to be declared positive, both primary endpoints had to achieve statistical significance. The ITT population was to be the primary analysis population with an LOCF technique employed for missing data.

Pramipexole Ascending-Dose Schedule

Week	Dose Level	Dosage (mg)	Total Daily Dose (mg)
1	1	3 x 0.125	0.375
2	2	3 x 0.25	0.75
3	3	3 x 0.5	1.50
4	4	3 x 0.75	2.25
5	5	3 x 1.0	3.00
6	6	3 x 1.25	3.75
7	7	3 x 1.5	4.50

A stated secondary endpoint for the study was time-to-failure where failure was defined as requiring treatment with L-dopa.

Subset analyses were also planned based on concomitant use of l-deprenyl and anticholinergic medications.

The sample size was computed using results in the DATATOP study. It was estimated that with 150 patients per treatment group, the study would have 90% power to detect small differences on the order of 2-4 points in change from baseline in Part III of the UPDRS (motor exam).

B. Subject Disposition and Baseline Comparison

The planned enrollment was 300.

335 patients were randomized: 164 pramipexole and 171 placebo. The investigators and centers are listed at the end of this Study 1 review.

Baseline Characteristics: No significant differences in the two treatment groups were detected at baseline in demographics or disease characteristics.

	Placebo N=171	Pramipexole N=164
Age	62 (30-85)	63 (33-85)
Sex	98M/73F	105M/59F
Race	94% White	95% White
Parkinson's Duration	1.7 yrs (0-7.2)	2 yrs (0-11.6)
Deprenyl Use	66%	68%
Anticholinergic Use	14%	12%
Part II Score	8 (1-22)	8 (1-20)
Part III Score	18.7 (3-53)	18.8 (1-63)
Hoehn & Yahr	1.9 (1-3)	1.9 (1-3)

Patient Flow: Only 2 patients (1 in each treatment group) did not meet the ITT definition, i.e. they did not have at least one efficacy assessment. Therefore, 333 patients are included in the efficacy analysis: 163 pramipexole and 170 placebo.

The following table outlines the withdrawals during the study.

Withdrawals

	Pramipexole	Placebo
Ascending Dose Phase	12	10
Maintenance Phase	16	24
TOTAL	28	34
	62	

The reasons for withdrawals are shown in the next table.

Patient Disposition

	Pramipexole	Placebo
Disease Worsening	4	15
Worsening of Pre-existing Disease	0	1
Other AEs	18	8
Poor Therapeutic Resp.	1	7
Protocol Violation	1	0
Lost to Follow-Up	2	0
Withdrew Consent	2	2
Other	0	1

136/164 pramipexole patients completed the trial. 137/171 placebo patients completed the trial.

C. Efficacy Evaluation

All the analyses below are LOCF analyses, unless specifically described otherwise.

There were 2 patients who received drug but did not have any post-baseline efficacy measurements (1 patient per treatment group). Thus, 333 patients (163 pramipexole, 170 placebo) comprise the ITT population.

1. UPDRS Part II

Sponsor's Table 5 on the next page shows the average Part II scores by visit for the two treatment groups. The sponsor provided cumulative distribution functions for the treatment groups and these are shown on the page after that.

The protocol specified analysis was a comparison between treatment groups of change from baseline to final maintenance visit (LOCF), adjusted by center and center-by-treatment interaction. The results of this analysis were highly statistically significant.

	LOCF Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (Visits 11-18)
Pramipexole	-1.9	-57
Placebo	0.4	-5
p-value	$\leq$ 0.0001	$\leq$ 0.0001

Table 5. Adjusted[a] Mean Change from Baseline in UPDRS Part II Total Score[b], Maintenance Interval
Intent-to-Treat – All Patients, LOCF

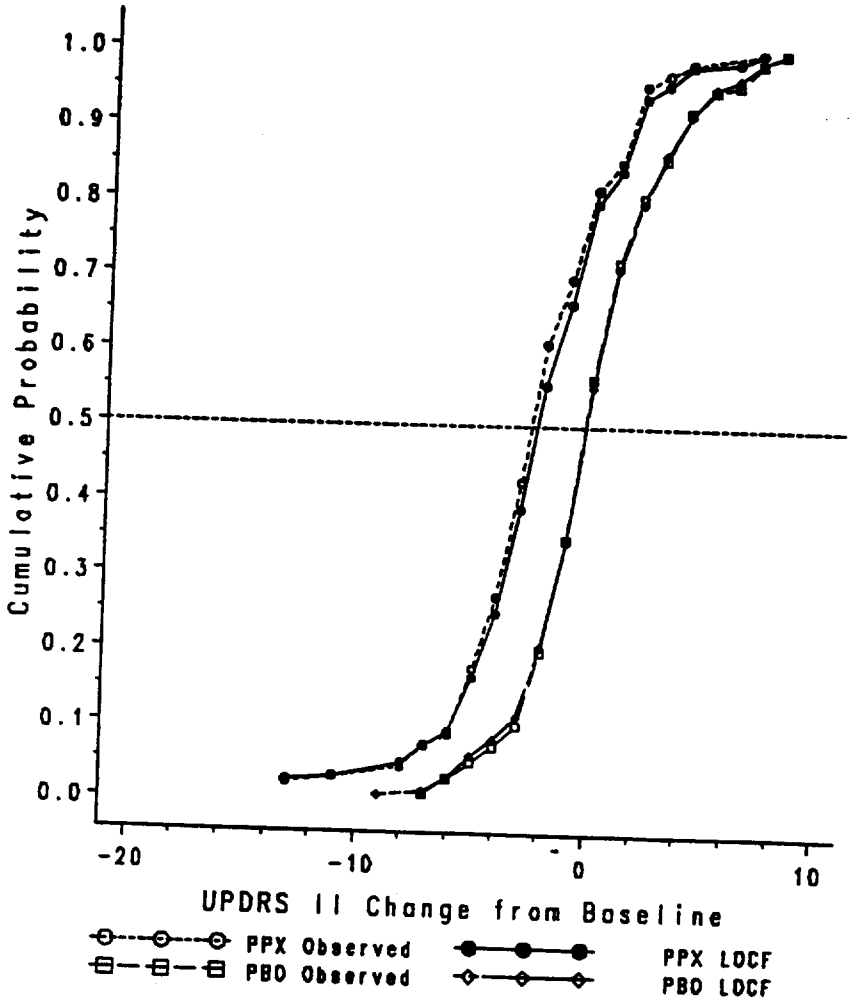
Treatment Group	Baseline[c]	Maintenance Week					
		0[d]	4	8	12	16	24
PPX (N=163)	8.2	-2.5	-2.5	-2.4	-2.3	-2.4	-1.9
PBO (N=170)	8.3	-0.9	-0.7	-0.4	-0.2	0	0.4
P-Value	–	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001

Source: Appendix C: Table 9.2.

a Adjusted by investigator and investigator-by-treatment interaction.
b Sum of 13 components of UPDRS Part II.
c Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.
d Week 0 is the endpoint of the ascending-dose interval.

Figure 1

Ogive Curve of UPDRS II Change from Baseline -- M/2730/0001



2. UPDRS Part III

Sponsor's Table 6 (next page) shows the average Part III scores by visit for the two treatment groups. Cumulative distribution functions are shown on the page after that.

The protocol specified analysis was a comparison between treatment groups of change from baseline to final maintenance visit (LOCF), adjusted by center and center-by-treatment interaction. The results of this analysis were highly statistically significant.

	LOCF Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (Visits 11-18)
Pramipexole	-5	-127
Placebo	0.8	-11
p-value	$\leq$0.0001	$\leq$0.0001

3. Modified Hoehn and Yahr Scale

Sponsor's Table 12 (next page) shows the average scores at the beginning and end of the maintenance period for the two treatment groups.

The sponsor also classified patients as: 1) improved, 2) no change, or 3) worsening. The breakdown of patients according to these classifications is presented in Sponsor's Table 13 (next page).

D. Plasma Levels

1. Plasma pramipexole levels were collected in order to assess mean population PK parameters and their variance in this population. The results of this analysis are not in the study report.

2. Plasma levels of concomitant deprenyl and anticholinergics were not measured during the conduct of this trial.

Table 6. Adjusted[a] Mean Change from Baseline in UPDRS Part III Total Score[b], Maintenance Interval
Intent-to-Treat – All Patients, LOCF

Treatment Group	Baseline[c]	Maintenance Week					
		0[d]	4	8	12	16	24
PPX (N=162)	18.8	-6	-5.4	-5.2	-5.2	-5.1	-5
PBO (N=168)	18.8	-2.6	-2.3	-1.6	-0.9	0.4	0.8
P-Value	–	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001

Source: Appendix C: Table 10.2.

a Adjusted by investigator and investigator-by-treatment interaction.
b Sum of 14 components of UPDRS Part III.
c Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.
d Week 0 is the endpoint of the ascending-dose interval.

Table 12. Summary of the Mean Modified Hoehn and Yahr Scale Classification for All Patients

Mean ± SE	Baseline[a]	Maintenance Week	
		0[b]	24[c]
PPX (N=163)	1.92 ± 0.044	1.77 ± 0.049	1.82 ± 0.052
PBO (N=171)	1.89 ± 0.048	1.83 ± 0.047	1.94 ± 0.05

Source: Appendix C: Table 18A.

a Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.
b Week 0 is the endpoint of the ascending-dose interval.
c Last maintenance-dose visit, prior to dose reduction.

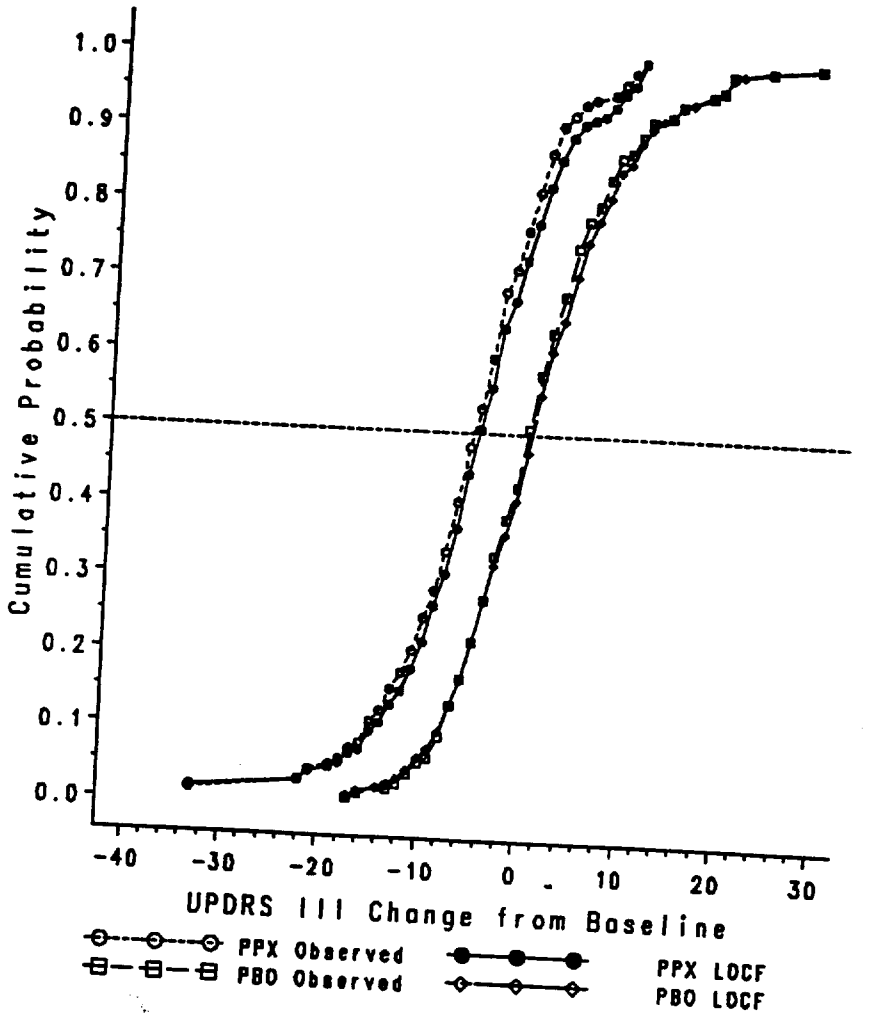
Table 13. Summary of the Change in Modified Hoehn and Yahr Classification from Baseline to Last Maintenance Visit All Patients

Classification Change Based on Modified Hoehn and Yahr Scale	Number (%) of Patients	
	PPX N=161	PBO N=170
Improvement	44 (27.2)	28 (16.5)
No Change	90 (55.6)	102 (60)
Worsening of Classification	27 (16.7)	40 (23.5)

Source: Appendix C: Tables 18A, 19.1A and 19.2A.

Figure 2

Ogive Curve of UPDRS III Change from Baseline -- M/2730/0001



E. Subgroup Analyses by Deprenyl and Anticholinergic Use

Sponsor's Table 7 demonstrates that only slight differences in the mean change from baseline for Parts II and III of the UPDRS exist between patients on and off deprenyl. Likewise, only slight differences in these scores exist between patients on and off anticholinergics.

F. Subgroup Analyses by Age, Sex, and Race

Only slight differences in the mean change from baseline for Parts II and III of the UPDRS were shown between male and female patients.

Only 17 patients were non-white so that a subgroup analysis by race is not meaningful.

Only slight differences in the mean change from baseline for Parts II and III of the UPDRS were shown between patients $\geq$ 65 and < 65 years.

Sponsor's Table 8 demonstrates the results of these analyses.

G. Adverse Events

Sponsor's Table 17 shows the AEs with an incidence of 10% or greater in the pramipexole group. Of these, nausea, constipation, asthenia, dizziness, insomnia, somnolence, and hallucinations showed the largest differences between the treatment groups.

There was a single death during the study, a pramipexole patient who had a myocardial infarction and died.

There were 10 pramipexole patients and 12 placebo patients with serious AEs. Most of these were malignancies or cardiac-related. No obvious differences between the treatment groups emerged.

Table 7. Mean Change From Baseline in UPDRS Parts II and III, Total Score by L-deprenyl and Anti-cholinergic Usage; All Patients

Concomitant Therapy	Treatment Group	Part II[a]				Part III[b]			
		N	Yes	N	No	N	Yes	N	No
l-deprenyl	PPX	112	-1.9	51	-1.5	111	-4.6	51	-4.6
	PBO	112	0.3	58	0.7	112	1.3	57	1.5
Anticholinergic	PPX	19	-1.3	144	-1.9	19	-4.5	143	-4.6
	PBO	24	0.1	146	0.4	24	1.4	145	1.4

Source: Appendix C: Tables 11.1A & 12.1A.

[a] Sum of 13 components of UPDRS Part II.

[b] Sum of 14 components of UPDRS Part III.

Table 8. Mean Change From Baseline in UPDRS Parts II & III, Total Score by Sex, Age, and Race All Patients

Treatment Group		N	Part II[a]	N	Part III[b]
Age					
<65	PPX	75	-2.0	74	-5.4
	PBO	86	0.1	85	0.6
≥65	PPX	88	-1.6	88	-4.0
	PBO	84	0.7	84	2.2
Sex					
Male	PPX	104	-1.8	103	-5.2
	PBO	97	0.4	97	1.3
Female	PPX	59	-1.9	59	-3.6
	PBO	73	0.3	72	1.4
Race					
White	PPX	156	-1.8	155	-4.7
	PBO	160	0.4	159	1.1
Black	PPX	2	0.5	2	3.5
	PBO	4	-0.8	4	2.0
Other	PPX	5	-2.4	5	-6.0
	PBO	6	1.5	6	7.7

Source: Appendix C: Tables 11.2A and 12.2A.

[a] Sum of 13 components of UPDRS Part II.

[b] Sum of 14 components of UPDRS Part III.

Table 17. Number (%) of Patients With Adverse Events (TES/Reported in ≥10% of the Patients in the Pramipexole Group) by Body System and Adverse Event Regardless of Relationship to Study Medication

Body System Event[a]	Treatment Group[b]	
	PPX (N=164)	PBO (N=171)
	No. Pts (%)	No. Pts (%)
Body as a Whole		
Infection	44 (26.83)	45 (26.32)
Pain	33 (20.12)	35 (20.47)
Asthenia	31 (18.90)	19 (11.11)
Headache	27 (16.46)	31 (18.13)
Pain back	22 (13.41)	17 (9.94)
Injury accident	21 (12.80)	18 (10.53)
Digestive System		
Nausea	64 (39.02)	35 (20.47)
Constipation	29 (17.68)	11 (6.43)
Dyspepsia	18 (10.98)	12 (7.02)
Nervous System		
Dizziness	57 (34.76)	45 (26.32)
Insomnia	42 (25.61)	22 (12.87)
Somnolence	30 (18.29)	15 (8.77)
Tremor	20 (12.20)	34 (19.88)
Hallucinations	18 (10.98)	5 (2.92)

Source: Appendix C: Table 21.1.

[a] COSTART coding system using preferred term.

[b] Number of patients in each treatment group is the number randomized who received at least one dose of study drug.

H. Conclusions

Pramipexole-treated patients, on average, saw a larger change-from-baseline on Part II of the UPDRS than their counterparts treated with placebo. This difference in average change-from-baseline was small, but highly statistically significant.

Pramipexole-treated patients, on average, also saw a larger change-from-baseline on Part III of the UPDRS than their counterparts treated with placebo. This difference in average change-from-baseline was again small, but highly statistically significant.

The protocol called for a statistically significant result on each of these outcome measures (a dual outcome) in order for a positive result to be declared for the trial as a whole.

The sponsor has shown that the effect was present whether or not concomitant deprenyl and anticholinergic medication were used.

The sponsor has also shown that age (above or below 65 years) and sex do not influence response greatly.

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Protocol M/2730/0001	
Investigator Name and Address	Number of Patients Randomized at Site
Aminoff, Michael J, M.D. Department of Neurology, Rm. M348 University of California San Francisco San Francisco, CA 94143-0216	7
Bennett, James P, Jr., M.D., Ph.D. Fontaine Research Park Neurology Suite 370 500 Ray C. Hunt Drive Charlottesville, VA 22903	13
Burch, Gordon, M.D. Roanoke Neurological Associates 2601 Franklin Road, S.W., Suite B Roanoke, VA 24014-1049	14
Factor, Stewart A., D.O. Professor of Neurology Department of Neurology (A70) Albany Medical Center New Scotland Avenue Albany, NY 12208	14
Farmer, Stephen, D.O. Grayline Clinical Drug Trials 706 Denver Street Wichita Falls, TX 76301	8
Fazzini, Enrico, D.O., Ph.D. 530 First Avenue 9th Floor, Suite 9Q New York, NY 10016	9
Friedman, Joseph, M.D. Department of Neurology Roger Williams General Hospital 50 Maude Street, 4th Floor Providence, RI 02908	15
Golbe, Lawrence I., M.D. UMDNJ Robert Wood Johnson Medical School Dept. of Neurology, 4th Floor 1 Robert Wood Johnson Plaza, CN-19 New Brunswick, NJ 08903-0019	17

Protocol M/2730/0001	
Investigator Name and Address	Number of Patients Randomized at Site
Hill, Thomas, M.D. Center for Clinical Research 911 West 38th Street, Suite 301 Austin, TX 78705	11
Hiner, Bradley, M.D. Marshfield Clinic 1000 North Oak Avenue Marshfield, WI 54449-5777	17
Hoehn, Margaret M., M.D. 3535 Cherry Creek North Drive, #303 Denver, CO 80209	8
Hubble, Jean, M.D. Department of Neurology Kansas University Medical Center 39th and Rainbow Blvd. Kansas City, KS 66103	13
Karp, Jeffrey, M.D. Mease Clinic 3253 McMullen Booth Road, Suite 200 Clearwater, FL 34621-2010	10
Kurth, Matthias, M.D. St. Joseph Hospital Barrow Neurological Institute 222 W. Thomas Road, Suite 401 Phoenix, AZ 85013	25
LeWitt, Peter, M.D. Professional Village Clinical Neuroscience Center 5821 West Maple Road, Suite 192 West Bloomfield, MI 48322	14
Nathan, Denis, M.D. Neurological Consultants, S.C. 2002 W. Howard Avenue Milwaukee, WI 53221	11

Protocol M/2730/0001	
Investigator Name and Address	**Number of Patients Randomized at Site**
Olanow, C. Warren, M.D. (1/19/93 - 6/12/94) Hauser, Robert A., M.D. (6/13/94 - Present) Assistant Professor of Neurology Department of Neurology Harbour Side Medical Tower 4 Columbia Drive, Suite 410 Tampa, FL 33606	15
Paulson, George, M.D. Chairman, Department of Neurology 452 Means Hall Ohio State Univ. School of Medicine 1655 Upham Drive Columbus, OH 43210	9
Richter, Ralph W., M.D. St. John's Doctor's Bldg. 1705 E. 19th Street, Suite 406 Tulsa, OK 74104	6
Shannon, Kathleen, M.D. Dept. of Neurological Sciences Rush Medical Center Rush Presbyterian St. Luke's Medical Center 1725 West Harrison, Suite 1106 Chicago, IL 60612	13
Siemers, Eric, M.D. Univ. of Indiana School of Medicine Dept. of Neurology, RG6 Regen Strief Health Center 1050 Walnut, 6th Floor Indianapolis, IN 46202	14
Tetrud, James, M.D. Parkinson's Institute 1170 Morse Avenue Sunnyvale, CA 94089-1605	14

Protocol M/2730/0001	
Investigator Name and Address	**Number of Patients Randomized at Site**
Truong, Daniel R., M.D. Parkinson & Movement Disorders University of California, Irvine College of Medicine Department of Neurology 154 Med. Surge I Irvine, CA 92717	14
Tuchman, Michael M., M.D. Palm Beach Neurological Group 3365 Burns Road - Suite 206 Palm Beach Gardens, FL 33410	17
Watts, Ray L., M.D. Emory University School of Medicine 6000 Woodruff Memorial Bldg. P.O. Drawer V Atlanta, GA 30322	15
Weiner, William, M.D. 1501 N.w. 9th Avenue Parkinson Bldg. Department o Neurology Miami, FL 33136	12

Study 4

A. Study Design

This was a multicenter, randomized, double-blind, placebo-controlled parallel group study of 4 different fixed doses of pramipexole and placebo. Randomization was stratified for l-deprenyl use.

The treatment periods incorporated an ascending dose period (as long as 6 weeks) followed by a fixed-dose maintenance period of 4 weeks (and a 1-week dose-reduction period).

250 patients were to be entered, 50 per treatment group. A total of 20 centers in the U.S. and Canada were planned with at least 10 patients per center.

The study was conducted by the Parkinson Study Group (Rochester, N.Y.). After the study was complete, data sets were provided to the Upjohn Company by the Parkinson Study Group.

Inclusion criteria were:

Patients with idiopathic Parkinson's disease of less than 7 years duration, Hoehn and Yahr Scale scores of I-III, age 30 years and older. Patients could not have taken L-dopa within the past 3 months.

Deprenyl, anticholinergics, or amantadine therapy at a stable dose for 30 days prior to the study and throughout the study were allowed.

Exclusion criteria were:

1. L-dopa or dopamine agonist medication in previous 3 months.

2. Atypical parkinsonian syndromes, to include drug-induced parkinsonian syndromes.

3. Dementia or active psychosis.

4. Third degree AV block or sick sinus syndrome; CHF Class III or IV; MI

within 6 months.

5. Occurrence of a seizure within 1 year.

6. Renal or hepatic impairment. Neoplastic disease.

7. Symptomatic orthostatic hypotension at screening.

8. History of stereotactic brain surgery.

14. Electroconvulsive therapy within 90 days.

The schedule of time and events is on the next page. Patients were seen for a single **screening visit** within 2 weeks of randomization. At the next visit, if they continued to meet the inclusion/exclusion criteria, patients were **randomized** to receive the first dose of study medication. An **ascending-dose phase** followed and could last as long as 6 weeks. If patients experienced dose-limiting toxicity prior to reaching their target dose, they could be lowered to the previous dose level. The protocol allowed patients to be lowered only 1 or 2 dose levels. Once lowered to a given level, patients were not to be re-challenged at the higher dose level.

The **maintenance phase** was to last 1 month or 4 weeks. This was followed by a 1 week **dose reduction phase.**

The ascending dose schedule is on the next page. Study medication was to be taken 1 hour before or 2 hours after meals.

The protocol states that concomitant deprenyl, amantadine, or anticholinergics could be used, but at a "stable dosage." This implies that changes in dosage of these drugs during the trial would not be allowed.

Patients were seen every 2 weeks during dose-escalation and during maintenance, for a total of 5 scheduled visits post-randomization. At each visit, the following were performed:

1. UPDRS, Parts I-III
2. Supine and standing BP and pulse
3. Adverse events

APPENDIX E
SCHEDULE OF ACTIVITIES

	Visit Name		Escalation			Maintenance		Taper
	Screen (14 days)	Baseline (Day 0)	Day 14 (week 2)	Day 28 (week 4)	Day 42 (week 6)	Day 56 (week 8)	Day 70 (week 10)	Day 77 (week 11)
Visit #	1	2	3	4	5	6	7	8
Med/Neuro History	x							
Physical Exam	x							
12-lead EKG	x						x	
Hoehn/Yahr	x	x					x	
Safety Labs	x				x		x	x*
UPDRS I-III		x	x	x	x	x	x	x
Vital Signs		x	x	x	x	x	x	x
NIM's	x	x	x	x	x	x	x	x
Adverse Events		x	x	x	x	x	x	x
Pharmacokinetics					x		x	
QOL		x					x	
Drug Dispensing		x	x	x	x	x	x	
Compliance Check			x	x	x	x	x	x

*repeat Day 70 abnormal labs

Escalating Pramipexole Dose Schedule

Dose Group	Pramipexole dose - mg/day					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Placebo	pbo	pbo	pbo	pbo	pbo	pbo
1.5 mg/day	pbo	pbo	pbo	0.375	0.75	1.5
3.0 mg/day	pbo	pbo	0.375	0.75	1.5	3.0
4.5 mg/day	pbo	0.375	0.75	1.5	3.0	4.5
6.0 mg/day	0.375	0.75	1.5	3.0	4.5	6.0

4. Concomitant therapy
5. Safety labs
6. PK blood sample
7. Medication compliance (tablet counts)

At the last visit, the Hoehn and Yahr scale, QOL assessment, and an EKG were additionally performed. The QOL assessments were 1) Functional Status Questionnaire (FSQ) with supplemental questions about employment and 2) EuroQol.

The **FSQ** contains 37 questions. It is designed to be self-administered by the subject in about 10 minutes. The questions are then divided into 6 domains:

- o basic ADLs
- o intermediate ADLs
- o social activities
- o mental health
- o quality of interaction
- o work performance

All questions use the previous month as reference (although it was completed at baseline and at end of maintenance--a 2-month timespan). Responses range roughly from 0-6, with some variation. Higher numbers represented better health. Scores within a domain are added and converted to percent of maximal possible.

There were also several additional questions regarding work (normal work hours, work time lost, or employment changes due to disease), which were analyzed separately.

The **EuroQol** contains 6 health-related questions and an analog scale on which patient rate their health state on a scale from 0-100, where 100 is the best possible health state.

The actual QOL scales are provided at the end of this Study 4 review. The protocol states, "For testing of treatment effects, the principal measures will be changes in the FSQ domain scores, the EuroQol utility score [= analog score], and time lost from work in the previous month."

The primary outcome variable was the change from baseline to end-of-maintenance of the sum of Parts I-III of the UPDRS.

The analysis plan stated that both linear and nonlinear regression models would be considered. "For analyzing efficacy and safety variables, there will be two analyses, one in which the independent variable will be the dose assigned by randomization, and a second analysis in which the actual dose received will be used rather than the dose level to which the subject was randomized."

Subset analyses were not specifically planned based on concomitant use of l-deprenyl, amantadine, and anticholinergic medications.

The sample size was computed using tolerability data from a previous pramipexole trial in which 30% of patients in the 4.5 mg/day group could not tolerate the target dose, while 4% of patients in the placebo group could not tolerate the target dose. With 50 patients per group in the current study, the study was powered to detect a similar difference.

The study was also powered at 0.97 to declare that a dose-response slope of 1.81 was different from zero. The smallest slope that could be detected with a power of at least 0.80 was 1.25.

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B. Subject Disposition and Baseline Comparison

The planned enrollment was 250.

264 patients were randomized as below. The investigators and centers are listed at the end of this Study 4 review.

Baseline Characteristics: No significant differences in the two treatment groups were detected at baseline in demographics or disease characteristics as shown on the next page.

In addition the data on concomitant deprenyl use, amantidine use varied between 13 and 18% for the different treatment groups. Anticholinergic use (benzatropine or trihexyphenidyl) varied between 10 and 20%.

Patient Flow: The reasons for withdrawals are shown on the next page. Most of the discontinuations occurred during the ascending dose interval (19 of 26).

SELECTED DEMOGRAPHIC AND BASELINE FACTORS

Parameter	Pramipexole - assigned dose				Placebo n=51	P value
	1.5 mg/day n=54	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55		
age (mean years)	60.2	62.2	62.7	62.8	60.4	0.67
sex (% male)	64.8	62.0	63.0	69.1	62.8	0.90
race (% caucasian)	96.3	98.0	96.3	98.2	96.1	0.58
duration of disease (mean years)	1.8	2.0	1.9	2.3	1.6	0.16
current selegiline use (% yes)	55.6	66.0	66.7	58.2	58.8	0.65
UPDRS total score (mean points)	29.0	28.3	27.3	32.9	28.7	0.08
Hoehn and Yahr score (mean points)	1.8	1.9	1.8	1.9	1.8	0.52

REASONS FOR STUDY DRUG DISCONTINUATION - NUMBER PATIENTS

Reason	Pramipexole - assigned dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
worsening PD	2	0	0	0	0
worsening other disease	1	0	0	0	0
other adverse event	7	0	4	8	0
administrative*	0	2	0	1	1
Total	10	2	4	9	1

PATIENT DISPOSTION AND TOLERABILITY - NUMBER PATIENTS (%)

Endpoint	Pramipexole - assigned dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
Number randomized	54	50	54	55	51
number (%) completing ascending dose	47 (87.0)	48 (96.0)	52 (96.3)	47 (85.5)	51 (100.0)
number (%) completing msintensance	44 (81.5)	48 (96.0)	50 (92.6)	46 (83.6)	50 (98.0)
number (%) completing at assigned dose - tolerability	44 (81.5)	46 (92.0)	43 (79.6)	37 (67.3)	49 (96.1)
number (%) completing with one or no dose reductions	44 (81.5)	48 (96.0)	50 (92.6)	44 (80.0)	50 (98.0)
number (%) dose limited during ascending dose interval due to clinical intolerance	2 (3.7)	3 (6.0)	7 (13.0)	10 (18.2)	1 (2.0)

C. Efficacy Evaluation

Only one patient was not included in the ITT analysis. This patient did not have any post-baseline efficacy assessments.

1. UPDRS Total Score Change From Baseline

The first table on the next page shows the change from baseline in total score for each of the dose groups **as assigned by the randomization scheme.** All groups had significant improvements compared to placebo, but no dose response relationship was apparent.

The second table on the next page shows the same change from baseline data for each of the dose groups, **but the dose groups are determined by actual dose received.** Again, all groups had significant improvements compared to placebo, but no dose response relationship was apparent.

Regression analysis (the primary analysis plan stated in the protocol) showed that the coefficient of the linear term was statistically significantly different from zero and the coefficient of the quadratic term was marginally significant from zero for the "assigned group" analysis. Both coefficients were statistically significantly different from zero for the "actual dose received" analysis. The presence of the quadratic term indicates a lack of a linear dose response relationship for both "assigned group" and "actual dose group" analyses. The third table on the next page summarizes these results.

UPDRS TOTAL SCORE CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	28.5	28.3	27.3	32.9	28.7
mean change*	-6.1	-5.8	-6.6	-7.1	-1.2
pairwise p value vs placebo	0.0027	0.0057	0.0008	0.0003	–
overall p value	0.0022	–	–	–	–

UPDRS TOTAL SCORE CHANGE FROM BASELINE

Parameter	Pramipexole - Actual Dose				Placebo n=60
	1.5 mg/day n=57	3.0 mg/day n=53	4.5 mg/day n=50	6.0 mg/day n=43	
baseline	28.7	28.9	27.0	32.6	29.2
mean change*	-6.5	-5.7	-7.7	-7.5	-0.4
pairwise p value vs placebo	0.0001	0.0005	0.0001	0.0001	–
overall p value	0.0001	–	–	–	–

UPDRS TOTAL SCORE REGRESSION ANALYSIS

Analysis	n	Linear Parameter Estimate	p value	Quadratic parameter estimate	p value
assigned dose group	263	-2.412	0.0296	0.252	0.0537
actual dose received	263	-2.974	0.0054	0.361	0.0056

2. Subgroup Analyses

No qualitative interactions were present for pramipexole effects for subgroups of concomitant **selegiline** therapy. The sponsor's analysis of pramipexole effect by **anticholinergic** therapy is flawed because (as acknowledged by the sponsor on page 331 of the Integrated Summary of Efficacy) deprenyl was inadvertently classified as an anticholinergic agent. No analysis of pramipexole effect by **amantadine** use is presented.

Also, no qualitative interactions were present for pramipexole effects for subgroups based on age (<65 years vs. ≥65 years), sex, race (caucasian vs noncaucasian) , or baseline Hoehn-Yahr score. Since very few patients were noncaucasian, no meaningful comparison of responses by race can be made.

3. Secondary Efficacy Variables

UPDRS Part I scores were low at baseline and therefore did not contribute much to the change in total UPDRS.

UPDRS Parts II and III scores each showed a similar pattern of change as the total UPDRS scores (see next page). Cumulative distribution functions for Parts II and III, separately, are on the following pages.

The Hoehn and Yahr data is also shown on the next page, expressed as mean scores as well as percent change.

UPDRS PART II - CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	8.0	8.0	7.3	8.8	8.2
mean change*	-1.8	-1.9	-1.8	-1.8	-0.3
pairwise p value vs placebo**	N.D.	N.D.	N.D.	N.D.	N.D.
overall p value	0.0613	–	–	–	–

*Adjusted for center and treatment by center interaction
**N.D. - not done since overall p value not significant
Source - Appendix D, Table 11.2A

UPDRS PART III - CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	19.4	19.3	19.2	22.9	19.6
mean change*	-4.2	-3.8	-4.7	-5.1	-0.6
pairwise p value vs placebo	0.0052	0.0151	0.0016	0.0005	–
overall p value	0.0048	–	–	–	–

*Adjusted for center and treatment by center interaction
Source - Appendix D, Table 12.2A

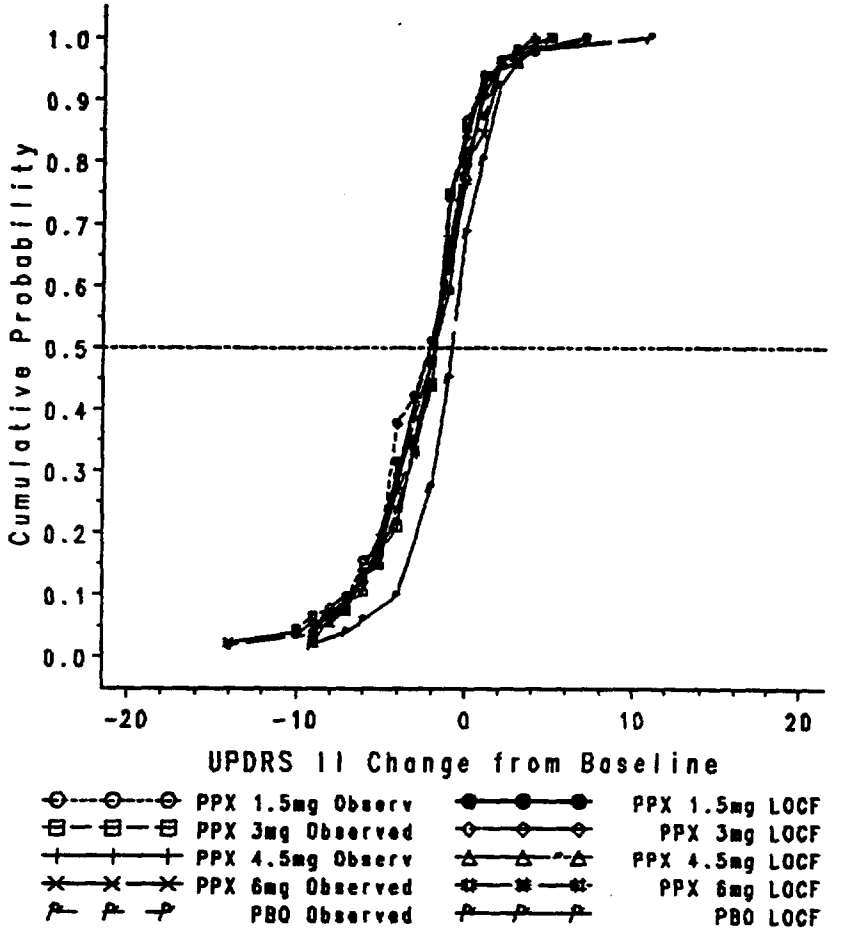
MODIFIED HOEHN AND YAHR SCALE - MEAN SCORES

Item	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
baseline	1.77	1.92	1.81	1.86	1.79
end maintenance	1.74	1.70	1.68	1.74	1.87

MODIFIED HOEHN AND YAHR SCALE - PERCENT CHANGE

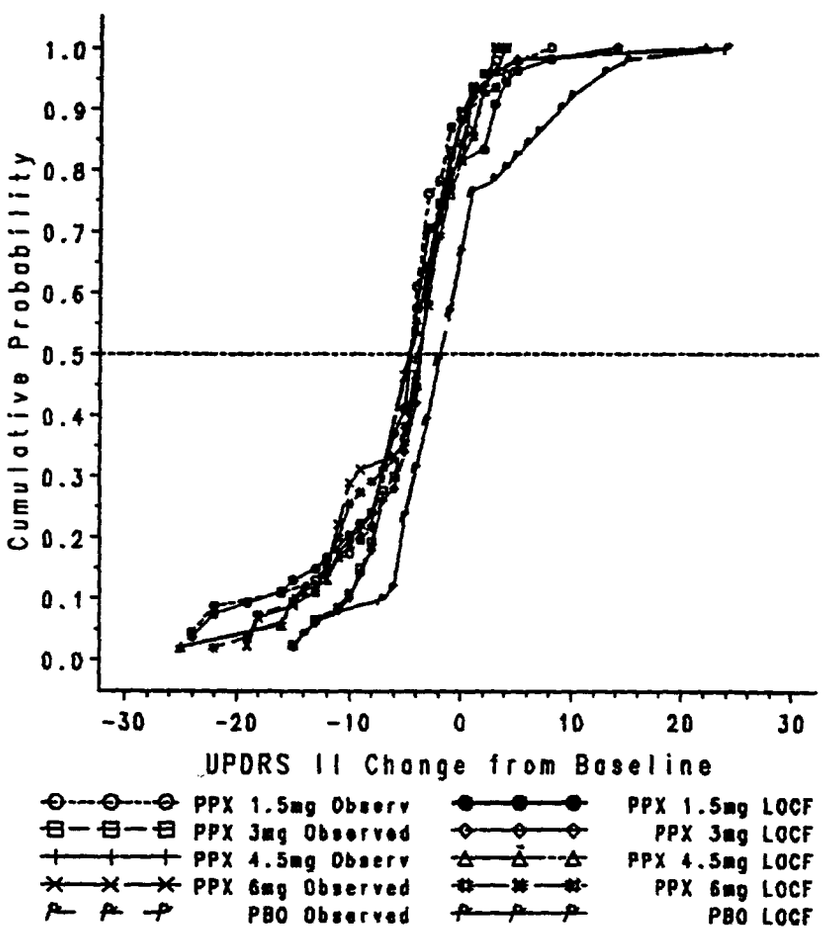
Category	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
improved from baseline (%)	19.2	36.7	25.0	30.2	13.7
worsened from baseline (%)	17.3	6.1	5.8	9.4	25.5

Figure 3
Ogive Curve of UPDRS II Change from Baseline -- M/2730/0004



PBO Observed overlaying PBO LOCF because there was no dropouts in PBO

Figure 4
Ogive Curve of UPDRS III Change from Baseline — M/2730/0004



PBO Observed overlaying PBO LOCF because there was no dropouts in PBO

4. Quality of Life Scales

The sponsor's table on the next page demonstrates mean change from baseline for different scales and components of scales. Responses are present for all but two patients (one in the 1.5 mg group and one in the 4.5 mg group). As a reminder, the scores are all converted to a 0-100 scale with 100 representing a best response. A positive change represents improvement, while a negative change represents worsening.

Note that the overall p-value is significant for only one domain, the FSQ basic ADL. Even for that domain, the magnitude of change is so small, except perhaps for the 1.5 mg/day group, as to be clinically insignificant. The overall p-value for the EuroQol analog scale approached significance (p=0.065), with the 3 mg/day and 4.5 mg/day groups demonstrating the largest differences compared to placebo.

Separately, the sponsor presents correlation coefficients for UPDRS change scores and QOL change scores. They all tended to be low.

MEAN CHANGES FROM BASELINE FOR QOL SCORES

Domain /item	Pramipexole - assigned dose				Placebo	Overall p-value
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day		
FSQ-Basic ADL	4.8**	1.6	2.0*	-0.7	-2.6	0.0255
FSQ-Interm. ADL	1.0	3.7	-1.5	-1.5	-0.1	0.1936
FSQ-Mental Health	1.0	2.0	0.1	0.9	1.5	0.9991
FSQ-Work Perf.	0.9	1.3	-1.9	-0.9	0.6	0.7353
FSQ-Social Activity	0.7	0.4	0.0	-1.3	-2.4	0.9836
FSQ-Quality of Interaction	0.1	-0.5	0.9	0.1	-0.5	0.8629
FSQ-Days (not) in Bed	0.2	0.0	0.0	0.0	0.0	0.8032
FSQ-Days (not) cut down on activities	1.0	0.8	0.5	-0.1	-0.3	0.4150
FSQ-Satis. w/ sexual relations	-0.1	0.0	0.1	0.0	0.0	0.8175
FSQ-Feelings about own health	0.1	0.4	0.2	0.1	0.2	0.1650
FSQ-Freq. of social activity	-0.1	-0.1	0.0	0.2	-0.2	0.2974
EuroQol-Analog	1.4	4.8	4.0	0.7	-2.3	0.0654
No lost work	0.0	0.2	-0.3	-0.2	-0.4	0.4259

**p-value vs. placebo=.0016
* p-value vs. placebo=.0686
Source: Appendix D, Table 18.1

D. Plasma Levels

1. Plasma pramipexole levels were collected in order to assess mean population PK parameters and their variance in this population. The results of this analysis are not in the study report.

2. Plasma levels of concomitant deprenyl and anticholinergics were not measured during the conduct of this trial.

E. Conclusions

A linear dose-response relationship was not demonstrated in this study. All doses performed equally.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TR No.: 7217-95-037

Upjohn STEP-UP
EUROQOL QUESTIONNAIRE (Part 1 of 2)

93-8286-28 3-94 DO NOT WRITE IN SHADED AREAS

PRINCIPAL MONITOR	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
G. R. PETERS, M.D.				

PROTOCOL NO.	STUDY PERIOD	DATE OF THIS REPORT	SITE NO.
M / 2730 / 0004	BASELINE	MO. / DAY / YR.	

INSTRUCTIONS: Please check the answer that best describes your (the patient's) health state today.

1. Mobility:
   - ☐0 I have no problems walking about
   - ☐1 I have some problems walking about
   - ☐2 I am confined to bed
2. Self-care:
   - ☐0 I have no problems with self-care
   - ☐1 I have some problems washing or dressing myself
   - ☐2 I am unable to wash or dress myself
3. Usual Activities:
   - ☐0 I have no problems with performing my usual activities (e.g., work, study, housework, family or leisure activities)
   - ☐1 I have some problems with performing my usual activities.
   - ☐2 I am unable to perform my usual activities.
4. Pain/Discomfort:
   - ☐0 I have no pain or discomfort
   - ☐1 I have moderate pain or discomfort
   - ☐2 I have extreme pain or discomfort
5. Anxiety/Depression:
   - ☐0 I am not anxious or depressed
   - ☐1 I am moderately anxious or depressed
   - ☐2 I am extremely anxious or depressed

6. Compared with my general level of health over the past 12 months, my health state today is:
   - ☐1 Better
   - ☐2 About the same
   - ☐3 Worse

COMMENTS:

INITIALS or SIGNATURE:	SHEET NO.	24

TR No.: 7217-95-037

Upjohn STEP-UP
EUROQOL QUESTIONNAIRE (Part 2 of 2)

93-0286-29 3/94

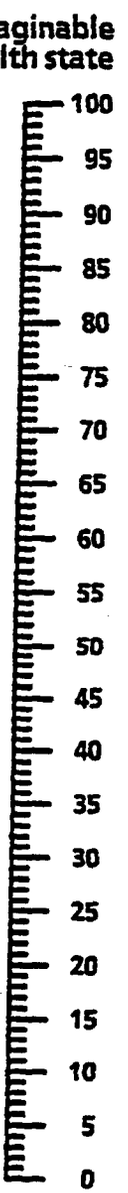
PRINCIPAL MONITOR	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
G. R. PETERS, M.D.				

PROTOCOL NO.	STUDY PERIOD		SITE NO.
M / 2730 / 0004	BASELINE		

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100, and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current health state is.

Your Own Health State Today



SCALE SCORE:

INITIALS or SIGNATURE:	SHEET NO.	25

TR No.: 7217-95-037

Upjohn STEP-UP

DAILY ACTIVITIES - *FUNCTIONAL STATUS QUESTIONNAIRE*© - Page 1 of 6

93-0786-12 3-94 *To be answered by the patient* *DO NOT WRITE IN SHADED AREAS*

PRINCIPAL MONITOR	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
G. R. PETERS, M.D.				

PROTOCOL NO.	STUDY PERIOD	DATE OF THIS EVALUATION	MO.	DAY	YR.	SITE NO.
M / 2730 / 0004	BASELINE					

This group of questions refers to many types of physical and social activities. We would like to know how difficult it was for you to do each of these activities, on the average, during the past month. By difficult, we mean how hard it was or how much physical effort it took to do the activity because of your health.
Circle the number:

4 if you usually had no difficulty doing it;
3 if you usually had some difficulty doing it;
2 if you usually had much difficulty doing it;
1 if you usually did not do the activity because of your health; or
0 if you usually did not do the activity for other reasons.

DURING THE PAST MONTH, HOW MUCH PHYSICAL DIFFICULTY DID YOU HAVE . . .	USUALLY DID WITH NO DIFFICULTY	USUALLY DID WITH SOME DIFFICULTY	USUALLY DID WITH MUCH DIFFICULTY	USUALLY DID NOT DO BECAUSE OF HEALTH	USUALLY DID NOT DO FOR OTHER REASONS
1. Taking care of yourself, that is, eating, dressing, or bathing?	4	3	2	1	0
2. Moving in and out of a bed or chair?	4	3	2	1	0
3. Walking several blocks (a few hundred meters or yards)?	4	3	2	1	0
4. Walking one block or climbing one flight of stairs? (30-40 meters or yards)	4	3	2	1	0
5. Walking indoors, such as around your home?	4	3	2	1	0
6. Doing work around the house such as cleaning, light gardening, home maintenance?	4	3	2	1	0
7. Doing errands, such as grocery shopping?	4	3	2	1	0
8. Driving a car or using public transportation?	4	3	2	1	0
9. Visiting with relatives or friends?	4	3	2	1	0
10. Participating in community activities, such as religious services, social activities, or volunteer work?	4	3	2	1	0

Continued . . .

TR No.: 7217-95-037

Upjohn STEP-UP

DAILY ACTIVITIES - *FUNCTIONAL STATUS QUESTIONNAIRE*© - Page 2 of 6

97-0286-11 1/94 *Answered by the Patient* *DO NOT WRITE IN SHADED AREAS*

PRINCIPAL MONITOR	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
G. R. PETERS, M.D.				

PROTOCOL NO.	STUDY PERIOD		SITE NO.
M / 2730 / 0004	BASELINE		

DURING THE PAST MONTH, HOW MUCH PHYSICAL DIFFICULTY DID YOU HAVE...	USUALLY DID WITH NO DIFFICULTY	USUALLY DID WITH SOME DIFFICULTY	USUALLY DID WITH MUCH DIFFICULTY	USUALLY DID NOT DO BECAUSE OF HEALTH	USUALLY DID NOT DO FOR OTHER REASONS
11. Taking care of other people such as family members?	4	3	2	1	0
12. Doing vigorous activities such as running, lifting heavy objects or participating in strenuous sports?	4	3	2	1	0

13. During the past month, how many days did illness or injury keep you in bed all or most of the day? (If none, write "0")

____ DAYS IN BED during the past month

14. During the past month, how many days did you cut down on the things you usually did for one-half day or more because of your own illness or injury? (Do not count the day(s) spent in bed)

____ DAYS during the past month

15. Are you unable to do certain kinds or amounts of work, housework, or school or university work because of your health?

	(Circle one)
YES, for less than 3 months	1
YES, for 3 or more months	2
NO, my health was not limited this way	0

16. Does your health keep you from working at a job, doing work around the house, or going to school or university?

	(Circle one)
YES, for less than 3 months	1
YES, for 3 or more months	2
NO, my health was not limited this way	0

17. How do you feel about your own health?

	(Circle one)
VERY SATISFIED	5
SATISFIED	4
NOT SURE	3
DISSATISFIED	2
VERY DISSATISFIED	1

Continued...

INITIALS or SIGNATURE:	SHEET NO.	28

TR No.: 7217-95-037

Upjohn STEP-UP

WELL BEING - *FUNCTIONAL STATUS QUESTIONNAIRE* - Page 3 of 6

93-0286-34 3-94 *Answered by the Patient* *DO NOT WRITE IN SHADED AREAS*

PRINCIPAL MONITOR	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
G. R. PETERS, M.D.				

PROTOCOL NO.	STUDY PERIOD		SITE NO.
M / 2730 / 0004	BASELINE		

These next questions ask about how you feel and how things have been with you during the past month. For each question, please circle the number for the one answer that comes closest to the way you have been feeling.

DURING THE PAST MONTH HOW MUCH OF THE TIME:	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
18. Have you been a very nervous person?	1	2	3	4	5	6
19. Have you felt calm and peaceful?	1	2	3	4	5	6
20. Have you felt down-hearted and blue?	1	2	3	4	5	6
21. Were you a happy person?	1	2	3	4	5	6
22. Did you feel so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
23. Did you isolate yourself from people around you?	1	2	3	4	5	6
24. Were you affectionate toward others?	1	2	3	4	5	6
25. Did you act irritable toward those around you?	1	2	3	4	5	6
26. Did you make unreasonable demands on your family and friends?	1	2	3	4	5	6
27. Did you get along well with other people?	1	2	3	4	5	6

Continued...

TR No.: 7217-95-037

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SOCIAL ACTIVITIES - *FUNCTIONAL STATUS QUESTIONNAIRE*© - Page 4 of 6

91-0266-15 3-94 *Answered by the Patient*

DO NOT WRITE IN SHADED AREAS

PRINCIPAL MONITOR	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
G. R. PETERS, M.D.				

PROTOCOL NO.	STUDY PERIOD		SITE NO.
M / 2730 / 0004	BASELINE		

28. About how many close friends do you have - people you feel at ease with and can talk with about what is on your mind? (You may include relatives.) (Enter number on line:)

____ CLOSE FRIENDS AND RELATIVES

29. During the past month, about how often did you get together with friends or relatives, like going out together, visiting in each other's homes, or talking on the telephone?

	(Circle one)
EVERY DAY	6
SEVERAL TIMES A WEEK	5
ABOUT ONCE A WEEK	4
2 OR 3 TIMES DURING THE MONTH	3
ABOUT ONCE A MONTH	2
NOT AT ALL	1

30. During the past month, how satisfied were you with your sexual relationships?

	(Circle one)
VERY SATISFIED	5
SATISFIED	4
NOT SURE	3
DISSATISFIED	2
VERY DISSATISFIED	1
DID NOT HAVE ANY SEXUAL RELATIONSHIPS	0

Continued...

INITIALS or SIGNATURE:	SHEET NO.	30

TR No.: 7217-95-037

Upjohn STEP-UP

EMPLOYMENT - *FUNCTIONAL STATUS QUESTIONNAIRE*® - Page 5 of 6

91-0286-96 3/94 *Answered by the Patient*

DO NOT WRITE IN SHADED AREAS

PRINCIPAL MONITOR	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
G. R. PETERS, M.D.				

PROTOCOL NO.	STUDY PERIOD		SITE NO.
M / 2730 / 0004	BASELINE		

The next question concerns your present working situation other than managing your home.

31. Which of the following statements best describes your work situation during the past month?

	(Circle one)	
WORKING FULL-TIME	1	Go to #32
WORKING PART-TIME	2	
UNEMPLOYED, LOOKING FOR WORK	3	Go to Next Page
UNEMPLOYED BECAUSE OF MY HEALTH	4	
RETIRED BECAUSE OF MY HEALTH	5	
RETIRED FOR SOME OTHER REASON	6	
OTHER	7	

DURING THE PAST MONTH, HOW MUCH OF THE TIME DID YOU:	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	NONE OF THE TIME
32. Do as much work as others in similar jobs?	1	2	3	4
33. Work for short periods of time or take frequent rests because of your health?	1	2	3	4
34. Work your regular number of hours?	1	2	3	4
35. Do your job as carefully and accurately as others with similar jobs?	1	2	3	4
36. Work at your usual job, but with some changes because of your health (for example, use special equipment, trade tasks with other workers)?	1	2	3	4
37. Fear losing your job because of your health?	1	2	3	4

Continued...

INITIALS or SIGNATURE:	SHEET NO.	31

TR No.: 7217-95-037

Upjohn STEP-UP

EMPLOYMENT - *SUPPLEMENTAL* - Page 6 of 6

91-0786-17 3-94 *Answered by the Patient* *DO NOT WRITE IN SHADED AREAS*

PRINCIPAL MONITOR	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
G. R. PETERS, M.D.				

PROTOCOL NO.	STUDY PERIOD		SITE NO.
M / 2730 / 0004	BASELINE		

INSTRUCTIONS: If, based on question 31 on the previous page, you are:
- working full or part time, go to part A below.
- retired for any reason or unemployed for health reasons, go to Part B below (skip part A).

Otherwise, skip parts A, B, and C. You have completed this questionnaire.

PART A. For those working full or part-time according to question 31:

A1. How many hours do you normally work per week? ___ hours

A2. In the last month, approximately how much work time have you missed due to problems resulting from your Parkinson's Disease?

___ Days (enter 0 if you did not miss any work time)

GO TO PART C BELOW (skip part B).

PART B. For those retired for any reason or unemployed for health reasons based on question 31:

B1. Are you currently unemployed, or did you retire early, <u>because of your Parkinson's Disease</u>:

☐1 Yes (go to next question)
☐0 No (go to Part C below)

B2. How long have you been retired or unemployed solely because of your Parkinson's Disease? (Do not count time since your normal retirement age):

___ years, ___ months

GO TO PART C BELOW.

PART C.

Please check the category below which best describes the kind of work you do (or did) on your current (or most recent) job:

☐1 Professional, technical or related
☐2 Administrative or managerial
☐3 Clerical or related
☐4 Sales
☐5 Service (including all food and lodging services)
☐6 Agriculture, animal husbandry, forestry, fishing
☐7 Production or related work, transport equipment operators or laborers
☐8 Armed forces
☐9 None of the above

(If you have trouble picking the best category please ask the study nurse or doctor for assistance. A detailed list of occupations by category is provided in the operations manual.)

INITIALS or SIGNATURE:	SHEET NO.	32

M/2730/0004	
Name and Address of Investigator	Number of Patients Randomized at Site
Brin, Mitchell, M.D. Bressman, Susan, M.D. Columbia University 710 W. 168th, Rm. 309 New York, NY 10032	15
Gauthier, Serge, M.D. McGill Ctr. for Studies in Aging St. Mary's Hospsital 3830 Lacombe Avenue Montreal, Quebec H3T 1M5 Canada	6
Grimes, J. David, M.D. Ottawa Civic Hospital Ottawa, Ontario K1Y 4E9 Canada	15
Harrison, Madaline B., M.D. Dept. of Neurology, Box 394 Univ. of Virginia Health Sciences Ctr. Charlottesville, VA 22908	10
Hauser, Robert, M.D. (6/13/94 - present) Olanow, C. Warren, M.D. (1/19/93 - 6/12/94) University of South Florida 4 Columbia Dr., Suite 410 Tampa, FL 33606	15
Hubble, Jean, M.D. Univ. of Kansas Medical Center Department of Neurology 3901 Rainbow Blvd. Kansas City, KS 66160-7314	10
Hurtig, Howard I, M.D. The Graduate Hospital University of Pennsylvania Department of Neurology 1 Graduate Plaza Philadelphia, PA 19146	18

M/2730/0004	
Name and Address of Investigator	Number of Patients Randomized at Site
Kurlan, Roger, M.D. University of Rochester Department of Neurology 601 Elmwood Avenue, Box 673 Rochester, NY 14642	15
Lew, Mark F, M.D. Univ. of Southern California Department of Neurology USC School of Medicine 1510 San Pablo, Suite 615 Los Angeles, CA 90033	20
Marek, Kenneth I, M.D. Yale Univ. School of Medicine Department of Neurology 333 Cedar Street New Haven, CT 06510	11
Perlmutter, Joel, M.D. Washington Univ. School of Medicine Neurology, Campus Box 8225 510 S. Kings Highway St. Louis, MO 63110	7
Rajput, Ali H, M.D. University of Saskatchewan Clinical Neurology, Rm 1663 Royal University Hospital Saskatoon, SK S7N 0X0 Canada	10
Rao, Jayaraman, M.D. LSU Medical Center 1542 Tulane Avenue New Orleans, LA 70112	15
Rodnitzky, Robert, M.D. University of Iowa Department of Neurology University Hospitals Iowa City, IA 52242	12
Sethi, Kapil D, M.D. Medical College of Georgia B1W-340 Dept. of Neurology 1120 15th Street Augusta, GA 30912	15

M/2730/0004	
Name and Address of Investigator	Number of Patients Randomized at Site
Shannon, Kathleen M, M.D. Rush-Presbyterian/St. Luke's Medical Center Dept. of Neurological Sciences 1725 W. Harrison, Suite 1106 Chicago, IL 60612	14
Suchowersky, Oksana, M.D. Univ. of Calgary/Foothills Hospital 3350 Hospital Drive, NW Calgary, Alberta T2N 4N1 Canada	10
Tanner, Caroline M, M.D. The Parkinson's Institute 1170 Morse Avenue Sunnyvale, CA 94089	14
Trosch, Richard, M.D. Sinai Hospital of Detroit Clinical Neuroscience Program Blumberg Professional Offices 14800 W. McNichols Rd., Suite 100 Detroit, MI 48235	19
Weiner, William, M.D. Univ. of Miami School of Medicine Department of Neurology National Parkinson Foundation 1501 NW 9th Avenue Miami, FL 33136	13

Study 17

This was designed to be a **single-blind**, placebo-controlled, parallel-group study of a maximal-tolerated-dose of pramipexole vs. placebo. By design 48 patients were to be enrolled.

Patients were early-onset PD patients who had not received more than 3 months of L-dopa in the past. Concomitant anticholinergics were allowed. Concomitant amantadine was prohibited. All patients were on deprenyl.

There was a 7-week dose-escalation phase, with a maximal daily dose of 4.5 mg/day. Patients were titrated to maximal tolerated dose (MTD). If side effects developed during dose escalation, dose could be reduced to a prior tolerated dose and that patient would begin the maintenance phase. Following dose-escalation, there was a 3 week maintenance period and then a 1 week dose reduction period.

Replacement of dropouts was allowed (p 5 of the protocol). "Patients who drop from the study prior to completing at least two weeks of the maintenance dose interval...or are less than 75% compliant with the study drug...will be replaced."

Assessments included Parts II and III of the UPDRS. The primary outcome was mean change from baseline on Parts II and III of the UPDRS at the end of maintenance.

Results:

Fifty-six patients were randomized; only 55 ever received a first dose, so that the ITT population includes 55 patients. The sponsor has provided an analysis of an evaluable data set, which excludes 2 patients that the sponsor believes were shown after randomization to not have idiopathic PD. One of the 2 pts was replaced, but the second patient was reclassified after the trial was over and, thus, could not be replaced.

The results for the evaluable, observed case analysis is shown below: ["Observed case" seems to be a misnomer here since, by protocol, if a patient had not been in the maintenance phase for 2 weeks, that pt was to be replaced.]

Adjusted Change From Baseline, UPDRS II

Pramipexole	5.19 (n=28)	
Placebo	2.16 (n=24)	p=0.002

Adjusted Change From Baseline, UPDRS III

Pramipexole	11.97 (n=27)	
Placebo	8.31 (n=24)	p=0.10

There were no deaths or serious AEs. There was only one discontinuation for AE, a placebo patient with worsening of PD. Ten patients (1 placebo; 9 pramipexole) had dose-limiting toxicity from AEs, to include hallucinations, violent dreams, insomnia, and drowsiness.

Conclusions:

Hallucinations resulted in dose-limiting toxicity in 3 pramipexole patients. Note that the primary outcome encompassed Parts II and III of the UPDRS, so that a favorable score on those subscales could be recorded in the face of serious AEs that required dose adjustments.

The maintenance period here was only 3 weeks long, making any extrapolation from these results difficult.

While more patients may have improved on the ADL scale while on pramipexole as opposed to placebo, some pramipexole patients had serious AEs (hallucinations) requiring dose adjustments. Given the brief maintenance period, it is unknown how long the risk-benefit ratio would have continued in favor of pramipexole.

It is reassuring that the estimates of change from baseline on the ADL scale here are so similar to those seen in Study 21 (a study very comparable in design to Study 17). The difference on the ADL scale is statistically significant here, but not in Study 21.

On the other hand, the estimates of change from baseline on the Motor Exam scale here are different from those in Study 21. The directionality favors pramipexole in both studies, but is statistically significant only in Study 21.

APPEARS THIS WAY
ON ORIGINAL

Study 21

This was designed to be a double-blind, placebo-controlled, parallel-group study of a maximal-tolerated-dose of pramipexole vs. placebo. By design 52 patients were required to complete the maintenance dose schedule; in order to achieve this, the protocol called for 72 patients to be randomized.

Patients were early-onset PD patients who had no received more than one week of L-dopa in the past. Concomitant anticholinergics and deprenyl were allowed. Concomitant amantadine was prohibited. Domperidone was allowed.

There was a 9-week dose-escalation phase, with a maximal daily dose of 4.5 mg/day. Patients were titrated to maximal tolerated dose (MTD). If side effects developed during dose escalation, dose could be reduced 1 or 2 levels. Following dose-escalation, there was a 2 week maintenance period and then a 1 week dose reduction period.

Assessment included Parts II and III of the UPDRS. The primary outcome was mean change from baseline on Part III of the UPDRS at the end of maintenance.

Results:

Only 24 patients were recruited out of the planned 72 before the sponsor stopped the study. The sponsor has provided an analysis of an **explanatory data set**, which excludes a pramipexole patient with a prior history of hallucinations and a placebo patient previously treated for 5 months with L-dopa. The sponsor maintains that these patients did not meet the inclusion/exclusion criteria.

The results for this explanatory data set are shown below:

	Change From Baseline	
Pramipexole	7.2 (n=10)	
Placebo	1.6 (n=12)	p=0.02

The sponsor also examined the results for Part II of the UPDRS (ADL). There was a trend toward improvement following treatment with

pramipexole, but no statistically significant difference. The mean change from baseline for pramipexole was 5 points, while the mean change from baseline for placebo was 2 points.

The sponsor maintains that an improvement of 30% on the motor exam is significant in terms of patient benefit (p 75 of the Technical Report). Using the entire cohort of 24 patients, I categorized patients as 30% improved or not. The results follow:

	30% Improved on Motor Exam
Pramipexole	6/11
Placebo	2/13

However, note that 2 placebo patients were withdrawn early (pts 29,76) because of "lack of efficacy" or protocol violation (late recognition that pt had 5 months prior treatment with L-dopa). These represent 2 potential "winners" on placebo who were prematurely taken out of the running. One would assume that "lack of efficacy" would at least have led to further dose escalation, rather than withdrawal. Meanwhile, the 6 pramipexole patients with 30% improvement are balanced by 2 pramipexole patients who discontinued with serious AEs.

Conclusions:

The study was stopped early because of low enrollment. The sponsor states that the protocol required weekly visits and that the early PD patients (who were often working) had a hard time making that sort of time commitment.

Two (out of 11) pramipexole patients discontinued because of hallucinations. Note that the primary outcome was the motor exam of the UPDRS, so that a favorable score on that scale could be recorded in the face of serious AEs that required discontinuation.

The maintenance period here was only 2 weeks long, making any extrapolation from these results difficult. (Note also that one pramipexole patient, pt 65, inadvertently skipped the 2-week maintenance phase so that the score at end of dose-escalation was used for outcome assessment.)

While more patients may have improved on the motor exam while on pramipexole as opposed to placebo, 2 pramipexole patients had serious AEs (hallucinations) requiring discontinuation. Given the brief maintenance period, it is unknown how long the risk-benefit ratio would have continued in favor of pramipexole.

Study 10

A. Study Design

This was a multicenter, randomized, double-blind, placebo-controlled parallel group study of pramipexole vs. placebo, added on to maintenance L-dopa (with a decarboxylase inhibitor) therapy. The treatment periods were designed to be at least 6 months in duration.

The target population were patients with a less than optimal response to L-dopa, characterized by the presence of motor fluctuations. 300 patients were to be entered, 150 per treatment group. A total of 24 centers in the U.S. and Canada were planned with up to 24 patients per center.

Inclusion criteria were:

1. Patients with idiopathic Parkinson's disease, Hoehn and Yahr Scale scores of II-IV during an on period, age 30 years and older. Scores of II-IV encompass patients with bilateral disease with minimal-severe disability and balance problems. A score of V would be given to a bedbound or wheelchair-bound patient. A score of I would be given to a patient with only unilateral disease.

2. Given a stable dose of L-dopa for 30 days prior to randomization, patients had to demonstrate continued motor fluctuations, specifically the so-called "wearing-off" effect, where the duration of effect from a single dose of L-dopa becomes progressively shorter over time.

Page 11 of the protocol added that, if the patient was taking deprenyl, amantadine, or and anticholinergic medication, the dose of that medication should be stable for 30 days prior to randomization.

3. Patients had to be able to keep an accurate daily diary of "on" and "off" periods during waking hours, with the help of caregivers.

Exclusion criteria were:

1. Atypical parkinsonian syndromes, to include drug-induced parkinsonian syndromes.

2. Dementia or active psychosis.

3. Second or third degree AV block or sick sinus syndrome; resting heart rate below 50; CHF Class III or IV; MI within 6 months; other clinically significant heart conditions.

4. Occurrence of a seizure within 2 years.

5. Renal or hepatic impairment. Neoplastic disease.

6. Surgery within 6 months which the investigator believes could impact patient's participation.

7. History of stereotactic brain surgery.

8. SBP less than 100 or a symptomatic drop in SBP or 20 or greater upon standing.

9. Neuroleptics within 60 days; alpha-methyl dopa within 60 days; metoclopramide within 60 days; flunarizine, cinnarizine, parenteral ergots, bromocriptine, pergolide, lisuride, MAO inhibitors other than deprenyl, methylphenidate, amphetamine, beta blockers if used to treat tremor, or reserpine within 30 days.

10. Adequate contraception and a negative pregnancy test for all women of childbearing potential.

11. Electroconvulsive therapy within 90 days.

The schedule of time and events is on the next page. Patients were seen for a single **screening visit** within 2 weeks of randomization. At the next visit, if they continued to meet the inclusion/exclusion criteria and if they demonstrated the ability to keep the daily diary, patients were **randomized** to receive the first dose of study medication. An

PRAMIPEXOLE PHASE III TRIAL IN ADVANCED PARKINSON'S DISEASE
PROTOCOL SUMMARY - 00679A (Double-Blind, Placebo-Controlled)

	Screening	Ascending-Dose Interval[2]							Maintenance-Dose Interval[2]									
Visit Number	1	2[1]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18[8]
Days since the last visit		1-14	5-9	5-9	5-9	5-9	5-9	5-9	5-9	10-16	10-16	10-16	10-16	10-16	10-16	28-36	28-35	28-35
Dose Level		1	2	3	4	5	6	7	M[3]	M	M	M	M	M	M	M	M	M
History	X																	
Physical Examination[4]	X												I					
Laboratory Tests[4]	X				X				X				X[9]			X[9]		X[9]
Chest X-Ray	X																	
12-Lead ECG[4]	X				X				X				X			X		X
Disability Ratings[4,5]	X	X	X	X	X	X	X	X	X		X		X		X	X		X
Dispense Daily Patient Records (on/off diaries)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Evaluate Daily Patient Records (on/off diaries)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[4] and Concomitant Meds[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization to Treatment		X																
Dispense Trial Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[6]	X	X	X	X	X	X	X	X	X		X		X		X	X		X
Medication Compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Motor Examination[7,8]		X	X	X	X	X	X	X	X		X		X		X	X		X
Dyskinesia Scales[7,8]		X	X	X	X	X	X	X	X		X		X		X	X		X

1. The levodopa/decarboxylase inhibitor daily dose and timing of dosing must be stable for 30 days prior to Visit 2.
2. Duration of the ascending-dose interval varies depending upon the optimal daily dose of study medication that is achieved. The optimal daily dose is defined as either the maximally tolerated dose of study medication or the dose associated with stable improvement (i.e., lack of further improvement despite up to two additional dose increases). The degree of improvement is based upon the clinical judgement of the investigator without examination of previous scores on various rating scales used in the trial.
3. Maintenance dose (M) is either the maximally tolerated dose or the optimal dose if adverse events do not prevent dose escalation during the ascending-dose interval.
4. Parts I, II, and IV of the UPDRS, Modified Schwab-England Disability Scale, and the timed-walking test (start at Visit 2). Modified Hoehn and Yahr Scale (start at Visit 1).
5. Vital signs (supine and 1 minute standing blood pressure and pulse rate) are taken at Visit 1 in triplicate per protocol, prior to study medication at Visit 2 only and at 2 hours post-dose of study medication at all visits beyond visit 1 as noted above.
6. UPDRS Part III (motor examination) is done two to three hours following a levodopa dose taken either before the clinic visit or at the start of a clinic visit.
7. Parkinson's Dyskinesia Scale done two to three hours following a levodopa dose.
8. Dose-Reduction Interval starts with Visit 18 and ends at Visit 19, the final visit in Part I. See Protocol Summary Part II for specific procedures to be completed for Visit 19.
- Required for patients who drop from the trial.
- Blood samples for determination of pramipexole serum concentrations to be obtained.

ascending-dose phase followed and could last as long as 7 weeks. If patients experienced dose-limiting toxicity prior to reaching the maximal dose, they entered the **maintenance phase** at that point (prior to 7 weeks). A patient who moved into the maintenance phase after only 1 or 2 weeks of the ascending-dose phase was considered to have missing data for the additional 5-6 weeks of the ascending-dose phase, resuming entries with visit 9. The maintenance phase was 6 months in duration and was followed by a 1 week **dose reduction phase.**

The ascending dose schedule is on the next page. Study medication was to be taken 1 hour before or 2 hours after meals. There were 7 possible fixed dose regimens, ranging from a total daily dose of 0.375 mg to 4.5 mg. The dose was to be raised until dose-limiting toxicity was reached, the maximum dose was reached, or there was a lack of further clinical improvement in the judgment of the investigator despite up to two additional increases in the dose of study medication.

The protocol does not have instructions for dose adjustments of study medications if patients developed AEs during the maintenance phase. That is, if a patient developed nausea during the maintenance phase, it is not clear if the dose of study drug could be lowered.

During the maintenance phase, the dose of L-dopa could be adjusted downward if dyskinesias, hallucinations, or psychiatric side effects developed. The dose could subsequently be increased, but not to a level in excess of the original daily dose. Doses of concomitant anticholinergics, deprenyl, and amantadine were to remain constant during the study.

Patient visits occurred every week during the ascending dose phase. Patient visits occurred every 2 weeks for the first 3 months of the maintenance phase and every month for the last 3 months of the maintenance phase.

Pramipexole Ascending-Dose Schedule

	Dose Level	Dosage	Total Daily Dose
Week 1	1	3 x 0.125 mg	0.375 mg
Week 2	2	3 x 0.25 mg	0.75 mg
Week 3	3	3 x 0.5 mg	1.50 mg
Week 4	4	3 x 0.75 mg	2.25 mg
Week 5	5	3 x 1.0 mg	3.00 mg
Week 6	6	3 x 1.25 mg	3.75 mg
Week 7	7	3 x 1.5 mg	4.50 mg

Monthly, during the maintenance phase, the investigator completed the following scales:

1. Parts I, II, and IV of the UPDRS. Part I rates mentation, mood, and behavior. Part II rates ADLs during the past week. Part IV rates complications of therapy, including dyskinesias.
2. Modified Schwab-England Disability Scale
3. Timed Walking Test
4. Modified Hoehn and Yahr Scale

At the same time intervals, the investigator completed the following 2 exams:

1. Part III of the UPDRS (the motor exam). Protocol Amendment #4 clarified that this was to be completed during an "on" period.
2. Parkinson's Dyskinesia Scale

These last 2 exams were to be performed 2-3 hours after the last dose of L-dopa, taken either at home or at the beginning of the clinic visit, and 1-4 hours after the last dose of test drug.

At the same monthly intervals, the investigator evaluated the **daily diaries** for the previous time interval. Patients were instructed to complete the diaries for at least 2 full days prior to their scheduled clinic visits. This was recorded in the CRF as the total waking hours for each day, the number of "off" hours for each day, and the average severity level for the "off" hours in a given day (1-4 scale).

Copies of all scales from the CRF are attached at the end of this Study 10 review. Note that several of the above scales yielded 2 scores, one representing best performance during an "on" period and one representing best performance during an "off" period. This applies to:

1. Part II of the UPDRS
2. Modified Schwab-England Disability Scale
3. Modified Hoehn and Yahr Scale

An operational definition of "on" and "off" was never provided in the protocol. Generally these terms are used to differentiate times when patients are responding well to medicines and periods when they are not

responding well. Off times could occur at predictable times, especially in the time preceding the next dose of medicine. Off times could also occur at unpredictable times, unrelated to time of medicine. The latter unpredictable off times could be brief, referred to as "freezing," or they could be more prolonged. Off time may not represent as low a level of functioning as might be seen in the total absence of medicine, but is generally referenced to a better level of functioning that occurs on the same daily dose of medication.

Replacement of patients was allowed by protocol if those patients discontinued the study for any reason other than AEs (to include worsening of underlying Parkinson's Disease) prior to completing half of the maintenance phase. **Protocol Amendment #1** added that patients who dropped out of the study prior to completing the maintenance phase were to return for a final visit at the time their final visit would have occurred.

Note that during the ascending-dose phase, patients assigned to the pramipexole group received both pramipexole and placebo tablets; patients assigned to the placebo group were not exposed to pramipexole.

Two primary outcome variables were stated in the protocol: Part II of the UPDRS (ADL) and Part III of the UPDRS (motor exam).

The analysis plan stated that "the primary efficacy endpoint for each of these parts of the UPDRS is the change in the score between baseline and maintenance where the maintenance score is the last available score prior to the dose-reduction interval." The primary analysis plan was not clearly specified in the protocol. **Protocol Amendment #4** clarified this situation. It stated that "In order for this study to be declared positive, both primary endpoints must achieve statistical significance." The ITT population was to be the primary analysis population with an LOCF technique employed for missing data.

The sample size was computed using results in the DATATOP study and making assumptions about how the early Parkinson's Disease population in DATATOP might differ from the target population in the current study. It was estimated that with 150 patients per treatment group, the study would have 90% power to detect small differences on the order of 2-4 points in change from baseline in Part III of the UPDRS (motor exam).

B. Subject Disposition and Baseline Comparison

The planned enrollment was 300, with plans to replace patients who did not complete half the maintenance phase for reasons other than AEs. On page 37 of the study report, the sponsor states that enrollment exceeded the planned enrollment because, by the time it became apparent that enough patients would complete the trial, other patients were already enrolled in earlier stages of the trial.

360 patients were randomized: 181 pramipexole and 179 placebo. The investigators and centers (22 U.S. and 4 Canadian) are listed at the end of this Study 10 review.

Protocol Deviations: 3% of patients entered without meeting all inclusion/exclusion criteria. These included systolic blood pressure < 100, concomitant use of bromocriptine, lack of advanced Parkinson's Disease symptoms, abnormal baseline labs, and prior pramipexole use.

4% of patients had their baseline Sinemet dose exceeded during the trial.

4% of patients took excluded meds during the study to include pergolide, bromocriptine, haloperidol, timolol, and metaclopramide.

37/69 patients who withdrew from the study did not return for the follow-up visit at what would have been Visit 18, as outlined in a protocol amendment.

15% of patients had some baseline testing done after the first dose of study medication. The sponsor states that the first dose was placebo for all patients so that the results should not have been affected.

At least 28% of patients had at least one evaluation performed outside the protocol-specified time interval.

Likewise, at select visits, 10% of patients demonstrated medication compliance less than 75% or greater than 125%.

Baseline Characteristics: No significant differences in the two treatment groups were detected at baseline in demographics or disease characteristics.

	Placebo N=179	Pramipexole N=181
Age	63 (39-89)	63 (31-84)
Sex	116M/63F	119M/62F
Race	96% White	95% White
Parkinson's Duration	9 yrs (0.8-27)	9 yrs (0.4-31)
Deprenyl Use	53%	56%
Anticholinergic Use	12%	14%
Part II "On" Score	8 (0-29)	7 (0-23)
Part II "Off" Score	17 (2-35)	17 (4-42)
Part III Score	23 (0-64)	23 (4-61)
Hoehn & Yahr "On"	2.3 (0-4)	2.3 (0-4)
Hoehn & Yahr "Off"	2.9 (1-5)	3.0 (1-5)

Patient Flow: One patient (placebo) withdrew before receiving drug, so that only 359 patients were treated. Altogether, 9 patients (including the one just mentioned) did not meet the ITT definition, i.e. they did not have at least one efficacy assessment. Therefore, 351 patients are included in the efficacy analysis: 179 pramipexole and 172 placebo.

The following table outlines the withdrawals during the study. In addition to the 68 withdrawals in the table, there was the 1 placebo patient already mentioned who withdrew prior to receiving the first dose. Therefore, there were 69 withdrawals altogether.

Withdrawals (Withdrawals Due to AEs)

	Pramipexole	Placebo
Ascending Dose Phase	12 (9)	22 (16)
Maintenance Phase	18 (15)	16 (14)
TOTAL	30 (24)	38 (30)
	68 (54)	

The timing of the withdrawals had the potential to be important as the protocol allowed for replacement of patients who withdrew prior to visit 15 for reasons other than AEs. However, since only 14 patients withdrew for reasons other than AEs, the latter point took on less importance. As far as I know, there were no replacements during the conduct of the trial. Sponsor's Table 7.3.3:1 on the next page outlines the number of withdrawals by visit for the two treatment groups.

The reasons for withdrawals are shown in the next table.

Patient Disposition

	Pramipexole	Placebo
Disease Worsening	3	9
Worsening of Pre-existing Disease	0	3
Other AEs	21	18
Protocol Violation	1	0
Lost to Follow-Up	0	2
Withdrew Consent	4	3
Other	1	4

151/181 pramipexole patients completed the trial. 140/179 placebo patients completed the trial.

Of the 360 patients who were randomized into the trial, 291 patients completed the protoc planned, and 69 patients withdrew. The visits after which these 69 patients withdrew are displayed in TABLE 7.3.3:1.

TABLE 7.3.3:1 Number of Patients Withdrawing from the Trial by Last Visit

Visit	Pramipexole	Cumulative Number (Percentage) of Pramipexole Patients Withdrawing by Visit	Placebo	Cumulative Number (Percentage) of Placebo Patients Withdrawing by Visit
2	0	0 (0%)	3	3 (8%)
3	2	2 (7%)	6	9 (23%)
4	2	4 (13%)	1	10 (26%)
5	1	5 (17%)	5	15 (38%
6	0	5 (17%)	1	16 (41%)
7	3	8 (27%)	3	19 (49%)
8	1	9 (30%)	3	22 (56%)[1]
9	3	12 (40%)	0	22 (56%)
10	4	16 (53%)	3	25 (64%)
11	6	22 (73%)	5	30 (77%)
12	1	23 (77%)	1	31 (79%)
13	1	24 (80%)	2	33 (85%)
14	1	25 (83%)	1	34 (87%)
15	2	27 (90%)	2	36 (92%)
16	3	30 (100%)	1	37 (95%)
17	0	30 (100%)	1	38 (97%)
18	0	30 (100%)	1	39 (100%)
Total	30		39	

Source Data: Appendix 15.12 LISTINGS 7.1 and 7.2

[1] Patient 1054 discontinued prior to receiving study medication.

Thirty (43%) of the withdrawing patients were from the pramipexole group, while 39 (57%) were from the placebo group. The placebo group had both more withdrawing patients, and also faster withdrawal than the pramipexole group. By Visit 8 over half of the placebo dropouts had occurred, while only 30% of the pramipexole group dropouts had occurred. TABLE 7.3.3:1 also gives the cumulative percentage of dropouts by group for each visit, and it is apparent that dropouts occurred more quickly in the placebo group.

C. Efficacy Evaluation

All the analyses in 1-10 below are LOCF analyses, unless specifically described otherwise.

In addition to the 9 patients excluded from all analyses because of lack of any efficacy measurements, some patients had to be excluded from the efficacy analysis for individual efficacy endpoints because of missing data. The sponsor lists all these cases, but they are rare enough that they are not reproduced here. For example, the largest number of patients excluded for a specific endpoint was 12 (3%), which was for the Average Severity of "Off" Time.

On page 62 of the study report, the sponsor addresses the issue of missing data. The sponsor notes the special case where a patient was to be rated for both the on and off periods. This applies to the UPDRS Part II, the Schwab-England Scale, and the Hoehn and Yahr Scale. The sponsor states that "on a few occasions" there was no off score recorded because the patient had no off periods during that particular reporting period. In that situation, the sponsor states that the on score was used to estimate the off score. My review of the data listings suggests otherwise. As shown in the table on the next page, an LOCF approach was used. The number of times that this situation arose is so small that it would not affect the overall results, however.

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Patients With No Reported OFF Time (by diary) at Visit 18 and No Recorded OFF Score on UPDRS Part II

Patient Number	Observed OFF Score (Imputed OFF Score)	Observed ON Score
Placebo Patients		
1035	* (12)	10
1041	* (14)	12
1154	* (13)	7
1294	* (4)	2

Pramipexole Patients		
1072	* (1)	0
1177	* (12)	4
1195	* (0)	2
1200	* (0)	9
1213	* (12)	5
1238	* (12)	1
1264	* (18)	10
1277	* (15)	17
1323	* (1)	0

* no valued recorded because of lack of "off" periods during that treatment period

[Data taken from Listings 4.5.2, 4.3.2, 4.4.2, and 4.3.1]

1. Percentage of On Time, On Time With Dyskinesia, and Off Time:

The percentage of awake time spent in the "off" state was not a primary outcome, but was a secondary outcome. I present this first because it seems to be integral to the whole study. First, the inclusion criteria mandated that patients have on-off phenomenon, especially end-of-dose failure. Second, the two primary outcome variables were defined in terms of on and off time (see below).

Note that, despite the prominent role of the "on-off" phenomenon in this trial, an operational definition is never clearly laid out in the protocol. The instructions for the patient daily diaries define "on" simply as a period of "good motor function." "Off" is defined as "able to move slowly or not at all." In the diaries, off periods were to be graded on a 1-4 scale with the mildest 1 rating defined as "mild slowness, stiffness, or resting tremor." Given this last qualification, one might infer that any emergence of underlying symptoms of Parkinson's Disease in a given patient would meet the definition of "off."

The UPDRS Part II score is an average of an on score and an off score. However, it does not weight the on score and off score with respect to changing amounts of time in the on period and the off period. Theoretically, a patient's on score and off score could both improve, but if more time was spent as off time, the patient would be worse on average, despite a better UPDRS Part II score.

The UPDRS Part III score was collected during an on period. It is called the motor exam portion of the UPDRS, but in fact, an important part of a patient's motor performance, dyskinesia, is not captured in Part III, but is displaced to Part IV.

The protocol defined a positive outcome as a joint outcome, a positive result on Part II and a positive result on Part III. Sponsor's Figures 9.3.1.1.3:1 and 2 on the next page demonstrate quite clearly for both the pramipexole and placebo groups that Parts II and III of the UPDRS are not correlated in Study 10. A patient with improvement on one scale has a fifty-fifty chance of improving on the other. That being the case, a more global assessment of patient function such as percentage off time is informative.

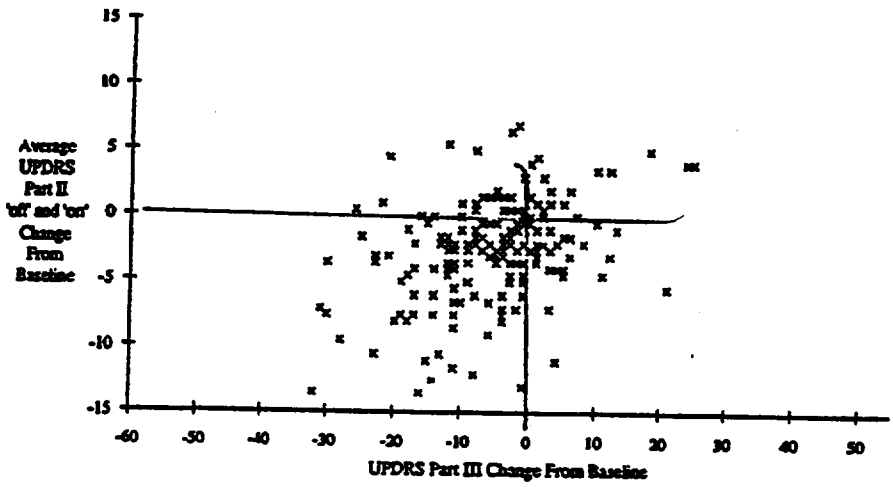

FIGURE 9.3.1.1.3:1 Pramipexole Group Change from Baseline for UPDRS Part II (Averaged) and Part III. Each Point Represents One Patient.

Last Observation Carried Forward Analysis

Source Data: Appendix 15.12.4

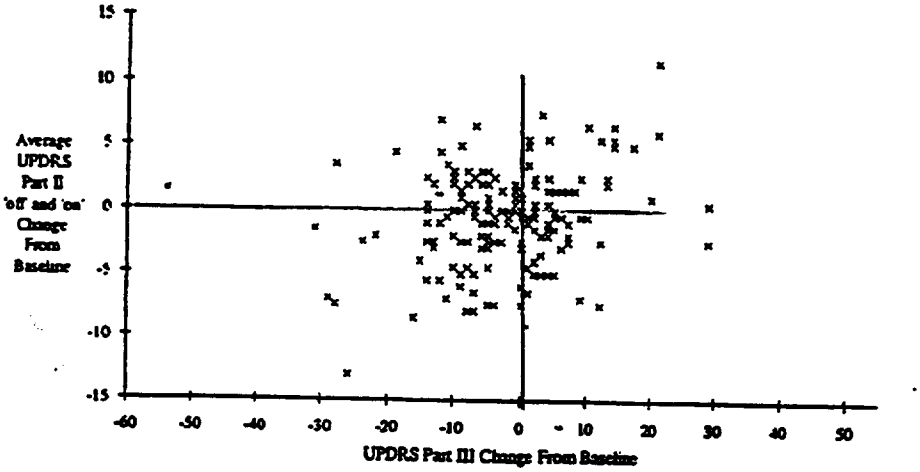

FIGURE 9.3.1.1.3:2 Placebo Group Change from Baseline for UPDRS Part II (Averaged) and Part III. Each Point Represents One Patient.

Last Observation Carried Forward Analysis

Source Data: Appendix 15.12.4

Sponsor's Figure 9.3.1.2.3:1 on the next page shows the average percentage of waking hours spent in an "off" state by visit for the two treatment groups. The information used for this evaluation was collected on the patient daily diary and then summarized by the investigator in the CRF at the time of patient visits. On the patient diary, patients were asked to choose between 4 options: on, off, on with dyskinesia, or asleep. When the investigator summarized this data on the CRF, only the amounts of "off" time and asleep time were transcribed. The sponsor presents the data in terms of percentage of awake time in an "off" state.

The observed case results for the same comparison are not presented by the sponsor.

The sponsor presents an analysis of change from baseline to final results on maintenance. The pramipexole group reduced their percentage of off time by 35% while the placebo group reduced their percentage of off time by 8% (p=0.0006).

Note that movement from "off" time could be in the direction of "on" time or "on with dyskinesia" or even "asleep." The sponsor has not provided data on these latter three options separately in the NDA. In fact, data on two of the latter three categories were not transferred from patient diaries to the CRFs. The sponsor addressed this in a September 27 submission.

In that submission the sponsor reports that, at the final maintenance visit, average off hours drop from 6 hrs at baseline to 3.9 hrs in the pramipexole group compared to from 6.2 hrs at baseline to 5.7 hrs in the placebo group. The average awake hrs changed very little throughout the study for both groups.

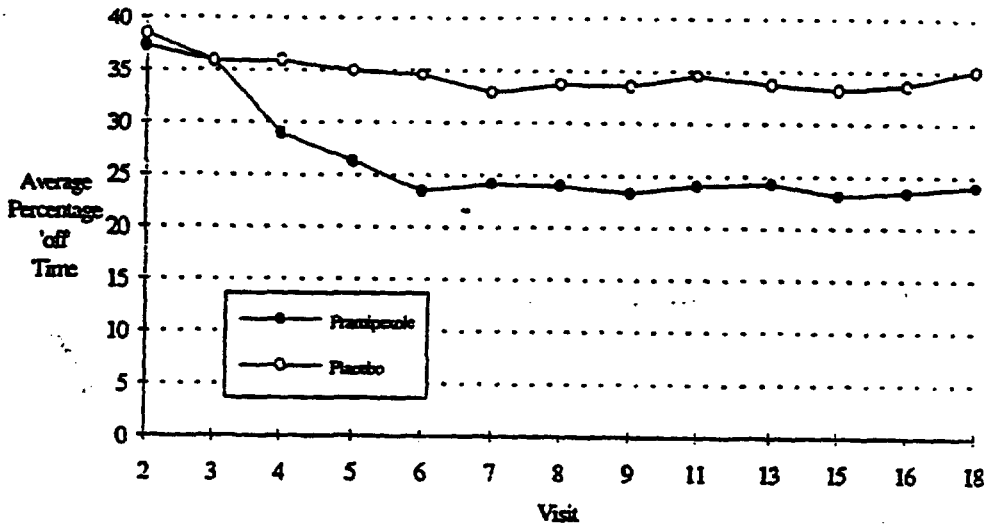

FIGURE 9.3.1.2.3:1 Average Percentage 'off' Time by Visit.

Last Observation Carried Forward Analysis

TABLE 9.3.1.2.3:2 Mean (S.D.) Average Percentage of 'off' Period Time Change from Baseline.

Last Observation Carried Forward Analysis

	Baseline	Final Maintenance Visit	Unadjusted Change from Baseline to Final Visit on Maintenance	Adjusted[1] Change from Baseline to Final Visit on Maintenance
Pramipexole n = 173	37.20 (19.91)	24.01 (22.45)	-13.18 (22.15)	-11.70
Placebo n = 172	38.28 (20.35)	35.13 (24.24)	-3.15 (23.20)	-2.82
p-value				0.0006

Source Data: Appendix 15.9.2 STATDOC 4.5.3

1 Adjusted by center and center-by-treatment interaction (as per protocol).

But there is an even more confusing issue raised by the data. In the table on the next page is a listing of patients who rated themselves as having no "off" time at visit 18, yet who were given "off" ratings on UPDRS Part II. This is incongruous. How could a patient have a score for a physiologic state that did not occur ? The answer is that off periods did occur for these patients, but were not captured in the diary data.

In the September 27 submission, the sponsor reports frequency tables of number of days in the CRF diary at each visit for the two treatment groups. Patients were told to record diaries for at least 2 days prior to the next clinic visit; the CRF provided space to transcribe diary data for up to 10 days. Obviously, this presents a problem when looking at the last 3 months of maintenance, when pts were seen only once monthly. Two days may not capture the true experience of the month.

In fact the instructions for the diaries state, "The number of hours off per day divided by the total number of waking hours will be averaged over each week of assessment and recorded on case report forms." This implies an intent to analyze diary data weekly, an intent that could not be realized because of the study design which collected only snapshots of diary information every 30 days.

Reassuring is the fact that the snapshots were collected every 30 days and show a consistent trend in favor of the pramipexole group.

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Patients With No Reported OFF Time (by diary) at Visit 18

Patient Number	Observed OFF Score	Observed ON Score
Placebo Patients		
1168	22	14
1169	20	4
1222	3	0
1311	17	6
1358	8	0
Pramipexole Patients		
1030	12	7
1093	8	1
1156	15	8
1157	14	9
1171	10	0
1228	5	2
1230	13	3
1232	21	10
1234	8	4
1250	14	11
1255	12	2
1295	8	0
1306	2	2
1316	3	1
1321	0	0
1368	12	8
1385	10	7
1413	8	2

Table D1
Frequency Tables of the Number of Days in the Diary at Each Visit
M/2730/0010

Visit	MC	Number of Days in the Diary										total N	p-value
		1	2	3	4	5	6	7	8	9	10		
Visit 2 (baseline)	PPX	6	47	29	32	13	18	11	5	3	11	175	0.896
	PBO	2	56	25	32	9	19	13	6	3	13	178	
Visit 3 (week 1)	PPX	0	53	24	27	12	20	28	9	2	3	178	0.829
	PBO	0	50	31	26	14	21	18	5	2	3	170	
Visit 4	PPX	0	50	28	27	7	30	26	4	2	3	177	0.911
	PBO	0	53	32	21	4	24	23	2	2	2	164	
Visit 5	PPX	0	53	17	25	9	20	23	9	3	1	160	0.459
	PBO	0	46	28	21	10	17	25	6	0	2	155	
Visit 6	PPX	0	50	19	22	12	20	18	7	1	2	151	0.643
	PBO	0	48	22	21	10	22	22	2	2	0	149	
Visit 7	PPX	0	44	17	21	8	15	22	0	4	1	132	0.592
	PBO	1	45	19	19	8	19	15	4	3	2	135	
Visit 8	PPX	0	38	11	16	5	13	17	3	2	0	105	0.922
	PBO	2	43	14	19	6	14	17	3	3	2	123	
Visit 9@	PPX	0	58	20	31	7	21	21	5	1	1	165	0.687
	PBO	0	53	26	23	7	18	24	2	3	0	156	
Visit 10	PPX	0	48	15	30	3	5	6	6	5	42	160	0.620
	PBO	1	46	23	32	0	4	6	4	6	34	156	
Visit 11	PPX	0	46	15	36	8	3	6	4	9	36	163	0.096
	PBO	1	39	26	32	1	2	5	3	2	40	151	
Visit 12	PPX	3	42	17	31	3	4	6	4	4	40	154	0.907
	PBO	3	35	22	32	1	1	5	4	3	39	145	
Visit 13	PPX	0	42	16	32	6	7	10	5	4	32	154	0.084
	PBO	2	39	22	27	2	1	9	0	2	36	140	

@ Maintenance Week 0
# End of Maintenance week 24

Table D1
Frequency Tables of the Number of Days in the Diary at Each Visit
M/2730/0010

Visit	MC	Number of Days in the Diary										total N	p-value
		1	2	3	4	5	6	7	8	9	10		
Visit 14	PPX	2	44	15	33	1	6	8	7	2	35	153	0.552
	PBO	2	39	20	27	1	3	6	1	5	32	136	
Visit 15	PPX	1	45	12	34	3	5	7	4	6	31	148	0.747
	PBO	1	41	21	30	2	4	2	3	50	30	139	
Visit 16	PPX	1	42	15	24	5	4	8	8	4	39	150	0.987
	PBO	1	39	17	28	4	3	8	4	3	35	142	
Visit 17	PPX	2	42	14	24	6	3	7	10	7	32	147	0.884
	PBO	3	40	19	24	2	4	6	6	5	31	140	
Visit 18 #	PPX	2	37	17	24	4	2	3	10	6	40	145	0.902
	PBO	3	42	19	23	3	3	4	6	7	28	138	

@ Maintenance Week 0
# End of Maintenance week 24

2. UPDRS Part II

Sponsor's Figure 9.3.1.1.1:1 (next page) shows the average Part II scores (off and on means) by visit for the two treatment groups. The sponsor provided cumulative distribution functions for the treatment groups and these are shown on the page after that.

Sponsor's Figure 13.2.1 (next page) shows the observed case results for the same comparison. Page 68 of the study report states that 37 of 69 patients who dropped out did not return for evaluation at what would have been their visit 18. These 37 patients are not part of the OC analysis.

The protocol specified analysis was a comparison between treatment groups of change from baseline to final maintenance visit (LOCF), adjusted by center and center-by-treatment interaction. The results of this analysis were highly statistically significant. Consistency across other analyses of the same outcome variable can be seen below:

	LOCF Change from Baseline to Final Maintenance Visit	OC Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (Visits 11-18)	OC Area Under the Curve over Maintenance Visits (Visits 11-18)
Pramipexole	-2.7	-2.8	-57	-54
Placebo	-0.5	-0.5	-18	-17
p-value	$\leq$ 0.0001	$\leq$ 0.0001	$\leq$ 0.0001	$\leq$ 0.0001

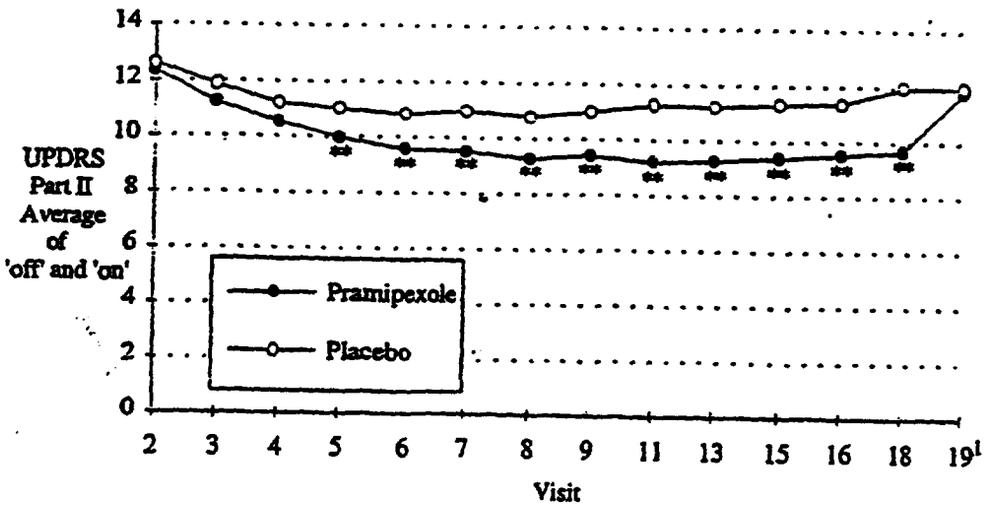


FIGURE 9.3.1.1.1:1 Average UPDRS Part II 'off' and 'on' Means by Visit.
Last Observation Carried Forward Analysis

Source Data: TABLE 9.3.1.1.1:1
* $p \leq 0.05$ ** $p \leq 0.01$ [1] Observed Cases Analysis Only

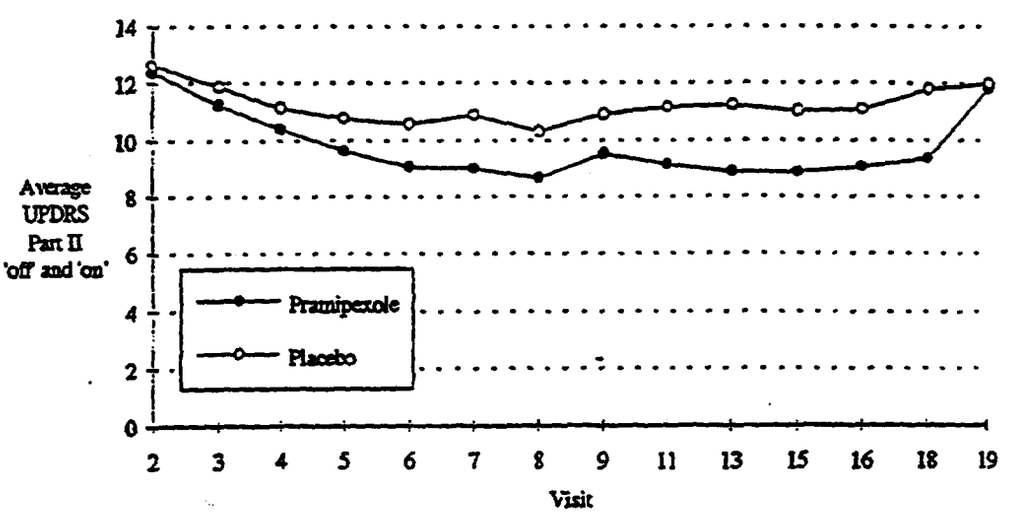
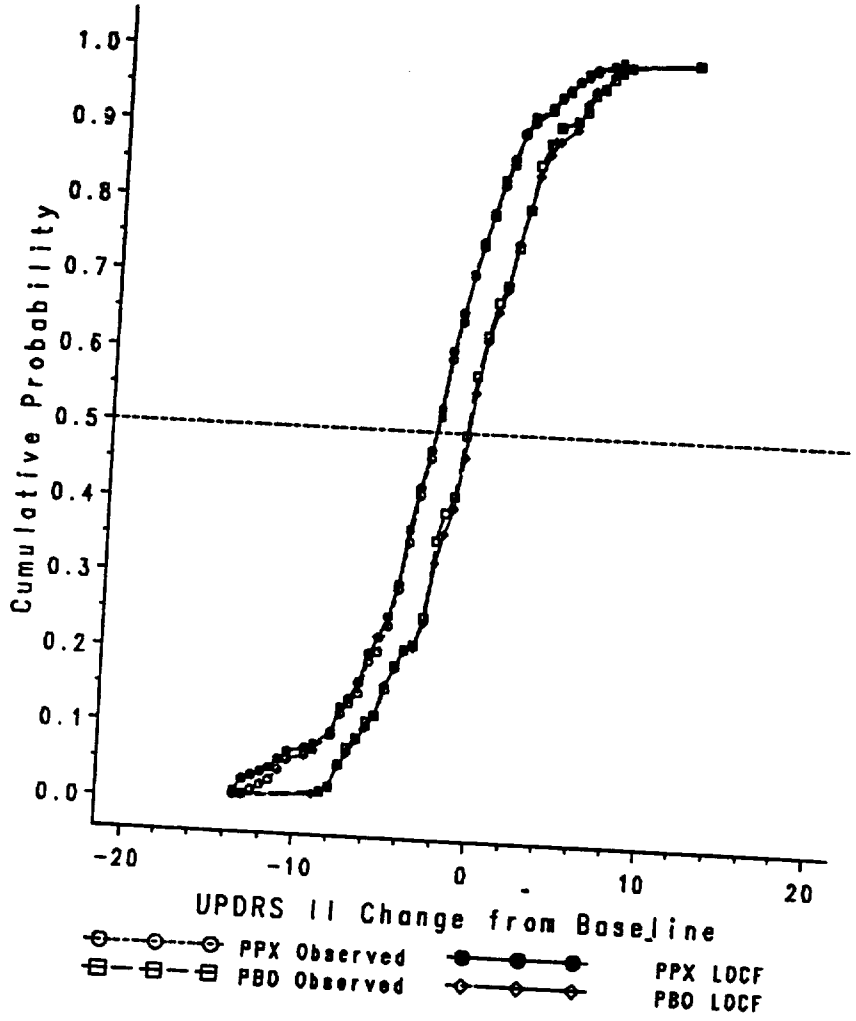


FIGURE 13.2.1 Average UPDRS Part II 'off' and 'on' Means by Visit.

Observed Cases Analysis

Ogive Curve of UPDRS II Change from Baseline -- M/2730/0010



Sponsor's Figure 9.3.1.2.2:1 (next page) shows the average Part II scores (on only) by visit for the two treatment groups.

Sponsor's Figure 9.3.1.2.1:1 (next page) shows the average Part II scores (off only) by visit for the two treatment groups.

For Part II, on, the difference in the treatment groups came from a number of components, with the largest components being: Turning in Bed, Cutting Food, and Hygiene.

For Part II, off, the difference in the treatment groups came from a number of components, with the largest components being: Freezing When Walking, Cutting Food, Walking, Hygiene, Turning in Bed, and Tremor.

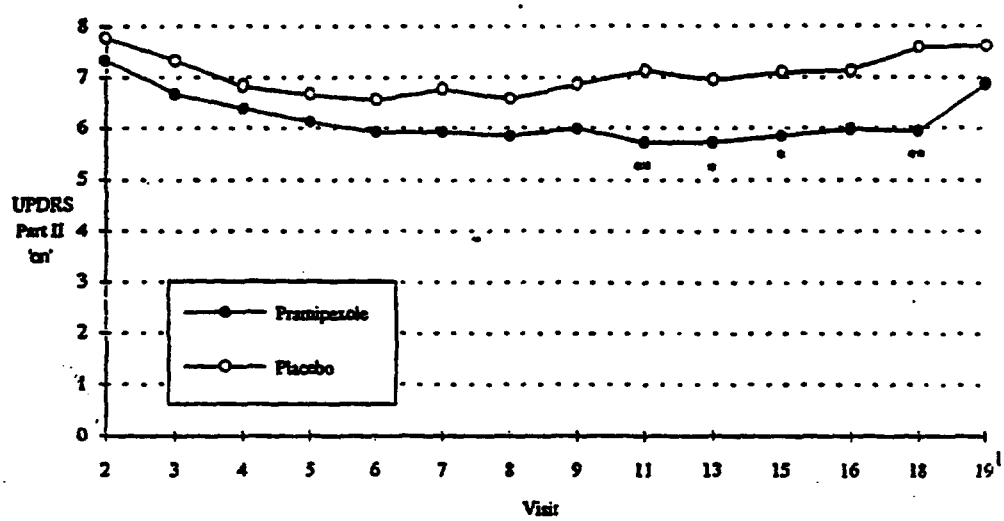


FIGURE 9.3.1.2.2:1 UPDRS Part II 'on' Means by Visit.

Last Observation Carried Forward Analysis

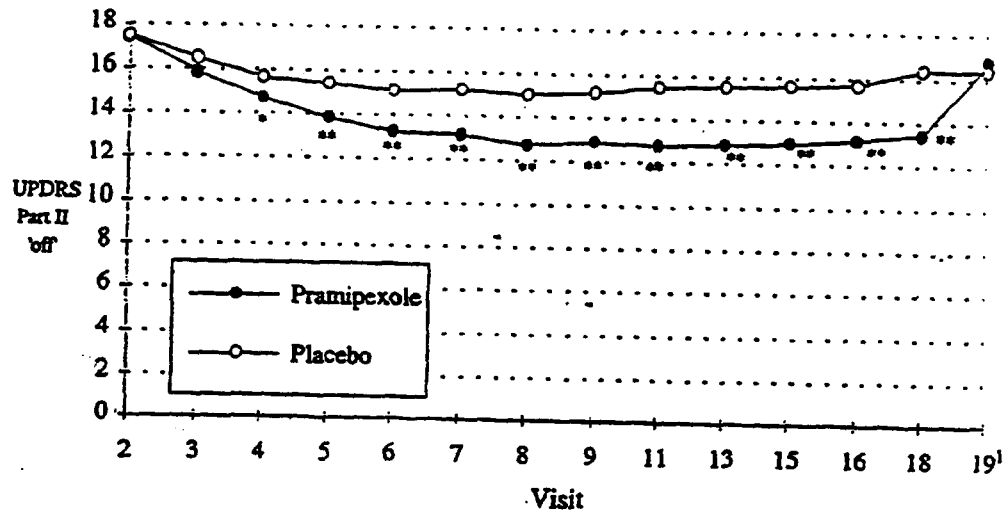


FIGURE 9.3.1.2.1:1 UPDRS Part II 'off' Means by Visit.

Last Observation Carried Forward Analysis

3. UPDRS Part III

Sponsor's Figure 9.3.1.1.2:1 (next page) shows the average Part III scores by visit for the two treatment groups. The sponsor provided cumulative distribution functions for the treatment groups and these are shown on the page after that.

Sponsor's Figure 13.2.2 (next page) shows the observed case results for the same comparison.

The protocol specified analysis was a comparison between treatment groups of change from baseline to final maintenance visit (LOCF), adjusted by center and center-by-treatment interaction. The results of this analysis were highly statistically significant. Consistency across other analyses of the same outcome variable can be seen below:

	LOCF Change from Baseline to Final Maintenance Visit	OC Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (Visits 11-18)	OC Area Under the Curve over Maintenance Visits (Visits 11-18)
Pramipexole	-5.6	-5.7	-114	-126
Placebo	-2.8	-3.7	-64	-75
p-value	0.01	0.08	0.01	0.02

For Part III, the difference in the treatment groups came from a number of components, with the largest components being: Leg Agility, Finger Taps, Rigidity, and Hand Movements.

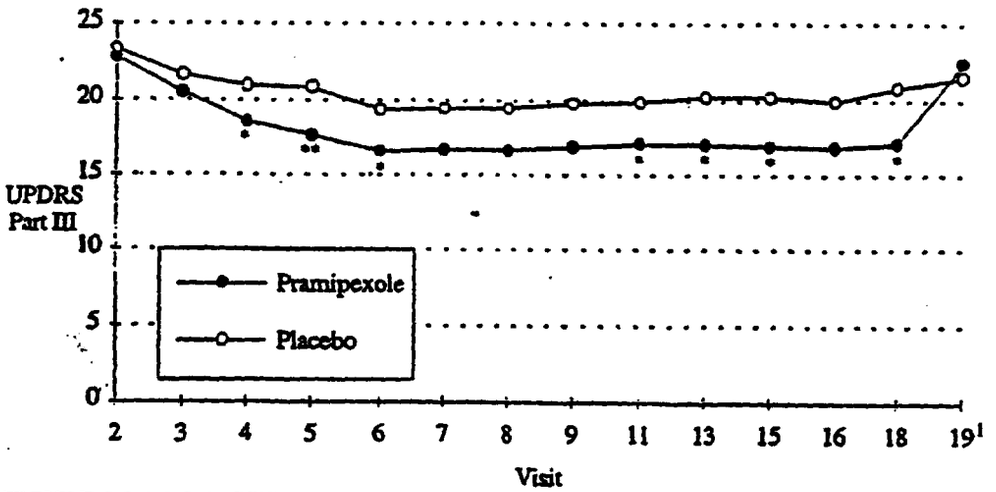


FIGURE 9.3.1.1.2:1 UPDRS Part III Means by Visit.

Last Observation Carried Forward Analysis

Source Data: TABLE 9.3.1.1.2:1

[1] Observed Cases Analysis Only

* $p \leq 0.05$ ** $p \leq 0.01$

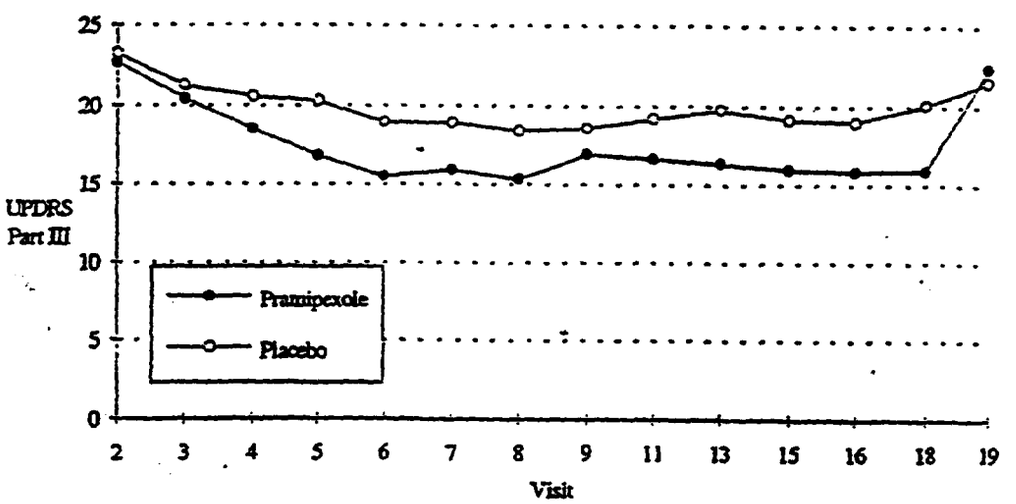
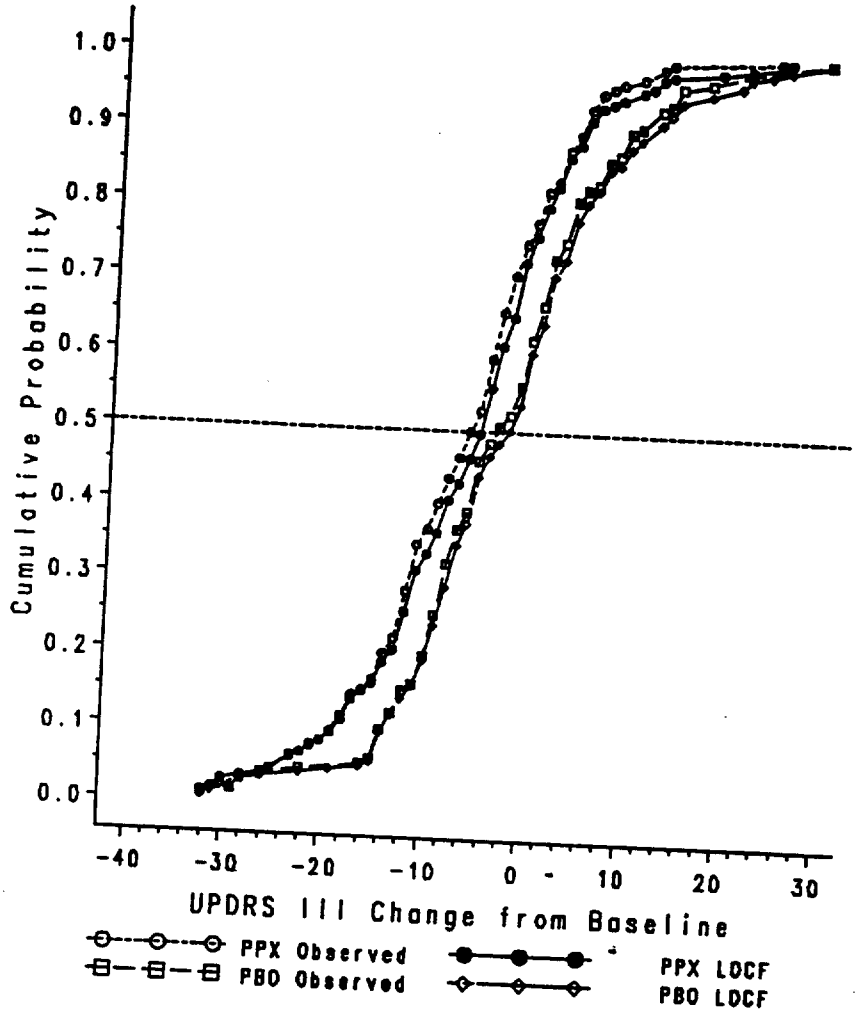


FIGURE 13.2.2 UPDRS Part III Means by Visit.

Observed Cases Analysis

Ogive Curve of UPDRS III Change from Baseline -- M/2730/0010



4. UPDRS Part I

Sponsor's Figure 9.3.1.2.10:1 (next page) shows the average Part I scores by visit for the two treatment groups. No real difference between groups is seen.

5. UPDRS Part IV

Sponsor's Figure 9.3.1.2.11:1 (next page) shows the average Part IV scores by visit for the two treatment groups.

6. Parkinson Dyskinesia Scale

Sponsor's Figure 9.3.1.2.12:1 (next page) shows the average PDS scores by visit for the two treatment groups. There is an interesting peak in scores for pramipexole patients at visit 9. Note that the scores that contribute to this visit average score represent a mix of experience on a new higher dose for patients who were increased to the maximum allowed dose at visit 8 as well as experience on a stable dose for patients who did not reach the highest dose and were moved to visit 9 after skipping intermediate visits. This might tell us that the highest dose caused a significant increase in dyskinesia in those patients that achieved that dose, an increase that was diluted out by the scores of patients that did not go to that level. Presumably, patients could have the dose lowered at visit 9 back down to the next highest dose.

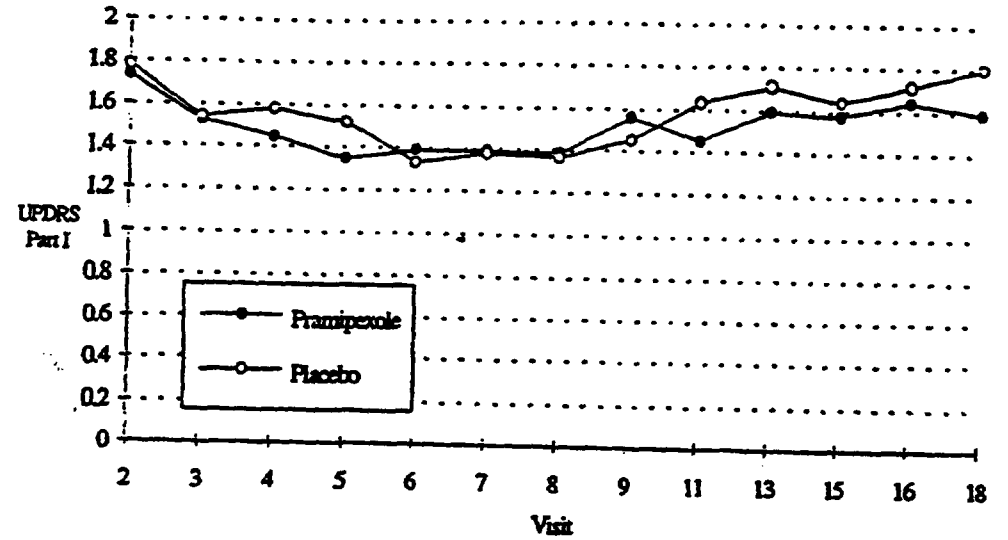


FIGURE 9.3.1.2.10:1 UPDRS Part I Means by Visit.

Last Observation Carried Forward Analysis

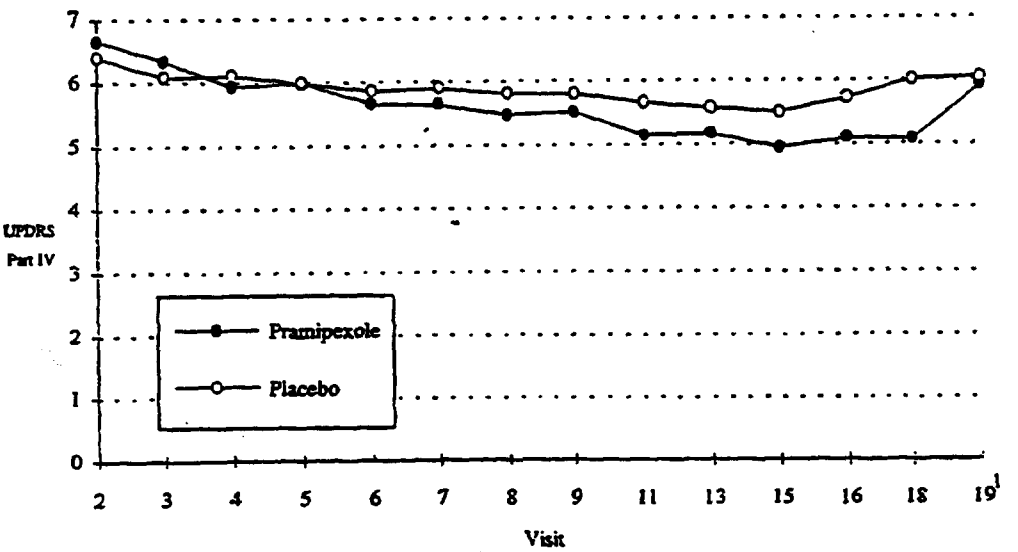


FIGURE 9.3.1.2.11:1 UPDRS Part IV Means by Visit.

Last Observation Carried Forward Analysis

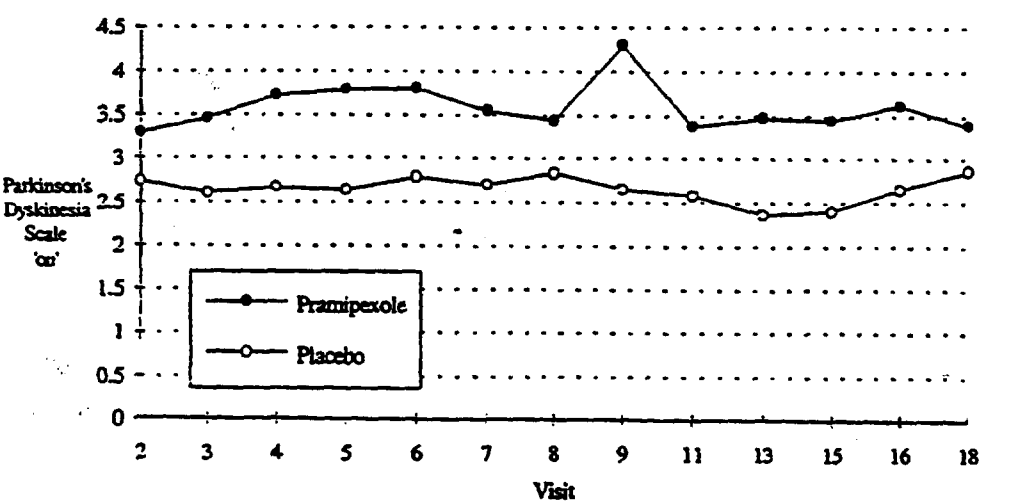


FIGURE 9.3.1.2.12:1 Parkinson Dyskinesia Scale 'on' Means by Visit.

7. Modified Schwab-England Disability Scale

This scale was completed for both the on and off periods.

Sponsor's Figure 9.3.1.2.6:1 (next page) shows the average "off" scores by visit for the two treatment groups.

Sponsor's Figure 9.3.1.2.7:1 (next page) shows the average "on" scores by visit for the two treatment groups.

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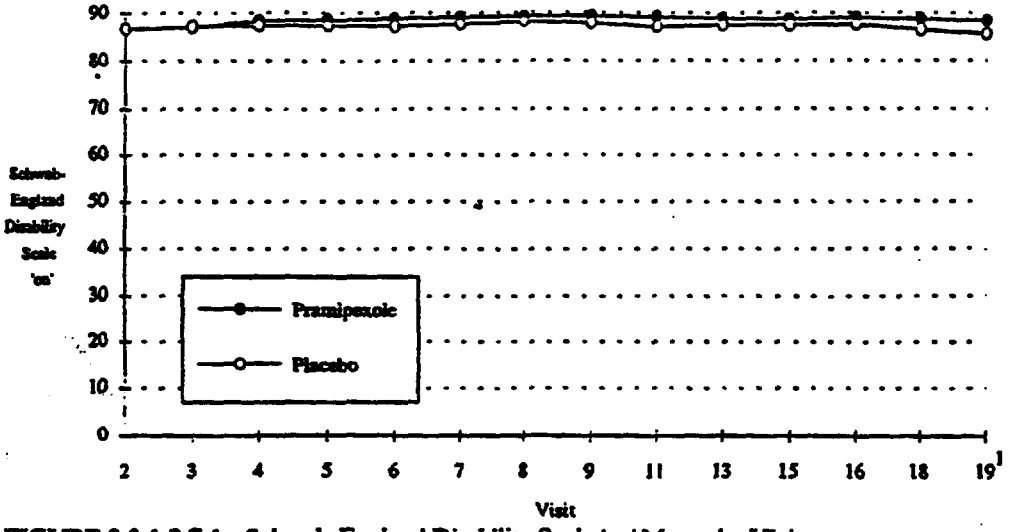

FIGURE 9.3.1.2.7:1 Schwab-England Disability Scale 'on' Means by Visit.
Last Observation Carried Forward Analysis

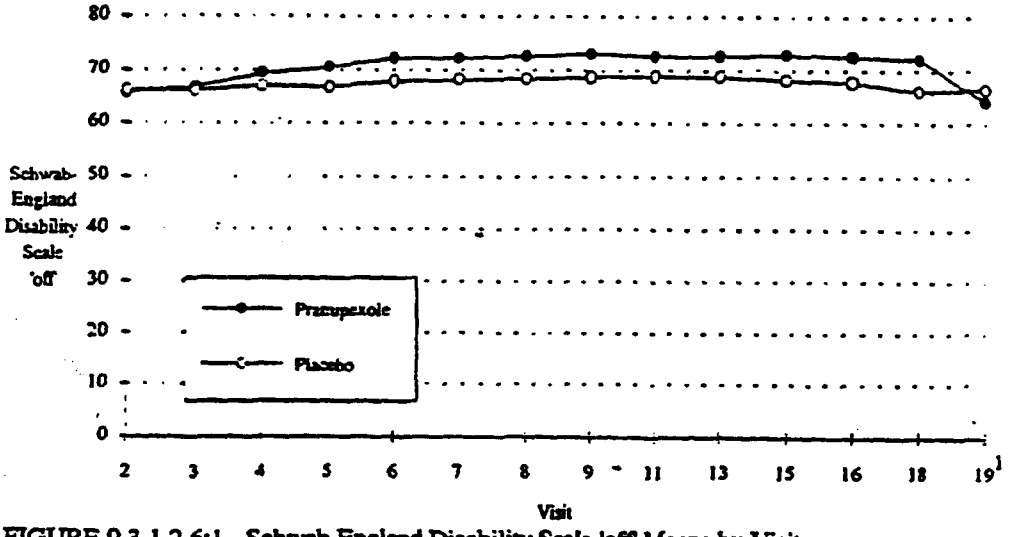

FIGURE 9.3.1.2.6:1 Schwab-England Disability Scale 'off' Means by Visit.
Last Observation Carried Forward Analysis

8. Modified Hoehn and Yahr Scale

This scale was completed for both the on and off periods.

Sponsor's Figure 9.3.1.2.8:1 (next page) shows the average "off" scores by visit for the two treatment groups.

Sponsor's Figure 9.3.1.2.9:1 (next page) shows the average "on" scores by visit for the two treatment groups.

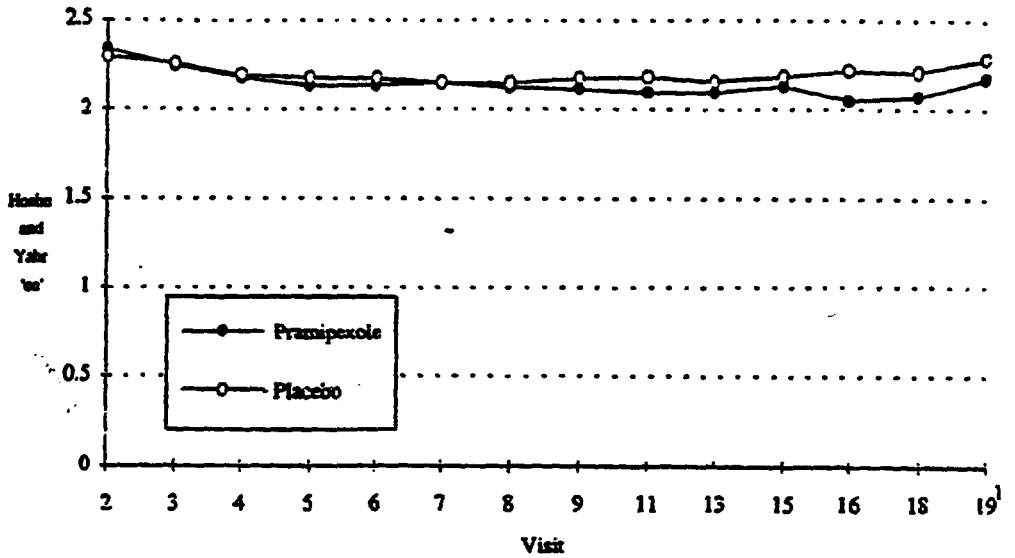

FIGURE 9.3.1.2.9:1 Modified Hoehn and Yahr Scale 'on' Means by Visit.
Last Observation Carried Forward Analysis

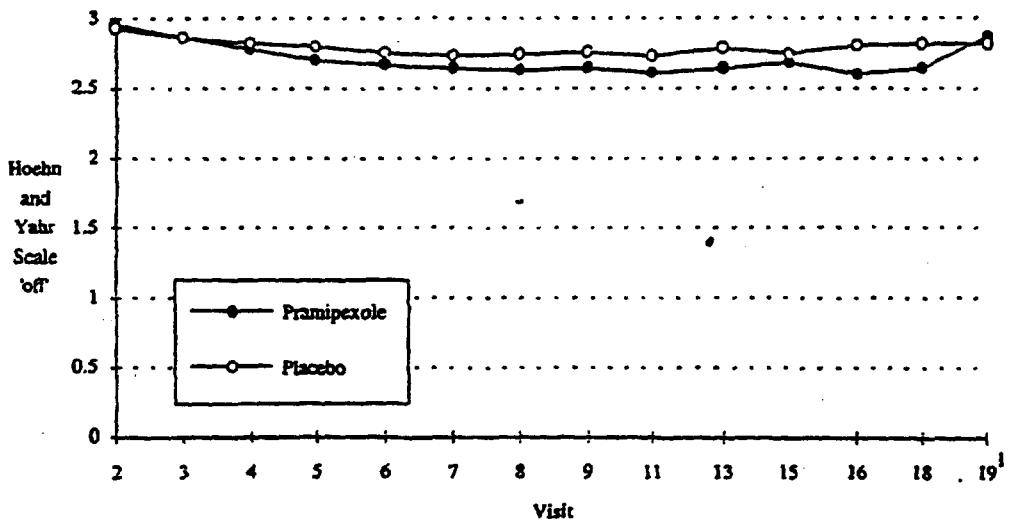

FIGURE 9.3.1.2.8:1 Modified Hoehn and Yahr Scale 'off' Means by Visit.
Last Observation Carried Forward Analysis

9. Timed Walking Test

Sponsor's Figure 9.3.1.2.13:1 (next page) shows the average times by visit for the two treatment groups. The curves cross several times, with no overall differences emerging.

10. Average Severity Level of Off Periods From Patient Diaries

Sponsor's Figure 9.3.1.2.4:1 (next page) shows the average severity score by visit for the two treatment groups.

Dosage of L-Dopa, Other Concomitant Anti-Parkinson's Drugs

By protocol, during the maintenance phase, the dose of L-dopa could be adjusted downward if dyskinesias, hallucinations, or psychiatric side effects developed.

Dosage data on L-dopa was collected at each visit, but the sponsor states (without further explanation on p95 of the study report) that problems arose with interpreting CRF data on dosage. "Ultimately it was decided that the CRFs for baseline and final maintenance visit had to be individually reviewed by a sponsor's medical monitor. This review was conducted while the treatment code was still blinded. Because this review was very time consuming, only data from these two visits were collected."

Sponsor's Table 9.3.1.2.5:1 (next page) gives the baseline visit mean dosage, the final maintenance visit mean dosage, and the unadjusted and adjusted change from baseline to final maintenance visit. The pramipexole group reduced L-dopa dosage by 25% while the placebo group reduced dosage by 6% ($p \leq 0.0001$).

For each visit during the study, the CRF contained a box that the investigator could check if there had been no change in L-dopa dosage since the previous visit. It is informative to know the proportion of patients in each treatment group that had no change in L-dopa dosage throughout the study: 24% pramipexole, 46% placebo. Given the protocol-specified rules for changing L-dopa dose, the different proportions of patients requiring L-dopa dosage changes would be consistent with the 19% higher frequency of dyskinesias and the 15% higher frequency of

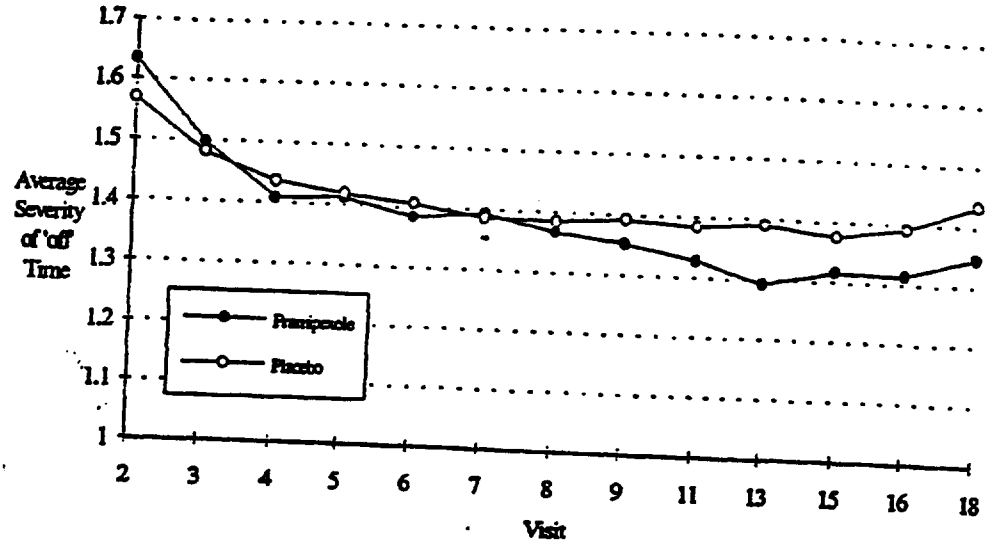

FIGURE 9.3.1.2.4:1 Average Severity of 'off' Time by Visit.

Last Observation Carried Forward Analysis

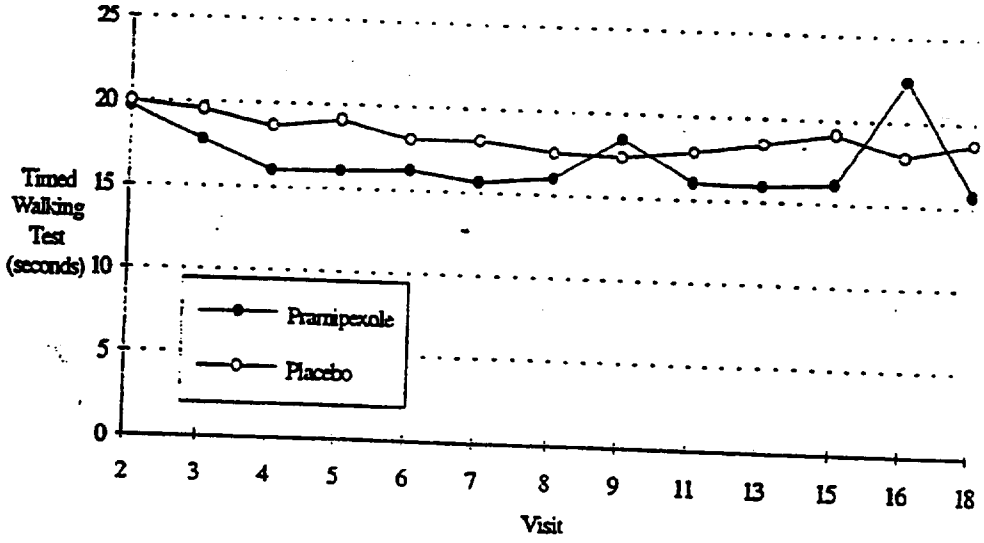

FIGURE 9.3.1.2.13:1 Timed Walking Test Means by Visit.

Last Observation Carried Forward Analysis

TABLE 9.3.1.2.5:1 Levodopa Dose (mg) Mean (S.D.) Change from Baseline.

Last Observation Carried Forward Analysis

	Baseline	Final Maintenance Visit	Unadjusted Change from Baseline to Final Visit on Maintenance	Adjusted[1] Change from Baseline to Final Visit on Maintenance
Pramipexole n = 179	843.37 (578.86)	653.89 (540.91)	-209.48 (272.55)	-229.68
Placebo n = 172	819.19 (466.08)	773.98 (453.72)	-45.20 (115.86)	-43.20
p-value				≤ 0.0001

Source Data: Appendix 15.9.2 STATDOC 4.7.1 & 4.7.2

1 Adjusted by center and center-by-treatment interaction (as per protocol).

hallucinations in the pramipexole group.

Changes in deprenyl, anticholinergic, and amantadine dosing during the trial were not allowed by protocol. Any changes should have been reported as protocol violations. No protocol violations on this issue are recorded in the study report.

In the September 27 submission, the sponsor reported that small numbers of patients did have their dosages of these drugs changed during the trial. However, the numbers are so small as to be insignificant.

The importance of the above questions should be obvious. All alternative explanations for a favorable effect in the pramipexole group must be ruled out.

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Table A4
Number of patients received Amantadine, Deprenyl, and Anti-Cholinergics
M/2730/0010

		Pramipexole	Placebo
	Total N randomized	181	178
Amantadine	Took Drug During Study*	33	25
	Stopped Drug During Study	1	0
	Increased Dosage	0	2
	Decreased Dosage	4	1
	Stopped/Restarted Drug	1	0
	No Change	27	22
Deprenyl	Took Drug During Study*	103	93
	Stopped Drug During Study	4	0
	Increased Dosage	1	0
	Decreased Dosage	5	2
	Stopped/Restarted Drug	1	1
	No Change	92	90
Anti-Cholinergics	Took Drug During Study*	25	26
	Stopped Drug During Study	0	0
	Increased Dosage	1	4
	Decreased Dosage	5	6
	Stopped/Restarted Drug	1	0
	No Change	18	16

* Not include patients who were on such drugs but stopped them prior to enrollment in the study, also does not include patients who started the drugs after the end of the maintenance dose phase.

D. Plasma Levels

1. Plasma pramipexole levels were collected in order to assess mean population PK parameters and their variance in this population. The results of this analysis are to be summarized in a separate report.

2. Plasma levels of concomitant L-dopa, deprenyl, and anticholinergics were not measured during the conduct of this trial.

Only 26 patients in the pramipexole group were using anticholinergic medications. 97 patients in the pramipexole group were using deprenyl. By design, all patients were using L-dopa.

E. Adverse Events

Sponsor's Table 11:1 shows the AEs with an incidence of 10% or greater in the pramipexole group. Only dyskinesia and hallucinations were statistically significantly different between the two treatment groups. Dose reductions of study medication controlled most cases of dyskinesia and hallucination.

Most AEs were typical of dopamine agonists and were mild to moderate in severity.

One pramipexole patient experienced repeated elevations of LFTs and was discontinued. Later rechallenge was tolerated. When comparing pramipexole and placebo patients with respect to lab change-from-baseline, statistically significant differences between the treatment groups were noted for: SGOT, SGPT, CPK, and LDH. The sponsor believes all these lab changes could be explained by pramipexole induced dyskinesias.

TABLE 11:1 Summary of the Most Common Adverse Events for the Pramipexole and Placebo Treatment Groups

	Pramipexole N=181		Placebo N=179		
	Number	Percent	Number	Percent	P Value
Dyskinesia	113	62	77	43	0.0003
Asymptomatic orthostatic hypotension	102	56	108	60	NS
Dizziness	75	41	67	37	NS
Parkinsonism aggravated	64	35	61	34	NS
Pain	62	34	60	34	NS
Insomnia	51	28	49	27	NS
Nausea	44	24	50	28	NS
Hallucinations	38	21	10	6	<0.0001
Symptomatic orthostatic hypotension	30	17	23	13	NS
Confusion	23	13	18	10	NS
Constipation	23	13	22	12	NS
Upper respiratory tract infection	21	12	29	16	NS
Somnolence	19	11	16	9	NS

Source Data: TABLE 13.1.16

F. Conclusions

Pramipexole-treated patients, on average, saw a larger change-from-baseline on Part II of the UPDRS than their counterparts treated with placebo. This difference in average change-from-baseline was small, but highly statistically significant.

Pramipexole-treated patients, on average, also saw a larger change-from-baseline on Part III of the UPDRS than their counterparts treated with placebo. This difference in average change-from-baseline was again small, but highly statistically significant.

The protocol called for a statistically significant result on each of these outcome measures (a dual outcome) in order for a positive result to be declared for the trial as a whole.

Pramipexole-treated patients, on average, also saw a larger change-from-baseline in percentage of waking hours spent in the "off" state compared to their counterparts treated with placebo. The shift from "off" could have been to "on with dyskinesia" and not simply to "on." This issue could be resolved by patient diaries, but not by CRFs. The sponsor has not shown an interest in pursuing this further.

The 3 improvements above came at a cost of more hallucinations and more dyskinesias as demonstrated in AE listings. In the UPDRS scale, hallucinations are only a component of Part I and dyskinesias are only a component of Part IV. The pertinent items from Parts I and IV for hallucinations and dyskinesias are not analyzed separately.

In short, Part III of the UPDRS may be a good scale for measuring Parkinson's Disease, but it may not be a good scale for measuring the patient population under study here: patients with motor fluctuations after 2-3 years of L-dopa therapy. Dyskinesias are a part of the motor fluctuations and are not included in Part III. The optimal state for these patients probably represents a fine balance in their dopaminergic states. Each patient will have a preference toward one end of the spectrum: too much dopaminergic stimulation with hallucinations, dyskinesias, but better mobility versus too little dopaminergic stimulation with decreased mobility. The labeling should clarify the trade off between the two states.

There is one last comment, more for the record than anything else. That is, the evidence accrued in this study, viewed in isolation, provides an alternate explanation for better performance in the pramipexole group than the use of pramipexole. To assume that pramipexole explains the better performance, one has to assume (reasonably I think) that chronic L-dopa in this patient population does not **cause** the "off" state and does not **worsen** performance on Parts II and III of the UPDRS. If L-dopa did these things, then the mere fact that dosage of L-dopa was reduced more in one group than the other could explain the better performance in one group. The prevalent theory, however, holds that the "on-off" phenomena and the decreased performance that occur after chronic use of L-dopa are all due to **decreased responsiveness to L-dopa.** It would then follow logically that the decreased average dose of L-dopa seen in one treatment group would serve to worsen, not improve that group's outcomes; improvement in that group could then be attributed to the addition of pramipexole (c.f. drug holidays in Parkinson's disease).

In short, pramipexole **substituted for L-dopa** resulted in less off time, better scores on UPDRS Parts II and III, more hallucinations, and more dyskinesias than when placebo was added to L-dopa.

RATING SCALES

Pramipexole 00679A – M2730/0010

PATIENT INITIALS (3)	DATE OF VISIT (month/day/year)	VISIT	INVEST NO	SHEET NO	PATIENT NO	PAGE
		2			1001	19

The same person should conduct each part of this evaluation throughout the trial.

PARKINSON DYSKINESIA SCALE (This exam MUST be completed when the patient is in an 'on' period)

This examination should be completed approximately two to three hours following a dose of decarboxylase inhibitor / levodopa therapy but prior to the initial dose of trial drug.

TIME OF EXAMINATION: ____ : ____ (24-hour clocktime) RATER'S INITIALS (3): ____ ____ ____

INTENSITY OF DYSKINESIA DURING 'ON' PERIOD:
Rate the patient's present intensity of dyskinesia during an 'on' period by using the following scale. If the patient is in an 'off' period, wait until the patient enters an 'on' period.

0 = Normal
1 = Intermittent
2 = Generalized, mild but continuous, may not be obvious to untrained observer
3 = Moderate, generalized, definitely noticeable to untrained observer
4 = Incapacitating

	0	1	2	3	4
Head	☐	☐	☐	☐	☐
RUE	☐	☐	☐	☐	☐
LUE	☐	☐	☐	☐	☐
RLE	☐	☐	☐	☐	☐
LLE	☐	☐	☐	☐	☐
Trunk	☐	☐	☐	☐	☐

MODIFIED SCHWAB-ENGLAND DISABILITY SCALE RATER'S INITIALS (3): ____ ____ ____

Rate the patient's best 'on' period and worst 'off' period during the past week by checking one box under each column.

ON	OFF	
☐	☐	100% - Completely independent. Able to do all chores without slowness, difficulty, or impairment. Essentially normal. Unaware of any difficulty.
☐	☐	90% - Completely independent. Able to do all chores with some degree of slowness, difficulty, and impairment. Might take twice as long. Beginning to be aware of difficulty.
☐	☐	80% - Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
☐	☐	70% - Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
☐	☐	60% - Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors: some impossible.
☐	☐	50% - More dependent. Help with half, slower, etc. Difficulty with everything.
☐	☐	40% - Very dependent. Can assist with all chores, but few alone.
☐	☐	30% - With effort, now and then does a few chores alone or begins alone. Much help needed.
☐	☐	20% - Nothing alone. Can be a slight help with some chores. Severe invalid.
☐	☐	10% - Totally dependent, helpless, complete invalid.
☐	☐	0% - Vegetative functions such as swallowing, bladder, and bowel functions are not functioning. Bedridden.

MODIFIED HOEHN AND YAHR SCALE RATER'S INITIALS (3): ____ ____ ____

Indicate the patient's Parkinson stage for both 'on' and 'off' periods by checking one box for 'on' and one box for 'off' below.

STAGE	ON	OFF	
0	☐	☐	No signs of disease
1	☐	☐	Unilateral disease
1.5	☐	☐	Unilateral plus axial involvement
2	☐	☐	Bilateral disease, without impairment of balance
2.5	☐	☐	Mild bilateral disease, with recovery on pull test
3	☐	☐	Mild to moderate bilateral disease; some postural instability; physically independent
4	☐	☐	Severe disability; still able to walk or stand unassisted
5	☐	☐	Wheelchair bound or bedridden unless aided

WHITE COPY:
CANARY COPY: INVESTIGATOR

TREATMENT EVALUATION					Pramipexole 00679A – M2730/0010	
PATIENT INITIALS (3)	DATE OF VISIT (month/day/year)	VISIT	INVEST NO	SHEET NO	PATIENT NO	PAGE
		2			1001	20

Last Dose	Date (month/day/year)	Time (24-hour clocktime)	Dose (e.g. 25 / 100)	Number of Tabs / Caps
Decarboxylase Inhibitor / Levodopa				

TIMED WALKING TEST TIME OF EXAMINATION: ____ : ____ (24-hour clocktime)

(This exam MUST be completed when the patient is in an 'on' period)

The Timed Walking Test should be completed approximately two to three hours following a dose of decarboxylase inhibitor / levodopa therapy but prior to the initial dose of trial drug.

Record the time needed to complete the test to the nearest whole second.

Time to complete: _____min. _____sec.

Was the use of a walker required? 0☐No 1☐Yes

Completed test within 10 minutes? 0☐No 1☐Yes

Time Interval	24-hour Clocktime	SUPINE VITAL SIGNS (after 5 minutes of quiet rest) Systolic/Diastolic BP (mm Hg)	Pulse (bpm)	STANDING VITAL SIGNS (after 1 minute standing) Systolic/Diastolic BP (mm Hg)	Pulse (bpm)	ORTHOSTATIC HYPOTENSION* (refer to protocol for definition)
Pre-Dose	___:___	/		/		0☐None 1☐Symptomatic* 2☐Asymptomatic*
Administer Trial Medication	___:___	Administer the contents of the first blister for Dose 1.				
2 Hours after Administration	___:___	/		/		0☐None 1☐Symptomatic* 2☐Asymptomatic*

* If orthostatic hypotension is present, record on the "Adverse Event Report" form. Indicate symptomatic or asymptomatic. If symptomatic, record specific symptoms.

WHITE COPY:
CANARY COPY: INVESTIGATOR

Appendix D

Daily Patient Records

The patient will record when "on-off" disabilities occur during waking hours. "On" periods are periods with good motor function, while "off" periods are periods when patients move slowly or not at all. In addition to recording the specific times of on and off periods during the day, patients should also score the degree of disability during "off" periods using the following 4-point scale:

1. (mild slowness, stiffness, or resting tremor)

2. (moderate slowness, stiffness, or resting tremor, but remaining functionally independent)

3. (severe disability, the patient requiring some help in several activities)

4. (immobile, severely incapacitated and totally dependent on others)

"On" periods with dyskinesia (i.e., when patients are able to move, but are troubled by involuntary or unintentional movements) will also recorded.

The patient will be asked to record activity for one-hour periods during waking hours. If more than one activity applies (e.g., "on" and "on" with dyskinesia), record the activity which predominated during the one hour period.

The number of hours off per day divided by the total number of waking hours will be averaged over each week of assessment and recorded on case report forms. In addition, the disability score during "off" periods per day will also be averaged over each week of assessment. "On-off" periods for at least 2 full days prior to the next clinic visit should be recorded by the patient within the diary.

Guardians, family members, or nursing personnel, etc., may assist the patient in completing the daily patient record. If there are errors, inconsistencies, discrepancies, or missing information, these should be resolved at the time of the clinic visit.

DAILY PATIENT RECORD			SND 919 00655
PATIENT INITIALS (3)	DATE RECORD COMPLETED (month/day/year)	VISIT (dispensed)	PATIENT NUMBER
		2	

INSTRUCTIONS:

Circle the appropriate description for each one-hour period during the day. If more than one applies, circle the clinical status description which predominated (lasted 30 minutes or more) during each period.

ON	= Good motor function
ON WITH DYSKINESIAS	= Able to move, but troubled by involuntary or unintentional movements
OFF	= Able to move slowly or not at all.

For each "OFF" period, check the highest degree of severity experienced. Four degrees of severity are defined below:

1	=	mild slowness, stiffness, or resting tremor
2	=	moderate slowness, stiffness, or resting tremor, but remaining functionally independent
3	=	severe disability, requiring assistance in several activities
4	=	immobile, severely incapacitated, and totally dependent on others

TIME INTERVAL	CLINICAL STATUS				Severity of "OFF" period			
					1	2	3	4
MIDNIGHT - 1 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
1 AM - 2 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
2 AM - 3 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
3 AM - 4 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
4 AM - 5 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
5 AM - 6 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
6 AM - 7 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
7 AM - 8 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
8 AM - 9 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
9 AM - 10 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
10 AM - 11 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
11 AM - 12 NOON	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
12 NOON - 1 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
1 PM - 2 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
2 PM - 3 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
3 PM - 4 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
4 PM - 5 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
5 PM - 6 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
6 PM - 7 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
7 PM - 8 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
8 PM - 9 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
9 PM - 10 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
10 PM - 11 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
11 PM - 12 MIDNIGHT	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
FOR OFFICE USE ONLY								
TOTAL NUMBER OF HOURS	24 - _____ asleep = _____ waking hrs.							

M/2730/0010	
Name and Address of Investigator	Number of Patients Randomized at Site
Adler, Charles H, M.D., Ph.D. Assistant Professor Mayo Clinic Scottsdale 13400 East Shea Boulevard Scottsdale, AZ 85259	13
Comella, Cynthia, M.D. Dept. of Neurological Sciences Rush Medical College Rush-Presbyterian St. Luke's Medical Center 1725 West Harrison Chicago, IL 60612	12
Curran, Terry, M.D. (6/24/93-12/12/93) Goodridge, Alan, M.D. (12/13/93-present) Division of Neurology The General Hospital Health Sciences Centre 300 Prince Philip Drive St. John's Newfoundland A1B 3V6	12
Eidelman, Benjamin, M.D. Acting Chairman, Dept. of Neurology University of Pittsburgh 337 East Scaife Hall Pittsburgh, PA 15261	11
Factor, Stewart A, D.O. Assistant Professor of Neurology Dept. of Neurology Albany Medical Center New Scotland Avenue Albany, NY 12208	20
Fazzini, Enrico, D.O. New York University Medical Center 530 First Avenue, Suite 9Q New York, NY 10016	20
Friedman, Joseph, M.D. Department of Neurology Roger Williams General Hospital 825 Chalkstone Avenue Providence, RI 02908	8

M/2730/0010	
Name and Address of Investigator	Number of Patients Randomized at Site
Golbe, Lawrence I, M.D. Clinical Academic Building 125 Patterson Street Neurology Suite 6th Floor New Brunswick, NJ 08901-1977	13
Guttman, Dr. Mark 377 Church St., Suite 407 Markham, Ontario L6B 1A1 Canada	22
Hubble, Jean, M.D. Assistant Professor Department of Neurology Kansas University Medical Center 39th and Rainbow Blvd. Kansas City, KS 66103	16
Jankovic, Joseph, M.D. Professor of Neurology Baylor College of Medicine Dept. of Neurology 6550 Fannin Street, Suite 1801 Houston, TX 77030	14
Karp, Jeffery, M.D. Tampa Bay Medical Research 3253 McMullen Booth Road, Suite 200 Clearwater, FL 34621-2010	14
King, Dr. David B 5523 Spring Garden Road, Suite 208 Halifax, Nova Scotia Canada B3J 3T1	20
Lieberman, Abraham, M.D. Chief, Motor Disorders St. Joseph Hospital Barrow Neurological Institute 222 W. Thomas Road, Suite 401 Phoenix, AZ 85013	20
Montgomery, Erwin, M.D. Associate Prof., Dept. of Neurology University Physicians Neurology Clinic 1745 North Campbell Avenue Tucson, AZ 85719	10

M/2730/0010	
Name and Address of Investigator	Number of Patients Randomized at Site
Olanow, C Warren, M.D. (1/19/93-6/12/94) Hauser, Robert A, M.D. (6/13/94-present) Assistant Professor of Neurology Department of Neurology Harbour Side Medical Tower 4 Columbia Drive, Suite 410 Tampa, FL 33606	12
Paulson, George, M.D. Chairman, Department of Neurology 452 Means Hall Ohio State Univ. School of Medicine 1655 Upham Drive Columbus, OH 43210	7
Perlmutter, Joel S, M.D. Assoc. Professor of Neurology Washington Univ. School of Medicine Dept. of Neurology 660 South Euclid P. O. Box 8111 St. Louis, MO 63110	6
Pfeiffer, Ronald F, M.D. (3/17/93-6/19/94) Bertoni, John, M.D.,Ph.D. (6/20/94-present) University of Nebraska Medical Center Division of Neurology 42nd Street and Dewey Avenue Omaha, NE 68105	12
Pincus, Jonathan, M.D. Chairman, Dept. of Neurology Georgetown University Hospital 3800 Reservoir Road, N.W. Suite 1 Bles Washington, D.C. 20007	10

M/2730/0010	
Name and Address of Investigator	Number of Patients Randomized at Site
Reich, Stephen G, M.D. Asst. Professor of Neurology Johns Hopkins University School of Medicine Outpatient Center 601 N. Caroline St., Suite 5070 Baltimore, MD 21282	5
Richter, Ralph, M.D. Professor of Neurology St. John's Doctors' Building 1705 E. 19 Street, Suite 406 Tulsa, OK 74104	20
Stoessl, Dr. John Dept. of Clinical Neurological Sciences University Hospital 339 Windermere Road London, Ontario N6A 5A5	14
Tetrud, James, M.D. Parkinson's Institute 1170 Morse Avenue Sunnyvale, CA 94089	18
Waters, Cheryl H, M.D., FRCP(C), FACP Assistant Professor of Neurology Chief, Division of Movement Disorders USC Movement Disorder Clinic Department of Neurology 1510 San Pablo St., Suite 615 Los Angeles, CA 90033	16
Weiner, William, M.D. 1501 N.W. 9th Avenue Parkinson Building Department of Neurology Miami, FL 33136	15

Studies 19 and 22

Title: A double-blind, placebo-controlled, randomized, multi-center study to asses the effects, safety, and tolerance of Pramipexole with concomitant treatment of levodopa (and decarboxylase inhibitor) in advanced Parkinson's disease.

Investigators:

Center	Location	Investigator(s)
19		
2	Austria	Schnaberth Pinter
7	Germany	Conrad
4	Germany	Gehlen
6	Germany	Glab
10	Germany	Kolmel
9	Germany	Oertel
5	Germany	Poewe
22		
1	Denmark	Boas
2	Denmark	Boesen
3	Denmark	Boisen
4	Denmark	Dupont
5	Denmark	Hansen
6	Denmark	Sorensen / Mogensen
7	Denmark	Jensen / Magnussen
8	Denmark	Mikkelsen
9	Denmark	Worm-Petersen

Objectives: The primary objective to assess the effect of Pramipexole (up to 5 mg) on Parkinsonian symptoms versus placebo in patients with advanced Parkinson's disease while on concomitant treatment with levodopa (and decarboxylase inhibitor). Effect is defined as a significant change in the total score of the Unified Parkinson's Disease Rating Scale (UPDRS).

The secondary objective is to asses the safety and tolerance of Pramipexole in variable dose combinations with levodopa (and decarboxylase inhibitor).

Study Design: Multi-center, randomized, prospective, ascending dose, double-blind, placebo controlled study.

Treatments: Ascending dose in weeks one through seven followed by a 4 week maintenance period and a one week taper to discontinue. The maximum dose achieved will be the maximum dose without the patient suffering from intolerable side effects (maximum of 5.0 mg per day in divided doses i.e. 1.25 mg QID).

Treatment(s)	Pramipexole or Placebo	
Week	**Dosage**	**Total Daily Dose**
1	2 x 0.1 mg	0.2 mg
2	4 x 0.1 mg	0.4 mg
3	4 x 0.25 mg	1.0 mg
4	4 x 0.5 mg	2.0 mg
5	4 x 0.75 mg	3.0 mg
6	4 x 1.0 mg	4.0 mg
7	4 x 1.25 mg	5.0 mg

Please see Table 1 and 2 for the Time and Events for studies 19 and 22, respectively.

Inclusion Criteria:

1. Men; women of non-child bearing potential;
2. Outpatients and Inpatients
3. Age: 18-75 years (Age: 30 - 75 years in study 22).
4. Patients with advanced idiopathic Parkinson's disease (classification according to ICD 9: 332.0) corresponding to stages II-IV according to the classification of Hoehn and Yahr.
5. Patients in whom the individual optimal dosage of levodopa (and decarboxylase inhibitor) causes disturbances such as akinesia, dyskinesia, dystonias, fluctuations.
6. Written informed consent.

Patients were to be maintained on their individual dose of L-dopa (and DCI).
If anticholinergics, amantadine, L-deprenyl, or tricyclic / tetracyclic antidepressant medications were used they should be maintained at a stable dose throughout the trial.

Exclusion Criteria:

1. Symptomatic forms of Parkinson syndrome (e.g. drug induced parkisonism, post-encephalitic parkisonism, Shy-Drager syndrome, Steele-Richardson-Olszewski-Syndrome).
2. Severe dementia
3. epilepsy
4. previous neurological operations

5. severe physical diseases
6. AV block of 2nd or 3rd degree, sick-sinus syndrome, congestive heart failure, myocardial infarction within 6 months before the start of the study.
7. Blood pressure above 180/100 mmHg (patients with a blood pressure below 180/100 mm Hg under concomitant treatment with saluretics, beta-blockers, may be included)
8. Hypotension with systolic blood pressure below 100 mg Hg.
9. Liver disease (SGPT > 82 U/l)
10. Kidney disease (creatinine > 2.5 mg / 100 ml
11. Uncontrolled metabolic diseases
12. Concomitant treatment with bromocriptine, lisuride, other dopamine agonist, apomorphine, MAO-A inhibitors, neuroleptics, alpha-methyldopa, reserpine, clonidine, guanabenz, calcium antagonists
13. Women of child bearing potential (contraceptives are not allowed).

In addition to the above exclusion criteria, in study 22, patients who did not respond to dopamine agonists in the past were excluded from the study. Patients with a history of orthostatic hypotension were excluded.

Study Population:
Please see Table 3.

Outcome Measure: The primary efficacy measure was the change in UPDRS total score (not additionally defined in the protocol) from baseline to the final maintenance period. The total UPDRS score was calculated as the sum of the subscores for I - IV (I - mentation, behavior and mood, II - activities of daily living during "on " and "off" periods, III - motor examination during the "on" periods, and IV - complications of therapy).

Efficacy:

Study 19: An ITT-analysis performed with changes in the UPDRS total score from baseline (visit 2) to the end of the maintenance period (visit 11, week 11) showed a change of 20.1 points (SD=16.0) in the pramipexole treated group vs. A change of 5.9 points (SD=12.8) for the placebo group. The P-value of the Wilcoxon test was 0.0002. In this study the UPDRS sub-score I was not significantly influenced by pramipexole. Please see Table 4.

Study 22: An ITT-analysis performed with changes in the UPDRS total score from baseline (visit 2) to the end of the maintenance period (visit 9, week 11) showed a change of 16.9 points (SD=14.9) in the pramipexole treated group vs. A change of 9.0 points (SD=16.1) for the placebo group. The P-value of the Wilcoxon test was 0.0184. In this study the UPDRS sub-score IV (complications of therapy) was not significantly influenced by pramipexole. Please see Table 4.

In calculating the UPDRS scores, the method of LOCF was utilized. In cases where "on" or "off" scores were to be used and an "off" score was missing, the "on" was utilized. In 19, the number of scores missing was comparable in the two groups, as were the number of values missing from the most important visits (baseline and final maintenance visits). In contrast, the percent of missing values was substantially higher in the active drug group vs. the placebo group for study 22). This

difference was most notable for the final maintenance visit. Please see Table 5.

It is interesting to note than at one center (6, Sorensen and Mogensen) in study 22, the patients receiving Pramipexole, showed less improvement than the placebo group. This is the only center where this trend was noted.

Concomitant L-dopa Treatment: In study 19, treatment did not result in changes in the concomitant L-dopa (DCI). In contrast in study 22, the change (reduction in dose) from baseline to the end of the maintenance period was 150.7 mg/d in the pramipexole group compared to a change of 10.6 mg/d in the placebo group. Please see Table 6.

Safety: Please see the separate safety review for a more detailed evaluation. No deaths were reported in either study. In study 19, one patient in the Pramipexole group experienced angina pectoris which resulted in hospitalization. One patient in the placebo group experienced worsening of his Parkinsonian symptoms and developed papillary bladder carcinoma. He recovered from the former during the study and the latter during the follow-up. Eight patients withdrew from the study due to adverse events. Three from the active group and five from the placebo group. In former, one patient withdrew due to sedation/tiredness, one due to decreased blood pressure and confusion, and one due sleepiness and myoclonia. In study 22, There were three withdrawals due to adverse events, 1 form the Pramipexole group for orthostatic hypotension and 2 from the placebo group, 1 for angina pectoris and one for severe repetitive tachycardia. Please see Table 7.

Summary:

1. Patient Selection: Study 22 excludes patients who have not responded to dopamine agonists.
2. Demographics: In study 19 there is a disparity between the number of patients in the active vs. placebo groups. In addition, in this study, there is a higher percentage of male subjects in the placebo group. There is an imbalance in the treatment groups. The age, weight, duration of PD, and total UPDRS scores are comparable between the active and placebo groups in both studies. There is a greater percentage of Hoehn & Yahr stage IV patients in the placebo group vs. active group in both studies. This would suggest that the active groups had patients with less severe PD, and might be expected to do better than the placebo groups. Further suggestion of this is seen in the stratification based on L-dopa and other anti-Parkinson's disease medications, where the placebo group has a larger percent of patient's in the > 600 mg of L-Dopa groups. In study, 22, the stratification is based only on the amount of L-Dopa and does not include other anti-Parkinson's disease medications.
3. Exclusion Criteria: In study 22, patients who did not respond to dopamine agonists were excluded from the study. This exclusion has the potential to bias patient selection, in that patients are selected, who have previously demonstrated that they will benefit from a dopamine agonist. Another exclusion criteria included in study 22 was that of excluding patients with orthostatic hypotension. This is a frequent complication of Parkinson's disease, as well as a potential side effect several medications used to treat PD. These exclusion should be considered in preparation of the product labeling.
4. Efficacy: The primary endpoint analysis based on the protocols is the total UPDRS score. In both

studies, in either evaluable or ITT analysis, there is significant improvement in the UPDRS Total score. Improvement is seen in subparts II (activity of daily living), III (motor examination), and IV (complications). Patients receiving active drug had better scores in the Global Clinical Assessment and percent of off time during waking hours. There was no treatment effect with respect to the dyskinesia scale.

5. The mean daily dose of pramipexole was 3.59 and 4.59 in study 19 and 22, respectively.

Conclusion: Based on the primary outcome proposed in the protocols, change of the UPDRS Total score, the sponsor has demonstrated efficacy of the active drug, Pramipexole, in studies 19 and 22.

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Table 1. Time and Events Table for Study 19.

Events	Screening	baseline	Titration period							Maintenance period		Dose reduction period
Visit [a]	1	2	3	4	5	6	7	8	9	10	11	12
Week [a]	week -3	-1	end of week 1	2	3	4	5	6	7	end of week 9	11	week 12
Informed consent	X											
Demographic data	X											
Medical history	X											
Neurological examination [c]	X										X	
Inclusion/exclusion criteria		X										
Randomization		X										
UPDRS, Hoehn & Yahr, Schwab-New England		X	X	X	X	X	X	X	X	X	X	
Dyskinesia Scale		X	X	X	X	X	X	X	X	X	X	
Dispense of patient record	X									X		
Evaluation of patient record		X									X	
BP, pulse	X	X	X	X	X	X	X	X	X	X	X	X[b]
Electrocardiogram [c]	X	X[b]			X		X[b]		X		X	X[b]
Laboratory tests [c]	X	X[b]			X		X[b]		X		X	X[b]
Dispense/return of study medication		X	X	X	X	X	X	X	X	X	X	X
Doings of concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Conclusion of participation - (Global Clinical Assessment [c])											X	

a) Visits in week -3, -1, 1, 2, 3, 4, 5, 6, 7, 9, 11 and 12 are mandatory if not otherwise stated.
b) Only, if relevant changes at a previous visit compared to the screening/baseline value occurred.
c) Investigations of week 11 should be performed at premature discontinuation.

Table 2. Time and Events Table for Study 22.

BOEHRINGER INGELHEIM

SND 919: Time and events schedule of the study 836.008

Events	pre-treatment		Treatment period: dose-escalation					maintenance dose		dose-reduction
Visit (a)	1	2	3	4	5	6	7	8	9	10
	end of week		end of week					end of week		week
Week (a)	-3	-1	1	2	3	4	5	6	7	8	9	10	11	12
Informed consent	x													
Demographic data	x													
Physical examination c)	x												x	
Medical history	x													
Neurological examination	x													
Inclusion/exclusion criteria		x												
Telephone randomization		x												
UPDRS c)		x	x	x	x	x	x	x	x					
Fluctuations c)		x	x	x	x	x	x	x	x					
Dyskinesia Scale c)		x	x	x	x	x	x	x	x					
Patient record d)	1 week daily								1 week daily					
Adverse events c)	x	x	x	x	x	x	x	x	x	x				x
BP, pulse c)	x	x	x	x	x	x	x	x	x	x				x b)
Electrocardiogram c,f)	x	x e)			x	x b)	x			x				x b)
Routine laboratory investigations c)	x	x e)					x			x				x b)
Prolactin serum level g)	x	x e)					x			x				x b)
Delivery of the study medication		x	x	x	x	x	x	x	x					
Dosage of the concomitant medication	x	x	x	x	x	x	x	x	x	x				x
Global Clinical Impression c)		x								x				
Conclusion of participation c)										x				

a) Visits in week -3, -1, 1, 2, 3, 5, 7, 9, 11 and 12 are mandatory if not otherwise stated.
b) Only, if relevant changes occurred compared to the baseline value
c) All investigation of week 11 should be performed also at premature discontinuation.
d) Please, add to the case report forms a copy of the patient record of the reported "on" and "off" periods during waking hours and the severity of disability during "off" periods
e) Repeat the investigation, if problems emerged at the 1st visit (Visit 2 = baseline).
f) Please attach a copy of the ECG to the case record forms
g) Blood will be drawn (6 - 7 ml) to determine prolactin serum levels

Table 3.

Demographics Studies 19 and 22								
	Study 19				Study 22			
	SND 919 (Pramipexole)		Placebo		SND 919 (Pramipexole)		Placebo	
	No.	%	No.	%	No.	%	No.	%
Total No. Of Patients Treated	34		44		36		33	
Male	20	58.82	31	70.45	20	55.56	20	60.60
Female	14	41.18	13	29.55	16	44.44	13	39.39
White	33		43		36		33	
Oriental	1		0					
Unknown	0		1					
Age (Years) Mean	59.3		60.66		63.2		62.1	
Weight (kg) Mean	71.86		73.99		69.7		71.0	
Duration of PD in Years Mean	7.80		8.49		10.1		9.9	
Hoehn & Yahr Stages II III IV	 7 22 5	 20.58 64.7 14.7	 13 20 11	 29.54 45.45 25	 15 18 3	 41.67 50 8.33	 10 17 6	 30.30 51.52 18.18
Total Score of UPDRS Mea	53.60		50.24		51.9		56.7	
L-Dopa Treatment **Other Anti-PD Medications** **Stratum 1 (600mg, no other meds)** **Stratum 2 (600mg, other meds)** **Stratum 3 (>600mg, no other meds)** **Stratum 4 (>600mg, other meds)**	 5 15 4 10	 14.71 44.12 11.76 29.41	 7 16 8 13	 15.91 36.36 18.18 29.55	 14 22	 	 11 22	

Table 4.

Supportive Efficacy Studies (19 and 22)												
	Study 19						Study 22					
	Pramipexole (N34) Week			Placebo (N44) Week			Pramipexole (N36) Week			Placebo (N33) Week		
ITT	**2**	**11**	**Diff.**	**2**	**11**	**Diff.**	**2**	**11**	**Diff.**	**2**	**11**	**Diff.**
UPDRS - Total Mean Score (sum of I - IV)	53.7	33.6	20.1	50.2	44.4	5.9	51.9	35.0	16.9	56.7	47.7	9.0
UPDRS - I (mentation, behavior, mood)	1.5	0.8	0.7	1.1	1.2	-0.1	2.4	1.9	0.5	2.3	2.5	-0.2
UPDRS -II (activities of daily living)	13.0	8.6	4.4	12.7	11.7	1.1	13.4	9.9	3.4	14.9	14.2	0.7
UPDRS - III (motor exam.)	33.5	20.3	13.2	30.5	26.0	4.5	29.6	17.5	12.1	32.1	24.1	8.1
UPDRS - IV (complications)	5.7	3.9	1.8	5.9	5.5	0.4	6.6	5.6	1.0	7.4	7.0	0.4
Dyskinesia scale	2.70	2.12		3.70	2.77							
Evaluable (ITT - withdrawals, see table 7)	**N29**			**N38**			**N30**			**N28**		
UPDRS - Total Mean Score	52.3	29.7	22.6	47.4	41.2	6.2	50.9	32.2	18.7	57.1	46.2	10.9
UPDRS - I (mentation, behavior, mood)	1.4	0.8	0.6	0.9	1.1	-0.1	2.4	1.8	0.5	2.1	2.3	-0.2
UPDRS -II (activities of daily living)	12.7	7.7	5.0	11.8	10.5	1.3	12.7	9.0	3.7	14.9	14.0	0.9
UPDRS - III (motor exam.)	32.6	17.3	15.2	29.1	24.5	4.6	29.8	16.4	13.5	32.9	23.3	9.6
UPDRS - IV (complications)	5.7	3.9	1.8	5.6	5.1	0.5	6.1	5.1	1.0	7.2	6.7	0.5
Patient Record (% of waking off time)	32.97 (28)	20.69		32.72 (41)	34.61		32 (33)	26		43 (33)	40	
Mean Daily Dose	**3.59 (29)**			**4.08 (38)**			**4.59 (32)**			**4.77 (21)**		

Table 5.

Missing UPDRS Values*				
	Study 19		Study 22	
	Pramipexole	Placebo	Pramipexole	Placebo
Percent of Patients	16 (47%)	21 (47%)	17 (47%)	7 (21%)
From Visit 2 (Baseline)	1	2	2	2
From Visit 9 (week 11) (End of Maintenance Period)	2	2	11	6

* Includes patients that dropped out of the trial and patients with missing values from only part of the UPDRS i.e. Part IV item no. 39.

T. 6.

Concomitant L-dopa Treatment								
	Study 19				Study 22			
	Pramipexole		Placebo		Pramipexole		Placebo	
Visit	Mean (mg/d)	SD	Mean (mg/d)	SD	Mean (mg/d)	SD	Mean (mg/d)	SD
From Visit 2 (Baseline)	537.5	314.4	592.6	264.0	727.8	339.8	775.0	418.7
From Visit 9 (week 11) (End of Maintenance Period)	511.0	308.8	583.5	273.3	577.1	340.9	764.4	411.5

Table 7.

Withdrawals (Adverse Events and Administrative) Studies 19 and 22				
	Pramipexole (N34) Baseline / Final Maintenance Visit	**Placebo (N44)** Baseline / Final Maintenance Visit	**Pramipexole (N36)** Baseline / Final Maintenance Visit	**Placebo (N33)** Baseline / Final Maintenance Visit
AE withdrawals	3 sedation / tiredness increased falls * drop BP / confusion drowsiness / myoclonia *during dose reduction period	5 nausea dizziness right bundle branch block felt inner restlessness influenza drowsiness dizziness arterial hypertension arterial hypertension (exclusion)	1 orthostatic hypotension	2 angina pectoris severe repetitive tachycardia
Admin. Withdrawals	1 withdrew consent	1 arterial hypertension	3 protocol violation withdrawal of consent lost to follow-up	1 protocol violation
Excluded due to treatment with increased amounts of anti-Parkinson's medications			2	2
Patient enrolled twice first to placebo then to Pramipexole	1			

Study 18

This was designed to be a **single-blind**, placebo-controlled, parallel-group study of a maximal-tolerated-dose of pramipexole vs. placebo. By design 48 patients were to be enrolled.

Patients were advanced PD patients on L-dopa who experienced motor fluctuations. Concomitant anticholinergics were allowed. Concomitant amantadine was allowed. Deprenyl was not allowed.

There was a 7-week dose-escalation phase, with a maximal daily dose of 4.5 mg/day. Patients were titrated to maximal tolerated dose (MTD). If side effects developed during dose escalation, dose could be reduced to a prior tolerated dose and that patient would begin the maintenance phase. Following dose-escalation, there was a 3 week maintenance period and then a 1 week dose reduction period.

Replacement of dropouts was allowed (p 5 of the protocol). "Patients who drop from the study prior to completing at least two weeks of the maintenance dose interval...or are less than 75% compliant with the study drug...will be replaced."

Assessments included Parts II of the UPDRS and patient diaries of on-off time. The primary outcome was a dual outcome: mean change from baseline on Part II of the UPDRS at the end of maintenance and percentage (and severity) of off time. The protocol never specified whether UPDRS Part II would be averaged for the primary analysis, or divided into separate outcomes for on and off scores.

Results:

Fifty patients were randomized (26 pramipexole; 24 placebo) at 6 centers in the United States.

The results for the evaluable, observed case analysis is shown below: ["Observed case" seems to be a misnomer here since, by protocol, if a patient had not been in the maintenance phase for 2 weeks, that pt was to be replaced.] One patient (1001) was considered unevaluable because the baseline L-dopa dose was exceeded during the study.

	Adjusted Change From Baseline,UPDRS II"off"	
Pramipexole	3.50 (n=24)	
Placebo	0.25 (n=20)	p=0.11

	Adjusted Change From Baseline,UPDRS II"on"	
Pramipexole	1.04 (n=24)	
Placebo	0.80 (n=20)	p=0.90

When maintenance scores were averaged over 3 weeks (as opposed to using only the final maintenance score) and then compared to baseline, a statistically significant difference seemed to emerge in favor of pramipexole by the sponsor's report.

The percentage off time did not differ between the two treatment groups.

A trend toward reduced severity of off time was noted.

No significant difference on UPDRS Part III was found.

Conclusions:

There was a trend toward reduced severity of off time as measured by patient diaries and UPDRS Part II "off" scores. When maintenance scores were averaged over 3 weeks and then compared to baseline, a statistically significant difference seemed to emerge in favor of pramipexole.

On the other hand, the percentage off time did not change for either treatment group. Also, the UPDRS Part II "on" scores did not differ for the two treatment groups.

The maintenance period here was only 3 weeks long, making any extrapolation from these results difficult.

One aspect of this study that is important is the exclusion of deprenyl as a concomitant medication. It may be important from the standpoint of drug interactions that trends in favor of pramipexole were seen in the absence of deprenyl.

Study 20

This was designed to be a double-blind, placebo-controlled, parallel-group study of a maximal-tolerated-dose of pramipexole vs. placebo. Because of slow enrollment, only 19 patients (9 pramipexole; 10 placebo) were enrolled. For that reason, no meaningful efficacy results emerged from this study in patients with advanced PD. According to the sponsor, "there were no apparent differences between treatment groups in the UPDRS or subscores."

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ON ORIGINAL

Conclusions:

The sponsor has demonstrated the effectiveness of pramipexole in early Parkinson's Disease in the absence of L-dopa. Additionally, effectiveness has been shown in advanced Parkinson's Disease with concomitant L-dopa therapy.

Studies in Early Parkinson's Disease

Four studies are summarized in the two tables below. A consistent improvement in UPDRS Part II (the activities of daily living scale) is shown across studies.

Likewise, a consistent improvement in UPDRS Part III is shown across studies. UPDRS Part III is referred to as the motor scale. I would argue that the scale captures the motor exam minus the domain of involuntary movements (to include dyskinesias).

Early Parkinson's Disease; No Concomitant L-Dopa

Change From Baseline on UPDRS **Part II**:

	Study 1	Study 4	Study 17	Study 21
Pramipexole	1.9	1.8	5.2	5.1
Placebo	-0.4	0.3	2.2	2.2

Change From Baseline on UPDRS **Part III**:

	Study 1	Study 4	Study 17	Study 21
Pramipexole	5	4.5	12.0	7.2
Placebo	-0.8	0.6	8.3	1.6

Studies in Advanced Parkinson's Disease

Four studies are summarized in the two tables below.

Note that UPDRS Part II (ADL) in these studies represents an average score of the "on" score and the "off" score. As such, without a per patient correction factor for amount of "on" time and "off" time, it must be interpreted carefully.

A consistent improvement is shown across studies.

Likewise, a consistent improvement in UPDRS Part III (the motor scale) is shown across studies. Again, I would argue that the scale captures the motor exam minus the domain of involuntary movements (to include dyskinesias).

Advanced Parkinson's Disease; Concomitant L-Dopa

Change From Baseline on UPDRS **Part II (average of on and off score)**:

	Study 10	Study 18	Study 19*	Study 22
Pramipexole	2.7	2.1	4.4	3.5
Placebo	0.5	0.5	1.0	0.7

Change From Baseline on UPDRS **Part III**:

	Study 10	Study 18	Study 19*	Study 22
Pramipexole	5.6	3.1	13.2	12.1
Placebo	2.8	1.4	4.5	8.0

* Study 19 is the only study in advanced PD where daily dosage of L-dopa was not differentially reduced in the pramipexole group as compared to the placebo group

Given the presence of the on-off phenomenon in patients with advanced Parkinson's Disease, the effect of pramipexole on total amount of "on" time is important to evaluate. As mentioned above, a positive effect here may even be a prerequisite for meaningful interpretation of the primary outcome, UPDRS Part II. Unfortunately, 1) an operational definition of "on" and "off" time was not provided in the protocol and 2) the CRF only recorded "off" time without differentiating between the 2 alternatives, "on" versus "on with dyskinesias." The latter may not necessarily represent a better state than "off" (no operational definition provided, but potentially fairly benign according to the patient diaries) and should not be represented as such.

Recommendations:

An approvable letter can be issued. Proposed labeling should point out the limitations of the data, as collected. Specifically, 1) UPDRS III does not encompass the entire motor exam and 2) a decrease in "off" time is not simply an increase in "on" time.

John Feeney, M.D.
Medical Reviewer
September 13, 1996

Review and Evaluation of Clinical Data

Safety Review

Application Information

NDA 20-667

Pharmacia & Upjohn

NDA Submission Date: December 28, 1995

Drug Name

Generic: Pramipexole

Proposed Trade Name: Mirapex™

Drug Characteristics

Pharmacological Category: Dopamine agonist

Proposed Indications: 1) Primary symptomatic treatment of Parkinson's disease.
2) Adjunctive treatment of Parkinson's disease.

Dosage Forms: Oral tablets in 0.125 mg, 0.25 mg, 1.0 mg, 1.25 mg, and 1.5 mg

Proposed Use:

Pramipexole should be given T.I.D.. Dosages should be increased gradually from a starting dose of 0.375 mg/day and should not be increased any sooner than every 5-7 days. In most studies a 7 week dose escalation scheme was followed: 0.125 T.I.D., 0.25 T.I.D., 0.5 T.I.D., 0.75 T.I.D., 1.0 T.I.D., 1.25 T.I.D., and at the 7th week to the maximum dose of 1.5 T.I.D. Withdrawal should occur gradually over a 7-day period.

Safety Reviewers: John D. Balian, M.D. & James F. Knudsen, M.D., Ph.D.

Date of Review: November 13, 1996

1 Summary of Pramipexole Safety Review

Pharmacia & Upjohn is requesting approval to market pramipexole for the treatment of idiopathic Parkinson's disease (PD). Overall, the ISS summarized the safety experience for 1408 patients with about 815 person-years (PYs) of pramipexole use, most of it (800 PYs) coming from the PD trials. Both early therapy (ET) and advanced therapy (AT) PD patients had over 100 PYs of pramipexole exposure that occurred after the first year of use. In the completed PD studies, there were 245 ET and 176 AT patients who reached 4.5 mg/day, the maximum recommended daily dose. Of these 421 patients, 190 were exposed to this dose for at least 12 consecutive weeks.

In the clinical pharmacology studies, pramipexole had significant cardiovascular (CV) effects on healthy volunteers. Symptomatic orthostatic hypotension (OSH) was identified as a dose-related phenomenon, first evident following a single oral dose of 0.2 mg (first dose phenomenon). The OSH was reported as dose-limiting (0.4 mg/day was the maximum tolerated dose in study 26) for the normal volunteers. The time to onset of OSH varied from 30 minutes to 6 hours. The duration of OSH varied from 1 hour or less to at least 8 hours, depending upon dose. The magnitude of drug-induced changes in standing blood pressure and pulse rate could not be adequately assessed in all patients because of the inability to stand for vital sign measurements, but in those measured it was significant, with a decrease from baseline in SBP of up to 66 mg Hg and 30mmHg in DBP. The latter subject was unable to stand again for 8 hours and continued to experience nausea and asthenia for up to 12 hours. Overall, other symptoms associated with OSH were dizziness, asthenia, malaise, nausea, and increased sweating. There were no clinically significant changes from baseline in ECG parameters reported compared with placebo.

In the phase 2/3 studies, a separate review and analysis for the ET and AT patients was done (for this review) in order to adequately describe pramipexole associated AEs. In the 3 ET randomized controlled trials (RCT), the frequency of study dropout associated with non-serious AEs was comparable in the pramipexole and the placebo groups. The frequency of study dropout associated with serious AEs was 2% in pramipexole and 1% in the placebo patients, with only one pramipexole patient experiencing an AE that was CV in nature. The 3 most common AEs, irrespective of severity, associated with dropout in the 3 ET studies were: hallucinations, nausea and dizziness. Only 1 patient dropped out due to syncope. Overall, syncope as an AE was reported in 5 (1.3%) pramipexole-treated and 2 (1.0%) placebo treated patients. There were 4 deaths in pramipexole patients, 3 of which were CV in nature.

In the 4 AT RCTs, the frequency of study dropout associated with either serious or non-serious AEs was less in the pramipexole than in the placebo groups. None of the 18 patients exposed to pramipexole who had serious AEs had syncope, bradycardia, or orthostatic hypotension and only 3 patients had an event that could be considered CV in nature. There was no clear pattern of AEs associated with dropout. There were 8 deaths in pramipexole patients, 3 of which were CV in nature. Across the AT placebo controlled studies in the ISS,

only hallucinations and dry mouth were reported in more than 5% of pramipexole patients and were at least 2 times more frequent than in placebo. Syncope was reported in 2.2% of pramipexole AT patients compared to 3.4% of placebo patients.

Across all patients exposed to pramipexole in the development program, there were no AEs clinically consistent or suggestive of hepatic failure or necrosis, urolithiasis, agranulocytosis, or aplastic anemia. Rhabdomyolysis was reported in one patient. One patient developed acute thrombocytopenia. There were no significant shifts in ECG parameters and laboratory analytes from baseline to study endpoint.

In summary, pramipexole use was not associated with increased risk for deaths, serious AEs, or dropouts in PD patients. While there was a clear increase in CV effects (syncope and OSH) attributable to pramipexole in the phase 1 healthy volunteers, no significant differences from placebo were observed in the phase 2/3 trials.

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2 Background

, in collaboration with the Pharmacia & Upjohn Company (Upjohn) developed pramipexole as a dopamine agonist for the "treatment of the signs and symptoms of idiopathic PD". Pramipexole is a synthetic amino-benzothiazole derivative with affinity for dopamine and α_2 receptors. It binds with highest affinity to the D_3 receptor subtype but it also binds the D_2 and D_4 receptors. It "stimulates fully" the dopamine receptors, with preclinical evidence of efficacy in animal models of Parkinson's disease (PD).

2.1 Overview of Safety Review

The sponsor had proposed for FDA approval to market pramipexole as primary therapy (referred in the NDA as monotheapy or early therapy {ET}) for Early Parkinson's Disease (EPD) and as adjunctive therapy (AT) for Advanced Parkinson's disease (APD), but at a pre-NDA meeting, the agency suggested that no specific referrals to monotherapy and adjunctive therapy be made, and instead a general claim for indication of "treatment of the signs and symptoms of idiopathic PD" be made.

In view of this, the sponsor's Integrated Safety Summary (ISS) provides pooled descriptions and analyses of the treatment emergent adverse events (AEs) without regard to ET or AT. The only separation of data in the ISS is that of data obtained from the so called "pivotal trials" or "the adequate and well controlled trials" and the rest of the data. These pivotal trials, consisting of 3 (studies M2730/0001, -/0004, and -/0010) double-blind, placebo-controlled, randomized controlled trials (RCTs) in PD, were designated as such for efficacy purposes, but the connotation and the analysis were then carried over by the sponsor to the safety analysis as well. The ISS contains 4 more similarly designed RCTs in PD, that were not designated as "pivotal" for efficacy purposes, and hence, for the safety review, the sponsor presents and analyzes these trials separately referring to them as "the other controlled PD trials".

Since the 2 populations identified by these indications could vary with respect to likelihood of background events because of differences in age, extent of underlying diseases, and other factors, we determined that it would be a better approach to separate the review and analysis of the ET and AT patient populations, wherever feasable. With the help of the sponsor a reanalysis of the data was performed. Since, there were no safety reasons to designate some studies as pivotal, data obtained from all similarly designed RCTs (3 studies from the ET trials and 4 from the AT trials) were used in the reanalysis.

This review, whenever posssible reflects this separate (and not pooled) approach, except when specific findings from the "pivotal studies", after separating them into ET (trials 1 and 4) and AT (trial 10) are utilized.

2.2 Development of Pramipexole

According to the sponsor, development of pramipexole as a treatment for PD was pursued because preclinical studies suggested that it had effectiveness in reversing parkinsonian signs, no dopamine agonist is currently approved for monotherapy of PD, and pramipexole's "full dopamine agonism". Based upon this preclinical receptor profile, the sponsor hypothesized that pramipexole would have advantages in efficacy and/or safety when compared to approved dopamine agonists.

Pramipexole's clinical development program began in Europe with administration to healthy volunteers in January 1988. As of 1/1/96, pramipexole has not been marketed in other countries and there have been no foreign regulatory actions regarding its approval.

2.3 Pramipexole Preclinical Studies

Pramipexole binds to the D2 receptor subfamily, with highest affinity to the D_3 receptor subtype but it also binds the D_2 and D_4 receptors stimulating these receptors fully. In comparison, the ropinirole NDA review mentions bromocriptine and pergolide each with affinity for D1 and D2 receptor subtypes, and ropinirole and its metabolites with high affinity to the central D2 dopamine receptors, but not to D1.

In animal safety data, the no-toxic effect dose for pramipexole was reported to be 0.5 mg/kg/day for rats. The LD_{50} of acute oral toxicity in mice was 1700 mg/Kg with signs of exophthalmos, piloerection, tremors, convulsions, and hypomotility. The LD_{50} of acute IV toxicity in rats was 210 mg/Kg with signs of exophthalmos, dyspnea, convulsions, ataxia, and hypomotility. Autopsy in both cases revealed hemocongestion of major organs.

Chronic toxicology studies revealed mammary gland changes (proliferation of glandular epithelium) in female rats in the mid- (2 and 3 mg/kg/day) and high (8 and 15 mg/kg/day) dose groups. Other AEs noted were behavioral changes in both sexes, decreased body weight gain, and cholesterol and triglycerides in females in the lowest doses. With mid- and high-doses, body weight gain was reduced in both sexes. In addition, sporadic modest elevations in liver enzymes and decreases in potassium levels occurred. Hematologic AEs included mild thrombocytopenia. Organ changes included decrease in liver and thymus weights, and enlarged corpora lutea. Leydig cell hyperplasia was observed mainly in the low-dose groups and there were two adenomas observed in male rats (one control one pramipexole-treated).

Chronic toxicology studies in rhesus monkeys were significant for bradycardia and increased R-R and Q-T intervals observed in males of the mid-dose group.

The main findings observed in toxicology studies included retinal degeneration in

albino rats, CNS effects (increase in motor activity, agitation, ataxia, and tremors), and decreased prolactin secretion. Both male and female albino rats receiving long-term (2 year) pramipexole at mid- (2 mg/kg/day) and high (8 mg/kg/day) dose groups experienced dose-dependent retinal degeneration. The degeneration was characterized by loss of photoreceptor cells usually occurring late in treatment. Rats of the low dose group (0.3 mg/kg/day) and the control group were free of the AE. In other studies involving rats lasting only one year, and in long-term studies in other species (mice, swine, and monkeys) this syndrome was not recorded.

No reproductive abnormalities in mating, pregnancy, or pup development were noted in the low- and mid-dose groups of rats studied. In the high-dose, irregular estrus occurred in about one-half of the females, and the number of pregnancies that resulted in successful delivery decreased. Also the delivered pups had impaired growth during the lactation phase. The increase in the infertility and the impaired growth seen in the pups may be related to the drugs effect of inhibiting prolactin secretion. The teratogenicity data are scant due to the small number of pups, but no obvious effects were noted. Similar studies in rabbits were devoid of reproductive toxicities at doses up to 10 mg/Kg.

Mutagenicity studies were negative. Carcinogenicity studies in mice revealed no significant incidences of neoplastic lesions. Carcinogenicity studies in rats were significant for a higher incidence of Leydig cell adenomas in the mid- (2 mg/Kg/day) and (8 mg/Kg/day) high-dose groups. Leydig cell hyperplasia and testicular adenomas in rats were also observed in the ropinirole NDA review. Both sponsors attributed these to the reduced plasma prolactin that caused a reduction in Leydig cell LH receptors, which triggers a compensatory increase in LH production and release leading to Leydig cell hyperplasia and adenomas. (These Leydig cell LH receptors apparently are not present in humans).

Pramipexole rapidly crosses the blood-brain and blood-placental barriers in studied rats and is excreted in the milk of lactating mothers.

The opiate receptor activity of pramipexole was not investigated.

In summary, the main findings observed in the toxicology studies with pramipexole were related to retinal degeneration in albino rats, CNS effects, and reproductive effects possibly due to decreased prolactin secretion in rats (as the sponsor hypothesized).

2.4 Review of Safety Issues Identified in The Sponsor's Proposed Labeling

In the annotated labeling, pramipexole is described as a nonergot dopamine agonist with high specificity for the D2 subfamily receptors with a preferential affinity for D_3 receptors. The sponsor claims that by depressing dopamine synthesis, release, and

turnover, pramipexole reduces dopamine-induced neuronal degeneration in animals and alleviates parkinsonian motor defects.

In the current proposed label, pramipexole is indicated in "the treatment of the signs and symptoms of idiopathic Parkinson's disease", as was suggested by the agency at a pre-NDA meeting. In a communique dated October 31, 1996, the sponsor proposed a different text for the indications section to reflect our concentration of reviewing the AT and ET populations separately. The proposed text is: "Mirapex™ tablets are indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, both as first-line treatment (without levodopa) in early disease and in combination with levodopa for advanced Parkinson's disease".

The recommended starting dose is 0.375 mg/day in three divided doses, with a gradual increase every 5-7 days to a desired maintenance dose, with a maximum of 4.5 mg/day. Although abrupt discontinuations were uneventful, the sponsor recommends a gradual taper.

In the animal toxicology section, there is a mention of occurrence of Leydig cell adenomas in male rats, decreased fertility in female rats, and the excretion of drug-related material into breast milk.

Under the warnings section of the labeling, the sponsor mentions the occurrence of postural hypotension in patients treated with pramipexole and recommends gradual titration and careful adjustment of the dose. The sponsor claims that tolerance to the hypotension develops. Another AE mentioned under the warnings section is hallucinations: when used as monotherapy (EPD) 9% (34/377) of patients receiving pramipexole and 2% (5/222) of patients receiving placebo reported hallucinations. While in APD, this AE occurs more frequently, 21% (38/181) of patients receiving pramipexole in combination with carbidopa/levodopa vs 6% (10/178) of patients receiving placebo in combination with carbidopa/levodopa.

In the precautions section, the sponsor mentions that caution should be exercised when treating patients with renal insufficiency, and pramipexole may potentiate the dopaminergic side effects of levodopa and "may cause and/or exacerbate preexisting dyskinesia".

Under the AEs section of labeling, in pooled data for both ET and AT Parkinson's patients, 11% (out of 702) receiving pramipexole and 14% (out of 550) receiving placebo dropped out of the controlled studies due to AE occurrence. Hallucinations (3%), dizziness (2%), extrapyramidal syndrome (EPS) (1%), confusion (1%), somnolence (1%), postural hypotension (1%), and nausea (1%) were the most common reasons for withdrawal. These AE dropout risk estimates included all US and non-US experience and did not separate APD from EPD.

Table 1 provides a summary of AE risk estimates that were listed in the AE section of the proposed labeling that were observed in randomized placebo controlled ET and AT studies (pooled). In table 1, events are listed if they occurred in more than 1% of the patients where the event rate was more than 2 fold greater than placebo.

Table 1. Adverse events that occurred in more than 1% of and were more than 2 fold greater in pramipexole ET patients than with placebo. (Taken from sponsor's proposed labeling which uses data from studies 1, 4, and 10.)

	pramipexole	placebo
	N=558(%)	N=400(%)
Decreased Weight	1.6	0.2
Peripheral Edema	4.1	2.8
Twitching	1.6	0.8
Hallucination	12.7	3.8
Somnolence	18.3	8.0
Akathisia	1.2	0.2
Decreased Libido	1.1	0.2
Myoclonus	1.1	0.5
Paranoid Reaction	1.1	0.5
Vision Abnormality*	2.9	0.2
Diplopia	1.2	0.5

*Floaters, visual spots, and peripheral vision disturbance.

Increased risk of somnolence and hallucination was associated with pramipexole's use.

In the patient information section, the sponsor is recommending that patients avoid driving automobiles and using heavy machinery until they know how pramipexole will effect them.

3 Methods of Safety Review

As mentioned in section 2.1, the sponsor has provided pooled data in the ISS (without regard to ET or AT), and presented the data in several formats: (1) adequate and well controlled PD trials (studies 1, 4, and 10--the studies designated as pivotal to the efficacy of pramipexole); (2) all completed PD trials; (3) ongoing PD trials; (4) all completed schizophrenia trials; and (5) pooled data. In the ISS, no distinctions are made between US and non-US trials (although no clear differences in design are apparent) or in ET vs AT trials. Again, as noted in section 2.1, this review follows a different format: separate data presentation for the ET and AT trials. The review focused on deaths, serious AEs, dropout risk, dropouts associated with AE occurrence, and common AEs.

Using both the paper and electronic (CANDA) versions of the NDA, treatment emergent AEs occurring with pramipexole use were evaluated separately in ET and AT patients. To verify the accuracy of the primary data that was available for review, the information listed in the data listings, the CRFs, and the death narratives were cross checked for accuracy. To evaluate the consistency and accuracy of the AE coding in the studies and COSTART in the Upjohn studies), subsumed investigator verbatims were compared to the corresponding preferred and COSTART AE codes. To further examine the validity of AE coding, selected and COSTART codes were reviewed in more detail. These codes were implicitly selected based upon the AE description in the proposed labeling, toxicity findings from preclinical testing, and findings noted during the NDA review. In view of the high incidence rates of syncope in the non-ergot dopamine agonist ropinirole (currently under review as an antiparkinson's drug), any supporting data for patients coded with the and COSTARTs "blackout", "faintness", "syncope, postural", "syncope, vasovagal", "symptomatic orthostatic hypotension", "circulation failure" were reviewed focusing on evidence of syncope or general CV events. Investigator verbatims for CV COSTART codes in studies 1, 4, and 10 were also reviewed to evaluate their specificity.

Since deaths were observed in the RCTs, before patients entered extensions, pramipexole mortality was compared to that in placebo separately for ET and AT patients. For the rate comparison, the sponsor used the exact number of days in computing person-years (PYs). PYs were estimated based on the medication records: the exact number of days were computed for each patient.

In addition to describing the mortality risks and rates, case summaries of all sudden or CV deaths were prepared by extracting data from the CRFs, narrative summaries and CRF tabulations. In addition, the CRFs, narrative summaries, and data tabulations were reviewed for the following groups of patients: (1) all deaths; (2) serious AEs; (3) AEs associated with dropout; (4) AEs coded as syncope, bradycardia, ventricular tachycardia/fibrillation or peripheral edema; and (5) patients

with any AEs suggestive of agranulocytosis, aplastic anemia, thrombocytopenia, serious skin reactions such as Stevens-Johnson Syndrome, hepatic failure or necrosis, renal failure or worsening of renal function, rhabdomyolysis, urolithiasis, hematuria or urosepsis, and retroperitoneal fibrosis or pulmonary fibrosis.

The AE experience observed in individual trials was contrasted to confirm that no major discrepancies in reporting occurred. The US and non-US data was not contrasted, but there were no clear differences in design or reporting.

4 Review of Findings

4.1 Description of the Pramipexole Development Program

Pramipexole was developed as a collaborative research effort between and The Pharmacia Upjohn (Upjohn) companies. Clinical development of pramipexole is being conducted under the folowing INDs:
IND
IND
IND

IND was submitted by on 5/14/90 to intitiate Phase II clinical trials. On 2/16/93 the sponsorhip of the IND was transferred to Upjohn. The current application is being filed under NDA 20-667 and is for the treatment of PD. Since other indications (schizophrenia and depression) are not sought at this time, most analysis and review refers to the PD trials, without ignoring the data obtained from all trials. No other NDA's have been previously submitted.

Appendix 4.1.1 provides a listing of all studies included in the ISS. The ISS described pramipexole treatment emergent AEs based upon observations from 19 Clinical Pharmacology studies, 16 completed phase II-III clinical trials, and 15 ongoing trials.

Of the 19 clinical pharmacology studies involving 297 (260 PPX and 37 placebo) subjects, 17 were conducted in healthy volunteers, 1 (protocol 60) was conducted in volunteers with impaired renal function, and 1 (n=3) was conducted in APD patients.

Of the 16 completed phase II-III clinical trials (i) 9 (studies---#1, 4, 17, and 21 in ET and studies---#10, 18, 19, 20, and 22 in AT) were PD studies involving 1253 (702 PPX and 551 placebo) patients; and (ii) 7 were completed studies in schizophrenia involving 322 (177 PPX, 50 comparator, and 95 placebo) patients. There are also 15 ongoing studies: (i) 10 ongoing PD studies involving both controlled and uncontrolled studies, the controlled studies are blinded so an exposure number is not available, while the uncontrolled ongoing studies involve 1056 patients of which only 529 are uniquely exposed, the other 527 were enrolled in the completed controlled studies and exposed to PPX; (ii) 3 ongoing studies in schizophrenia; and (iii) 2 ongoing studies in

depression.

A tabulation of patient accountability of the completed studies is detailed in table 4.1.1:

Table 4.1.1 Patient Accountability (All Completed Studies)				
		Number of Patients		
	Pramipexole	Placebo	Comparator	Total
Phase I (Clinical Pharmacology)	260	37	-	297
Phase II/III (PD Total)	702	550	-	1252
EPD	416	262	-	678
APD	286	288	-	574
Phase II/III (Schizophrenia Studies)	177	95	50	322
Total Phase II/III	1139	645	50	1871

The sponsor has given the following numbering system to the trials: M2730/00x, where x stands for the number of the study, i.e. 1, 2,---, 37, etc.. In this review, the final number (x) will be used to identify a study. The sponsor has selected three Phase II/III studies M/2730/0001 (study 1), M/2730/0004 (study 4), and M/2730/0010) (study 10) as the key studies for the evaluation of the effectiveness of pramipexole for the treatment of idiopathic PD (as discussed earlier, no specific referrals were made initially to either early or advanced PD in the indication). The sponsor chose these three trials since they met the criteria of adequate and well-controlled studies: studies with clear objectives, well defined methods of analysis, valid controls, and sufficient statistical power to allow a valid comparison with placebo.

As discussed earlier, the sponsor has presented safety data from all completed trials, but based the main safety analysis of this NDA submission on the 9 completed PD studies of phase II/III trials, and in particular the "pivotal" trials, pooling the data without regard to ET and AT populations. Again, as discussed earlier, the review did not follow this approach.

Of the 9 completed PD studies in phase II/III trials, 3 (studies 1, 17, and 18) were entirely conducted in the US, 2 (studies 4 and 10) were conducted in the US and Canada, and 4 (studies 19, 20, 21, and 22) were entirely foreign (non-US and non-Canadian) in conduct. All, except for study 20 were multicenter trials. Four trials (studies 1, 4, 21, and 17) were with patients not taking levodopa --defined as "early" PD-- while 5 (studies 10, 19, 20, 22, and 18) were with patients taking levodopa -- defined as "advanced" PD. Of note, the three pivotal studies (1 and 4 with EPD and

10 with APD) were US and Canadian in conduct.

The three pivotal or as the sponsor refers to them "the adequate and well-controlled" studies were multicenter, randomized, double-blind, and placebo-controlled in patients with PD who were not taking levodopa (defined as "early")--(protocols 1 and 4), or in patients with PD who were maintained on optimal doses of levodopa (defined as "advanced")--(protocol 10). Protocols 1 and 10 were flexible-dose studies during which patients received treatment with placebo or pramipexole from 0.375 to 4.5 mg/day with an initial ascending dose phase (up to 7 weeks), folowed by a 24 week maintenance phase, and a 1 week dose-reduction phase. Protocol 4 was a dose-response, parallel study where patients received pramipexole 1.5, 3.0, 4.5, 6.0 mg/day, or matching placebo. There was a 6 week ascending dose phase, followed by a 4 week maintenance phase at the targeted dose, and 4-8 day dose-reduction period. All other completed PD studies were also double-blind and placebo-controlled with the exception of two pilot studies (17 and 18), which were single-blind. Otherwise, there were no significant differences in design between ET and AT studies or the US and the foreign studies.

Patients from PD studies 1, 4, 10, 17, 18, 19, 20, and 22 were given the option of enrollment in extension studies (the current ongoing studies). Table VIII.G-15 in the ISS (page 8/3/47) enumerates the patients participating in more than one PD study. The total number of patients enrolled in the ongoing PD studies is 1056, 527 enrolled from the pramipexole arm, 371 from the placebo arm of the completed PD RCTs, and the rest are new enrollees.

The only phase 2/3 studies with comparative designs were in schizophrenia trials.

4.2 Summary of Pramipexole's Pharmacokinetics

Pramipexole is rapidly absorbed with an approximate bioavailibilty of 90% (indicating minimal first pass metabolism) and peak plasma concentrations occurring approximately 1-3 hours after dosing. Renal excretion (> 80%) is the primary route of elimination as unchanged parent compound and the elimination half-life is 8.5 hours in young volunteers and 12 hours in older volunteers. Clearance in healthy female volunteers was 14-30% lower than in healthy male volunteers. Clearance is decreased significantly in renally impaired patients. Protein binding was less than 20%.

Since pramipexole has minimal first pass metabolism, no in vitro or in vivo studies were performed to determine the presence of a P450 pathway.

Increases in Cmax and AUC were proportional with dose over the range 0.375 to 4.5 mg. Food decreased the rate of pramipexole absorption at steady state both in PD patients and healthy volunteers.

The sponsor conducted a study to explore the potential influence of age on renal processing (drug elimination) in study 0069. Age did not influence the absorption of pramipexole, nor the apparent volume of distribution after oral administration, however, as expected, the mean clearance for the elderly patients was approximately 30% lower than the young volunteers. Also, as a result of the reduction in glomerular filtration with increasing age, there was an increase in the elimination half-life from approximately 8.5 hours to 12 hours. In patients with renal insufficiency pramipexole total clearance and renal clearance decreased by 70% and 91%, respectively. The potential influence of hepatic insufficiency on pramipexole pharmacokinetics was not evaluated.

4.3 Description of the ISS Population

As table 4.1.1 in section 4.1 shows, in the 9 phase 2/3 completed PD RCTs, there were 702 patients who were exposed to pramipexole. Of these, 416 and 286 were observed in ET and AT studies, respectively.

Appendix 4.3.1 shows the demographics of the RCTs. In these trials there were no statistically significant differences between the pramipexole and placebo groups with respect to age, sex or race. The demographic characteristics of the combined ET and AT population were generally representative of the expected demographics of PD patients. In the pramipexole exposed group, the ages ranged from 31-87, with an average of around 62.8 years and the vast majority of patients (61%) were between 50-70 years old, while about 24% of the patients were >70 years of age. The overwhelming majority (96%) were Caucasian and 64% were male.

There was little difference in age between ET and AT patients across the ISS. AT patients had a longer duration of PD at baseline than that of ET patients; 9 years compared to 1.5-2 years. The average UPDRS Part II and III (the efficacy variables analyzed) were lower in the ET groups. AT patients had received l-dopa therapy for about 7 years and were rated in Hoehn and Yahr Stage II-IV at baseline, while by definition (protocol inclusion criteria) ET patients could not have received l-dopa therapy and were rated as Hoehn and Yahr Stage I-III.

Concomitant use of antiparkinsonian medications also varied between AT and ET patients and by study. As with l-dopa therapy, AT patients were not restricted in the extent of prior use of other dopaminergic therapy. However, both ET and AT patients were allowed continued use of amantadine, anticholinergic, and selegeline (l-deprenyl) therapy, but their dosage could not change. "Rescue" therapy with Sinemet was allowed, but exactly how this was applied was left up to each investigator.

Patients with clinically significant active cardiac disease were excluded from the trials. Disease co-morbidity prevalence was not compared in the ISS.

4.4 Review of Sponsor's AE Surveillance, Coding of AEs and Approach to Evaluating the Safety of Pramipexole.

According to the sponsor, surveillance for AEs occurred at each study visit in all studies. A treatment emergent AE was defined as any event or disease which was not present at baseline, or which if present increased in frequency or severity while in study, irrespective of any belief by the investigator regarding causality. Surveillance focused on all events including asymptomatic changes in laboratory findings, exacerbation of pre-existing conditions, intercurrent illnesses, and drug interactions.

Because of the dopamine agonist activity of pramipexole and because it caused hypotension and orthostatic hypotension in phase 1 studies, supine and standing BPs were collected across phase 2 and 3 studies. Patients were checked for postural changes by comparing 5 minute supine BPs with 1 minute standing BPs. In phase 2/3, while the method of BP measurement was standardized across studies, the timing of BP measurement with respect to drug dose was not standardized, unlike the phase 1 studies, where supine and standing BP were measured at specific time points following dosing. This sponsor uses postural hypotension and orthostatic hypotension interchangeably.

In coding the AEs, dictionary while Upjohn used the COSTART dictionary. As Upjohn took overall responsibility of the submission, it reassigned the preferred terms to COSTART preferred terms.

Because certain investigator verbatims were judged to be related to an event of particular interest, some specific coding rules were applied. The investigator verbatims "blackout spells", "fainting", "syncopal spells", "cardiovascular collapse", and "orthostatic collapse" were coded with the COSTART "syncope". The investigator verbatims "drowsiness", "sleepiness", and "sedation" were coded with the COSTART "somnolence".

There were instances of coding inconsistencies. For example, the adverse event descriptive term "fall" was subsumed under the COSTART terms gait abnormality, ataxia, and accidental injury. Other adverse events listed under more than one COSTART terms were "dizziness on standing", "faintness upon standing", and "lightheadedness". These were subsumed under COSTART terms postural hypotension of the cardiovascular body system, as well as under the COSTART term dizziness related to the CNS body system. The minor inconsistencies are not likely to influence the analysis, and overall, the sponsor's coding approach was found to be appropriate.

In reviewing the NDA, it appears that the approach described by the sponsor to ascertaining and describing treatment emergent AEs was followed in all studies. In addition to having the investigator code AEs as to degree of medical severity, the

sponsor identified AEs meeting the regulatory definition of serious. The ISS defines concurrent illness as any illness that occurred prior to study entry. These conditions were considered treatment emergent AEs if the conditions worsened during the course of the study.

The NDA summarized deaths, serious AEs, and overall dropouts from completed and ongoing studies using a cutoff date of 1/31/95. Patients had a unique identifier and most patients were counted only once except where placebo patients entered a pramipexole extension (371 patients). Two patients in the ISS were randomized to receive placebo but ended up not receiving any treatment.

In the ISS, the sponsor described common AE occurrence by focusing on AEs considered causally related to pramipexole. Potential causality was defined as a greater than 10% increase and greater than placebo. Since dose escalation was used in all clinical studies, a dose response analysis could have been confounded by time since first exposure. In addition, The sponsor counted some patients more than once in this analysis. Patients that had an increase in clinical severity (mild, moderate and severe) at different doses could have been counted as many as three times, but such patients were counted once within a corresponding dose. AE occurrence was also described by time since first exposure. In this analysis, patients were counted only once with the date of first occurrence used to calculate time.

To evaluate potential modification of risk attributable to pramipexole by concurrent medications, underlying diseases, or in demographic subgroups, AEs that occurred $>= 5\%$ were used to calculate relative risk (RR). Percentages of occurrence were calculated separately for ET and AT patients. The following concurrent medications were selected: selegiline, anticholinergic agents, amantadine, domperidone, beta blockers, thiazide diuretics, tricylic antidepressants, acetylsalicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and tocopherol. Concurrent illnesses defined as present at baseline, were coded to respective COSTART terms. The following concurrent diseases were selected: arthritis, CV disease, constipation, depression, dizziness, hypercholesterolemia, hypertension, insomnia, and prostate disease.

Appendix 4.15.1 shows the hematology, chemistry, and urinary laboratory analytes with predefined limits that were set as normal ranges. The sponsor identified patients with laboratory analytes at or above the value of potential clinical concern. For hepatic enzymes, clinical concern was set at 2.5 times the ULN. All study protocols required at least baseline and ending laboratory determinations with some studies requiring more frequent blood sampling. A complete listing of patients who dropped out associated with any laboratory analyte abnormality was provided.

All ET and AT studies had 12 lead electrocardiograms (ECGs) performed. All studies had a screening ECG, but the frequency of follow-up ECGs varied from only one

follow-up in study 4 to 6 follow-ups in study 10. All ECGs were available for review.

4.5 Audit Findings and Specificity of the AE Coding.

The investigator verbatims listed in the CRFs of the 17 deaths and from a sample of AE withdrawals and serious AEs were congruent with those in the data tabulations and described in the narrative summaries. Conversely, the narrative summaries, while providing more clinical detail, particularly about past medical history, described AEs that were generally identified in the CRF.

In general, the COSTART coding of the investigator verbatims seemed reasonable except for the few instances mentioned in section 4.4. Of special note are the AEs of "dizziness on standing", "faintness upon standing", and "lightheadedness" which were listed under more than one COSTART term: postural hypotension or dizziness. Because of the coding inconsistencies (AEs listed under more than one COSTART term), the specificity of "orthostatic hypotension" may likely be reduced. The protocol definition of orthostatic hypotension for all studies in the ISS was defined as a decrease in systolic BP of 20 mm Hg and/or a decrease in diastolic of 10 mm Hg, irrespective of presence of symptoms.[1] However, in the ISS, the COSTART code "orthostatic hypotension" also was used to code postural symptoms (dizziness on standing) with or without objective change in BP. This approach appears to have been applied because several patients, particularly in the phase 1 studies, could not have their standing BPs measured because of orthostatic symptoms and in some cases, syncope. While this approach may increase the sensitivity of the code to identify clinically significant events, its specificity most likely has been reduced (increasing false positives) biasing any difference between pramipexole and a comparison group towards the null. Of course, the sensitivity of the code probably varied across studies anyway, since BP was measured irrespective of the timing of dose for some studies.

Other COSTART codes were also applied in a non-specific way. Several reports of falls associated with use of pramipexole have been coded as "gait abnormality", "ataxia", or "accidental injury".

In addition to a general check of the validity of data submitted in the NDA, the supine and standing BPs that were recorded for studies 1, 4, and 10 were also reviewed and nothing unusual in the reporting system was found. This review focused on obvious inconsistencies and biases and didn't use formal sampling to statistically test for potential bias.

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[1] We will use this definition to reflect objective orthostatic hypotension in subsequent discussion.

4.6 Extent of Exposure

4.6.1 Extent of Exposure, Overall and Stratified by Duration of Use

In the 16 completed RCTs, a total of 879 unique patients were exposed to PPX for a total of 274.4 patient years. Table 4.6.1.1 displays patient exposure in patient years:

Table 4.6.1.1 Duration of Patient Exposure in Patient Years Phase II/III Trials

Type of Trial		Pramipexole	Placebo
Phase II/III (Completed PD Trials)	N Patient Years	702 258.8	551 225.5
Phase II/III (Completed Schizophrenia Trials)	N Patient Years	177 15.9	95 9.3
Total Phase II/III Completed Trials	N Patient Years	879 274.4	646 234.8
All Phase II/III Trials-- Completed and Ongoing	N Patient Years	1408 815	

Appendix 4.6.1.1 is a detailed (separated by disease type) table of the number of patients and estimated Person-Years (PYs) of pramipexole use. PYs were estimated based on the medication records: the exact number of days were computed for each patient and are presented here in 0-24 months, >6-24 months, and >12-24 months intervals.

Overall (including the extension trials that are ongoing), there were 1419 pramipexole patients observed in phase 2/3 studies. Dose information is not available on 11 patients, therefore a total of 1408 patients with 815 PYs of pramipexole use are included in the exposure data, most of it (800 PYs) coming from the PD trials.

4.6.2 Extent of Exposure by Dose

Appendices 4.6.2.1 and 4.6.2.2 show the mean and maximum dose exposures of ET and AT patients by weeks. Table 4.6.2.1 displays the number of pramipexole patients achieving $\geq$ 4.5 mg total daily dose (the maximum dose recommended):

Table 4.6.2.1
Pramipexole Patients Achieving $\geq$ 4.5 mg Total Daily Dose

Population	Number of Patients Achieving $\geq$ 4.5 mg at any Time During Study	Number of Patients Achieving $\geq$ 4.5 mg for $\geq$ 12 Consecutive Weeks	Total Number of Pramipexole Patients Exposed
Completed Studies			
All Patients	474	190	879
All PD Patients	421	190	702
All AT Patients	176	85	286
All ET Patients	245	105	416
All Schizophrenia Patients	53	0	177
Completed + Ongoing Studies			
All Patients	1034	552	1408
All PD Patients	981	552	1231
All AT Patients	377	248	556
All ET Patients	604	304	675
All Schizophrenia Patients	53	0	177

As the above table indicates, in the phase 2/3 completed and ongoing studies, 1034 of the 1408 patients and 981 of the 1231 PD patients studies achieved the highest dose of 4.5 mg/day (604 ET and 377 AT patients). Of the 1034 patients that reached 4.5 mg/day, 552 were exposed to this dose for more than 12 consecutive weeks. In the completed PD studies, 421 of the 702 PD patients achieved the highest dose of 4.5 mg/day (245 ET and 176 AT patients). Of the 421 patients that reached 4.5 mg/day, 190 were exposed to this dose for more than 12 consecutive weeks.

4.6.3 Extent of Dosing in Selected Demographic Groups

There was no difference in the total daily pramipexole dose between ET and AT patients based on gender or age. There were too few non-white patients to generalize about any dosing differences by race. Dose was not described as a function of concurrent medications or by baseline co-morbidity. Tables 4.6.3.1-4 display these findings:

Table 4.6.3.1. AT Patients: Pramipexole Total Daily Dose (mg) by Sex						
Sex	N	Mean	Std Dev	Std Err	Min	Max
Male	149	3.75	1.30	0.11		
Female	86	3.56	1.44	0.16		

Studies Included: M27300010, M27300019, M27300020, M27300022

Table 4.6.3.2. ET Patients: Pramipexole Total Daily Dose (mg) by Sex						
Sex	N	Mean	Std Dev	Std Err	Min	Max
Male	229	3.77	1.49	0.19		
Female	126	3.57	1.51	0.13		

Studies Included: M27300001, M27300004, M27300021

Table 4.6.3.3. AT Patients: Pramipexole Total Daily Dose (mg) by Age						
Age	N	Mean	Std Dev	Std Err	Min	Max
$\leq$ 45	11	3.36	1.56	0.47		
46-55	45	3.70	1.47	0.22		
56-65	78	3.74	1.32	0.15		
66-75	87	3.71	1.30	0.14		
> 75	14	3.33	1.47	0.39		

Studies Included: M27300010, M27300019, M27300020, M27300022

Table 4.6.3.4. ET Patients: Pramipexole Total Daily Dose (mg) by Age						
Age	N	Mean	Std Dev	Std Err	Min	Max
$\leq$ 45	28	3.91	1.55	0.29		
46-55	61	3.32	1.59	0.20		
56-65	108	3.76	1.41	0.14		
66-75	130	3.83	1.48	0.13		
> 75	28	3.48	1.57	0.30		

Studies Included: M27300001, M27300004, M27300021

* Only patients who entered the maintenance interval are included

4.7 Phase 1 Safety

The sponsor has divided the 19 phase 1 studies into 3 types: 3 basic PK studies (29, 30, and 47); 7 studies with "factors affecting PK" (60--ongoing, 61, 62, 63, 64, 65, and 69); and 9 safety and tolerance studies (3, 23, 25, 26, 27, 28, 31, 51, and 73). In the 19 phase 1 studies of the ISS, there were 13 single-dose studies with the pramipexole dose ranging from 0.1-0.4 mg, while in the 6 multiple-dose (with maximum duration of 30 days) studies the pramipexole dose ranged from 0.375-4.5 mg/day. Eight of the single-dose (25, 28, 29, 30, 51, 61, 64, and 65) and 2 of the multiple-dose (62 and 63) were crossover. Four of the studies investigated different pramipexole formulations: study 29 compared pramipexole given intravenously (IV) to an oral solution and a tablet form; study 73 was an eye drop formulation; studies 30 and 62 compared two planned marketed formulations; and study 31 was a transdermal formulation.

All 9 safety and tolerance studies, except for study 73, were conducted in healthy, young males. Study 73, the ocular study, enrolled 6 males and 6 females. The age range in this group was 18-60 years.

Two of the basic PK studies were conducted in healthy males, while the other enrolled males and females. The age range in this group was 25-64 years.

Two of the 7 studies with "factors affecting PK" were conducted in males, another four enrolled males and females, while the age-gender study (60), is currently ongoing and is enrolling elderly (up to 80 years of age) patients of both sexes.

There was only one phase 1 trial with patient (APD) volunteers with N of 3.

Across the phase 1 studies, no deaths or serious AEs were reported.

In the 9 safety and tolerance studies, one placebo patient and 3 pramipexole patients discontinued due to orthostatic hypotension. In studies 25 (single dose), 26, and 3 (both multiple dose), symptomatic orthostatic hypotension (OSH) was identified as a dose-related phenomenon and dose-limiting (maximum tolerated dose of 0.4 mg for study 26). OSH was evident following a single oral dose of 0.2 mg (first dose phenomenon) in study 26.

The time to onset of OSH varied from 30 minutes to 6 hours. The duration of OSH varied from 1 hour or less to at least 8 hours depending upon dose. The magnitude of drug-induced changes in standing blood pressure and pulse rate could not be adequately assessed in all patients because of the inability to stand for vital sign measurements. Changes from baseline observed in the vital signs of three subjects recorded drops in the SBP, DBP, and HR as follows: subject 1, a decrease of 66 mg/Hg in SBP, no change in DBP, and a decrease of 36 bpm in HR; subject 2, a

decrease of 35 mg/Hg in SBP, a decrease of 30 mg/Hg in DBP, and no change in HR (30 minutes after administration of 0.4mg); and subject 3, a decrease of 17 mg/Hg in SBP, a decrease of 26 mg/Hg in DBP, and an increase of 16 bpm in HR. Subject 2 was unable to stand again for 8 hours and continued to experience nausea and asthenia for up to 12 hours. Other symptoms associated with OSH were dizziness, asthenia, malaise, nausea, increased sweating.

There were no clinically significant changes from baseline in ECG parameter reported during the evaluation periods compared with placebo, but one pramipexole patient discontinued due to a "non-serious" atrial tachycardia.

In the 10 PK studies, 9 volunteers discontinued: 1 patient (#26, study 60) for GI bleeding; 2 due to increases in BP; 2 for not feeling well; 1 due to abdominal colic; 1 due to irritability after receiving one dose of Sinemet; and 2 due to nausea and vomiting. In protocol 63, there were 6 patients (#s 1, 3, 5, 7, 9, and 10) who had orthostatic symptoms and 8 patients (#s 1, 2, 3, 5, 7, 8, 9, and 10) who had decreases of systolic BP of more than 20 mm Hg. These changes occurred during the ascending phase of the pramipexole dosing. Also in protocol 65, 2 patients reported dizziness and nausea on standing with some reduction of standing BP at 3 hours post-dosing.

In the safety and tolerance studies, a slight PR interval increase in the ECGs were noted, upon standing.

There were no changes of clinical importance observed in the laboratory parameters. Serum prolactin concentrations were measured in 2 phase 1 studies in healthy volunteers and statistically significant decreases were noted at the first sampling time (30 minutes post dose), maximum effect was reached at 2-4 hours post dose, and were still significantly decreased compared to baseline at 8 hours post dose.

Appendix 4.7.1 summarizes the AEs observed in non-patient volunteers. In these volunteers headache, asthenia, abdominal pain, pain, chills, infection, malaise, back pain, pallor, postural hypotension, vasodilatation, nausea, anorexia, vomiting, constipation, dyspepsia, flatulence, diarrhea, dizziness, nervousness, somnolence, insomnia, concentration impaired, agitation, rhinitis, sweating, pruritis, and decrease in creatinine clearance occurred at a percentage difference of $> 5\%$ (pramipexole $n=240$ and placebo $n=69$). There were 3 reports of syncope in the pramipexole treated healthy volunteers and none in the placebo.

4.8 Mortality in Phase 2/3 Studies

4.8.1 Pramipexole Mortality Compared to Placebo

Through January 31, 1995, there were 17 deaths observed in the development program, of which, 15 cases (deaths or the event leading to death) occurred within 30 days of the last dose of pramipexole or placebo. Of the 17 deaths, 14 occurred with pramipexole and of the 14, 10 occurred in the AT studies and 4 in the ET studies. There was 1 pramipexole death within 30 days of last use in study 1, and 3 deaths in study 10. Table 4.8.1.1 shows the estimated mortality rates for pramipexole and placebo separately in ET and AT patients, and in Schizophrenia patients:

Table 4.8.1.1. Rate of Mortality Observed

	Deaths	N	PYs	Rate / 100 PYs	RR** 95% CIs
Completed Trials					
ET Patients					
Pramipexole	1	416	139.64	0.72	0.80 (0.051, 12.65)
Placebo	1	262	111.61	0.90	
AT Patients					
Pramipexole	3	286	119.14	2.52	2.874 (0.303, 27.23)
Placebo	1	289	113.94	0.88	
Schizophrenia					
Pramipexole	0	117	15.59	0.0	
Placebo	0	95	9.22	0.0	
Completed and Open-Label Ongoing Trials					
ET Patients					
Pramipexole	4	675	363.12	0.11	not applicable#
Placebo	1	262	111.61	0.9	
AT Patients					
Pramipexole	8	556	436.30	1.83	not applicable#
Placebo	1	289	113.94	0.88	
Schizophrenia					
Pramipexole	0	117	15.59	0.0	
Placebo	0	95	9.22	0.0	

** Rate Ratio (Relative Risk) of Pramipexole is defined as: (Death/PYs of PPX)/ (Death/PYs of Placebo)

Because all patients in the ongoing part received pramipexole.

Three patients in study 0012 died but are not included in this table because the randomization codes, # of patients, and drug exposure data were not available. Among these patients, two (#23 and 424) received PPX (and died more than 30 days after the day of the last dose), one (#118) received placebo.

In the completed ET trials, the 6-month mortality risk was 0.24 per 100 patients (1/416) for pramipexole and 0.38 (1/262) for placebo. In the completed AT trials, the 6-month mortality risk was 1.1 per 100 patients (3/286) for pramipexole and 0.4 per 100 patients (1/289) for placebo.

The pramipexole mortality rate per 100 PYs was 3.5 fold greater in AT compared to ET pramipexole exposed patients, but equivalent in the placebo patients. In either ET or AT patients, pramipexole mortality was less than that observed with ropinirole (see Ropinirole NDA review; in a recent publication[2] describing mortality of the Honolulu Heart Study cohort, the mortality rate in 65-69 year olds who developed PD was about 5 per 100 PYs.)

There were no deaths reported in the schizophrenia and depression (completed or ongoing) studies. There were no deaths reported in the 19 Phase 1 studies.

4.8.2 Description of Deaths Observed During Pramipexole's Use

Of the 14 pramipexole deaths, 8 were potentially CV in nature. These 8 deaths are summarized below.

Patient 2433 was a 72YOM who entered the ET study 0001. Parkinson's Disease had been diagnosed 6 months previously. The patient's medical history included coronary artery disease (CAD), myocardial infarction (MI) and triple coronary artery bypass graft surgery (CABG) in 1991, and congestive heart failure (CHF) with resultant liver disease. At baseline, the patient's vital signs were normal. His baseline ECG showed first-degree heart block, left atrial pathology, an old inferior myocardial infarction, poor R-wave progression, and nonspecific ST-T wave changes. The baseline chest X-ray showed moderate cardiomegaly, minimal scarring in the left lung, and emphysematous changes in the upper lobes. During the study, the patient concomitantly received hydrochlorothiazide and lisinopril. The patient was receiving pramipexole 3 mg per day when, on day 29, he experienced mild nausea, which he attributed to an empty stomach. The investigator considered this to be possibly

[2] Morens DM. Evidence against the operation of selective mortality in explaining the association between cigarette smoking and reduced occurrence of idiopathic parkinson disease. Am J Epidemio 1996; 144:400-404.

follow-up telephone call by study staff that evening, the patient stated that the nausea had resolved. On day 32, the patient had an MI and died. The investigator considered these medical events to be unrelated to study medication. Autopsy revealed cause of death to be an MI.

Patient 1065 was a 72YOM who entered the AT study 0010. He had a 5 year history of PD. The patient was maintained on carbidopa-levodopa. Past medical history was significant for an asymptomatic chronic aortic valve murmur with aortic stenosis since 1988, and drug allergies to penicillin and erythromycin. The patient had never smoked and consumed an average amount of ethanol. On dosing day 29 (pramipexole 3.0 mg/day) the patient complained of shortness of breath. The patient was admitted to the hospital and diagnosed with severe pneumonia and severe CHF. While in the hospital, the patient was treated with erythromycin as well as other antibiotics for the pneumonia. He was also given furosemide for CHF. After 7 weeks in the hospital, the pneumonia apparently resolved. The patient was then discharged from the hospital and transferred to a rehabilitation center. After 4 days the patient's condition deteriorated and he was admitted to the coronary intensive care unit. A doppler was done and it indicated destruction of 2 heart valves. The patient died. The patient's wife stated that he died of pulmonary edema (CHF). The investigator indicated neither was related to study drug. The cause of death was coded as CHF.

Patient 1021 was a 64YOM who entered the AT study 0010. He had a 12 year history of PD who began study medication on 10/5/93. Past medical history included dementia, hallucinations, leg cramps, and lightheadedness with an unknown onset date. The initial ECG at study entry showed normal sinus rhythm without evidence of a past infarct. Medication at entry included carbidopa-levodopa 50/200 and amantadine. The patient was an ex-smoker who had not consumed ethanol. At Visit 16, the patient had an ECG per protocol which showed an old inferoposterior wall MI with laboratory results showing a CPK level of 790 IU/L (ULN 235) and AST (SGOT) at 176 U/L (ULN 65). The MB fraction of the CPK was elevated at 11%. The patient apparently had an asymptomatic infarct some time prior to this study visit. In the morning the patient was found dead at home by his wife. The investigator felt that the patient had an infarct of severe intensity as the cause of death although there was no autopsy performed.

Patient 2227 was a 71YOM who entered the ET study 0001 followed by the open-label phase of the study (0002). He was diagnosed with PD 2 years prior to entry in the double-blind phase. The patient's relevant medical history included hypertension, which started 2 years prior to entry in the double-blind phase. During the study, he concomitantly received L-deprenyl 10 mg per day. During the maintenance-dose interval of the double-blind phase, he received pramipexole 2.25 mg per day. In the open-label phase, he completed the ascending-dose interval and entered the maintenance-dose interval receiving pramipexole 0.75 mg per day. The patient's clinic visit on day 60 was unremarkable. The following day (day 61), the patient

went for a walk and subsequently died at home from a possible pulmonary embolism (PE). There were no precipitating adverse events. The investigator considered the PE to be unrelated to the study medication. There was no autopsy performed to document the occurrence of PE.

Patient 2441 was s 80YOM who entered the ET study 0001 followed by the open-label phase of the study (protocol 0002). He was diagnosed with PD 4 years prior to entry in the double-blind phase. The patient's relevant medical history included angina pectoris, CAD, and bypass surgery (all 14 years prior to entry in the double-blind phase), hyperlipidemia (9 years), and shortness of breath and lightheadedness of unknown etiology (1 year). At the first study visit, the patient's ECG showed minimal voltage of LVH, possibly due to an inferior infarct approximately 3 years prior to entry in the double-blind period, and occasional ventricular complexes. He received no concomitant medications for PD during the study. He completed the ascending-dose interval of the open-label phase and entered the maintenance-dose interval receiving pramipexole 4.5 mg per day. On day 126 the patient was hospitalized because of severe chest pain. Prior to admission to the hospital, the patient had taken nitroglycerin sublingually and his symptoms had resolved. Results of an ECG showed atrial fibrillation. The patient was treated with diltiazem (bolus and IV drip) and normal sinus rhythm was restored. His CPK values remained normal (83 U/L), and CK-MB was 7.1 U/L (8.6%). He was discharged from the hospital on day 129. The following day (day 130), the patient collapsed and died. The cause of death was reported as probably a massive M.I. The chest pain, atrial fibrillation, and M.I. were considered by the investigator to be unrelated to the study medication.

Patient 36 was a 65YOM who entered the AT open-label/ongoing study 0014. He had PD for a duration of 21 years which was treated with levodopa/decarboxylase inhibitor and biperiden. Patient history included mild cardiac insufficiency, and swallowing difficulties. He was also receiving hydrochlorothiazide/amiloride for cardiac insufficiency, and trimethoprim/sulfamethoxazole, and acetylcysteine for bronchitis. The patient was receiving pramipexole 4.0 mg/day and levodopa/benserazide, and biperiden. The patient suffered from dyspnea on 12/20/93 which was suspected to be related to a mild cardiac failure: this was treated with furosemide and then amelioride. The episodes of dyspnea reappeared. A lung embolism was suspected but not confirmed on a pulmonary scintigraphy. A relapsing bronchitis possibly due to aspiration because of Parkinson's disease-related swallowing difficulties was diagnosed. The patient was hospitalized from 8/16/94 to 8/20/94 and the diuretic discontinued. On 8/11/94 recurrent syncopes occurred, sometimes obviously following episodes of dyspnea. The neurologist interpreted these syncopes as most probable of the pressor-postpressor type. As a consequence of these events, the daily dose of pramipexole was reduced from 4.0 to 3.0 mg/day by the patient. The patient died on 9/1/94 following syncope. The family doctor stated cardiovascular arrest was the cause death. No autopsy was performed.

Patient 23 was a 75YOM who entered the AT ongoing study 0012. Patient history included posterior M.I., multiple bypass surgery, pulmonary emphysema, extra heart beats, and left anterior hemiblock. Concomitant medications included dihydroergotamine mesylate for low blood pressure, triamterene/hydrochlorothiazide for edema, and acetylsalicylic acid for the condition following the bypass surgery. Pramipeoxle was reduced from 2.25 mg/day to 0.75 mg/day from 10/20/94 to 10/31/94 due to moderate visual hallucinations. He had extra heartbeats on 10/22/94 which were treated with potassium. On 11/9/94 he had moderate dyspnea. Pramipexole was increased again to 2.25 mg/day on 11/10/94. Severe global heart insufficiency was reported on 11/20/94 and required patient hospitalization on 11/25/94. Torasemide treatment began on 11/22/94 and Dihydroergotamine Retard® and Isoptin 80® (verapamil) were discontinued. Study medication was discontinued. He was discharged from the hospital. He died at home of unknown cause. The investigator assessed that there is no reasonable possibility that the global heart insufficiency was caused by the study drug.

Patient 424 was a 76YOM who entered the AT ongoing study 0012. He had Parkinson's disease since 1985. Patient history included acute M.I. and ischemic heart disease. The patient was a known asthmatic for 10 years on chronic bronchodilator therapy. The patient was admitted to the hospital due to shortness of breath on 7/29/94. The patient was diagnosed with hyper-inflated chest with wheezes and breathlessness due to acute infective exacerbation of asthma. Pramipexole was discontinued. The patient was treated with bronchodilators, prednisolone, and erythromycin and was discharged. The patient was readmitted to the hospital with acute breathlessness. The patient was diagnosed with left ventricular failure secondary to ischemic heart disease and exacerbated chest infection. The patient's condition deteriorated with evidence of heart failure and he died. The cause of death was chronic obstructive airway disease with left ventricular failure. Although there was no autopsy to confirm.

4.9 All-Cause and AE Dropout Risks

4.9.1 ET Studies

Table 4.9.1.1 shows the reasons for study dropout in ET patients (completed double-blind placebo-controlled PD trials) by treatment groups.

Table 4.9.1.1 Premature discontinuations: ET Trials (1, 4, & 21)				
Reason For Discontinuation	Number (%) of Patients			
	Pramipexole (N=388)		Placebo (N=235)	
	N	%	N	%
Adverse Events	46	11.9	25	10.6
Lack of efficacy	1	0.3	8	3.4
Protocol Violation	1	0.3	0	0
Lost to Follow-up	3	0.8	0	0
Other	5	1.3	5	2.1
Total Patients	56	14.4	38	16.2

Using a data cutoff date of 1/31/95, the all-cause dropout risk was 14.4% (56/388) in pramipexole ET patients compared to 16.2% (38/235) in placebo.

There were differences in reasons for dropout by treatment group. The AE dropout risk was 11.9% with pramipexole (46 patients) compared to 10.6% with placebo (25 patients). A larger percentage of patients was withdrawn from study because of lost to follow-up with pramipexole than placebo and the opposite was the case for lack of efficacy.

The all-cause dropout risk and AE dropout risk associated with pramipexole use was variable across ET studies. In study 1, the all-cause dropout risk was 17% (28/164) for pramipexole and 20% (34/171) for placebo treated patients. In pramipexole treated patients, the AE dropout risk was 13% (22/164) compared to 14% (24/171) with placebo. In study 21, the all-cause dropout risk was 18% (2/11) for pramipexole and 23% (3/13) for placebo treated patients, and these dropouts were due to AEs.

In study 4, the all-cause dropout risk was 6 times greater with pramipexole, 12% (25/213) than with placebo 2% (1/51). This difference was mostly due to a difference in dropouts associated with AEs. In pramipexole treated patients, the AE dropout risk was 10% (22/213) compared to 0% (0/51) with placebo. This

difference in AE dropout risk seeems to be due to the fact that study 4, as mentioned earlier was a dose-response tolerability study and reached doses of 6.0 mg/day in one of its arms. Clinical intolerance occurred more at this highest dose, whereas in the other protocols the maximum dose reached was 4.5 mg/day.

The clinical characteristics of the AEs associated with dropout are discussed in section 4.10.

4.9.2 AT Studies

Table 4.9.2.1 shows the reasons for study dropout in AT patients (completed double-blind, placebo-controlled PD trials) by treatment groups.

Table 4.9.2.1 Premature discontinuations: AT Trials (10, 19, 20, & 22)

Reason For Discontinuation	Number (%) of Patients			
	Pramipexole (N=260)		Placebo (N=265)	
	N	%	N	%
Adverse Events	30	11.5	42	15.8
Lack of efficacy	0	0	1	0.4
Protocol Violation	1	0.4	2	0.8
Lost to Follow-up	0	0	2	0.87
Other	9	3.5	7	2.6
Total Patients	40	15.4	54	20.4

The all-cause dropout risk was 15.4% (40/260) in pramipexole AT patients compared to 20.4% (54/265) in placebo.

The AE dropout risk was 11.5% with pramipexole (30 patients) compared to 15.8% with placebo (42 patients).

The clinical characteristics of the AEs associated with dropout are discussed in section 4.10.

4.10 Clinical Characteristics of AEs that were Associated with Dropout

Across all phase 2/3 studies, 127 pramipexole patients dropped out of study associated with a serious AE occurrence. No separate lists were provided for the dropouts due to serious AEs for the ET patients and AT patients. Appendix 4.11.1 provides a listing of all serious AEs associated with dropout across all studies. These events were reviewed using the narrative summaries and other supporting data. Overall, there were no cases of agranulocytosis, aplastic anemia, serious skin reactions such as Stevens-Johnson Syndrome, hepatic failure or necrosis, and renal failure or worsening of renal function that were associated with dropout. One patient was discontinued for immune thrombocytopenia and 3 more because of elevated CPKs, with one patient experiencing rhabdomyolysis. Cases are discussed in 4.11 along with other serious AEs.

4.10.1 Clinical Characteristics of AE Dropouts in ET Patients

4.10.1.1 Serious AEs Associated with Dropout in ET Patients

The serious AE dropout risk in ET patients using pramipexole was 2.1% (8/388), while 1.3% (3/235) using placebo. Based upon a review of the investigator verbatims of the 8 patients with serious AEs associated with pramipexole dropout in ET patients, 1 had an AE that was cardiovascular in nature, and this patient eventually expired, (this patient# 2433, study 1 is summarized in the mortality section 4.8.2). The 7 remaining patients were recorded under investigator verbatims of drowsiness (associated with an MVA), decreased platelets, abdominal pain, somnolence (ran off the road in car), paranoid psychosis, sensory hallucinations, and confusion/hallucination.

4.10.1.2 Most Common AEs associated with Dropout in ET Patients

Table 4.10.1.2.1 lists the AEs, irrespective of severity, that were associated with dropout in more than 1% of patients:

Table 4.10.1.2.1

ET Patients

Adverse Events Which Caused Study Termination

Occurring with Frequency > = 1%

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	388	235
CONFUS	4 (1.03)	0 (0.00)
DIZZINESS	8 (2.06)	2 (0.85)
EXTRAPYR SYND	6 (1.55)	15 (6.38)
HALLUCIN	12 (3.09)	1 (0.43)
HEADACHE	5 (1.29)	0 (0.00)
NAUSEA	8 (2.06)	1 (0.43)
SOMNOLENCE	6 (1.55)	0 (0.00)

Studies included M/2730/0001, M/2730/0004, and M/2730/0021

Hallucinations, nausea, dizziness, somnolence, EPS, headache, and confusion were the only AEs associated with dropout in more than 1% of pramipexole patients. They also occurred at least 2 times more frequently than with placebo. Based upon our review of all dropouts from studies 1, 4, and 21, only 1 patient (patient 182, pramipexole exposed) dropped out due to syncope (0.3%).

4.10.2 Clinical Characteristics of AEs Associated with Dropout in AT Patients

4.10.2.1 Serious AEs Associated with Dropout in AT Patients

The serious AE dropout risk in AT patients using pramipexole was 3.1% (8/259), while 2.3% (6/266) using placebo. Based upon a review the investigator verbatims of the 8 patients with serious AEs associated with pramipexole dropout in AT patients, 2 had AEs that were cardiovascular in nature (patient #s 1021 and 1065) and both were discussed in the mortality section 4.8.2.

4.10.2.2 Most Common AEs associated with Dropout in AT Patients

Table 4.10.2.2.1 lists the AEs, irrespective of severity, that were associated with dropout in more than 1% of AT patients:

Table 4.10.2.2.1
AT Patients
Adverse Events Which Caused Study Termination
Occurring with Frequency >= 1%

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	260	264
CONFUS	3 (1.15)	6 (2.27)
DIZZINESS	3 (1.15)	4 (1.52)
DYSKINESIA	5 (1.92)	2 (0.76)
EXTRAPYR SYND	4 (1.54)	13 (4.92)
HALLUCIN	7 (2.69)	1 (0.38)
HYPOTENS POST	6 (2.31)	3 (1.14)

Studies included M/2730/0010, M/2730/0019, M/2730/0020, and M/2730/0022

Hallucinations, dyskinesia, and postural hypotension were associated with dropout in more than 1% of pramipexole patients and occurred 2 times more frequently than with placebo. No pramipexole patients dropped out because of syncope, while 3 patients (#s 1399, 1411, and 1302) dropped out because of syncope, all from protocol 10.

4.11 Serious AEs Associated with Pramipexole

In the ISS, serious AE risks were not described separately for ET and AT patients, as noted earlier a separate analysis was performed for this review. In the 3 ET RCTs the serious AE risk was 5.1% (20/388) with pramipexole and 5.5% (13/235) with placebo. Of these 20 pramipexole patients with serious AEs, 7 were CV in nature. One of these 7 was discussed in the mortality section, of the remaining 6, 2 were MIs, 2 were angina pectoris, and 1 each of pulmonary embolism and left ventricular dysfunction (reported as dyspnea).

Seven of the remaining 13 patients with serious non-CV AEs in the ET studies, were described under section 4.10.1.1. Of the remaining 6 patients, 2 had prostate cancer and 1 patient each were reported to have the following: fractured hip, thyroid nodule, basal cell carcinoma, and early rectal cancer.

In the 4 AT RCTs, the serious AE risk was 7% (18/259) with pramipexole and 7.5% (20/266) in placebo. Of the 18 patients with serious AEs, 3 were CV in nature, of which 2 have been discussed in section 4.8.2, and the other (patient 30, study 19) was reported to suffer from angina pectoris and stenocardia. The remaining 15 patients were reported to have the following: pneumonia, dyskinesia, fractures, somnolence, bladder cancer, paranoia, nausea, neck pain, CPK elevation, increase of periods, back pain, abdominal pain, confusion, and multiple myeloma.

The patients coded with dyspnea had other ongoing AEs such as CHF or pneumonia.

Appendix 4.11.1 provides a listing of all serious AEs occurring in pramipexole and placebo patients. There were no serious AEs consistent with liver failure or necrosis, agranulocytosis, aplastic anemia, hemolytic anemia, or seizures. Several cases are worth summarizing for their possible association with the study medication.

Cardiovascular

In ongoing study #0036, patient #663 experienced severe orthostatic hypotension after the initial dose of pramipexole. This patient was a 72 YOWM (70"/173lb) with a history of PD diagnosed in 1994 and treated with selegiline and levodopa-carbidopa. Concomitant medications were numerous and included: estrogen, Cyproterone, entrophen for prostatic CA, lactulose for constipation and phenazo-pyridine and lorazepam. He did not smoke. The patient received one dose of pramipexole (0.125mg). One hour following initial dose, the patient was reported to have experienced what was termed "severe orthostatic hypotension", with symptoms characterized by feeling faint and lightheadedness. He appeared pale with a rapid pulse. The supine blood pressure was 130/80mmHg and the standing blood pressure was reported to be essentially 0. The patient was unable to stand for 3.5 hours post-dosing. When able to stand, his standing blood pressure was 106/62mmHg. The ECG reading was reported to be normal. The patient was admitted to

the hospital for overnight observation, bedrest and IV fluids. The next day the patient was discharged but complained of lightheadedness and dizziness. Study medication was discontinued following the first dose. Incidentally, the patient had no previous history of symptomatic orthostatic hypotension. At baseline his supine vital signs were 141/76 (84); upon standing they were 129/76 (88). The investigator indicated that the event was probably related to study medication.

Hematologic

Patient #130 (protocol 0004) discontinued on study day 47 because of severe (life threatening) thrombocytopenia. The baseline platelet count was 148,000 cells/mm^3; on day 40 the count was 72,000/mm^3. This was a 72 year old male who was on a 4.5mg per day of pramipexole. The narrative summary and CRF (Volume 576) of the patient revealed that this was a patient who had Parkinson's disease diagnosed approximately 4 years previously. This patient had a past medical history of hypertension (since 1994) and received nifedipine during the study. He began treatment with nifedipine 216 days prior to study entry. On day 40 as mentioned previously the platelet count had decreased significantly. The hemoglobin value and WBC count were unchanged from baseline. On day 43, repeat laboratory results showed a platelet count of 58,000 cells/mm^3. The patient was discontinued from the study. On day 47 the platelet count was 55,000 cell/mm^3. On day 55 bone marrow aspiration showed a slight hypercellularity and trilineal hyperplasia, indicating no bone marrow suppression. The patient was followed by a hematologist. The investigator considered the decreased platelet count to be possibly related to study medication and/or nifedipine. No further information is available on this patient.

Respiratory

Patient #30 (study 0004) was a 77 YOM with pre-existing heart disease and left ventricular dysfunction. The patient had a history of hypertension and coronary arteriosclerosis since 1987 and had cardiac bypass surgery in 1988. During this study, he concomitantly received nifedipine and acetylsalicylic acid and deprenyl for Parkinson's disease. At baseline his vital signs and ECG were normal. On day 8, he began reporting moderate edema in his left ankle but no cardiac symptoms. The patient was receiving 3mg/day of pramipexole when on day 32 he began having dyspnea. On day 36 while receiving 4.5mg/per day of pramipexole the patient was hospitalized because of continued dyspnea. He was found to have pulmonary congestion and ventricular dysfunction. He was discontinued from the study. On day 50, he underwent cardiac bypass surgery. On day 99, the patient was discharged from the hospital.

Serious Laboratory Abnormalities

Patient 1092 was a 49 YOWM (67"/159 lb) with a 5 year history of Parkinson's (carbidopa-levodopa Rx) on multiple medications. Patient had episodes of dizziness, lightheadedness, dyspnea and pain in neck, back and chest for 4 days (7/12/93) prior to a blood pressure reading on 7/16/93 which revealed asymptomatic hypotension (supine vs = 122/88: 80 and standing vs = 100/70; 72) compared with baseline readings of: 121/80 (84) for supine and 110/80 (90) for standing. Seven days (7/23/93) after the orthostatic hypotension at the next laboratory determination an increase in CPK was noted and he was hospitalized diagnosed and treated for rhabdomyolysis. He had a marked increase in CPK--10,631 IU/L (>40 ULN, NR= 0-235). The CPK was fractionated and found to be 100% CPKmm. His baseline on 6/25/93 was 243 IU/L. Patient also had other abnormal laboratory results reflecting release of intracellular contents from skeletal muscle injury, e.g., LDH, AST and uric acid (escaped muscle purine catabolism). His CPKs decreased when drug was stopped. The narrative summary contained in volume 102 stated that patient had multiple bruises. This information was not seen in the CRF.

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4.12 AEs Associated with a Change in Pramipexole Dose

AEs that were associated with a reduction in pramipexole dose were similar to the pattern seen with discontinuations.

4.13 AE Risks Associated with Pramipexole Use Irrespective of Severity

4.13.1 Overall

4.13.1.1 ET Patients

Appendix 4.13.1.1.1 lists AEs that were reported in ≥1% of ET patients assigned pramipexole in placebo controlled ET studies.

Table 4.13.1.1.1 lists the AEs that were reported at twice the rate of placebo and ≥1% (the rest of the AEs in appendix 4.13.1.1.1 were comparable to or less frequent than placebo):

Table 4.13.1.1.1
ET Patients
Adverse Events Occurring Twice as Frequently as Placebo

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	388	235
Fever	4 (1.03)	1 (0.4)
Nausea	107 (27.6)	42 (17.9)
Constipation	53 (13.7)	14 (6.0)
Anorexia	17 (4.4)	5 (2.1)
Dysphagia	7 (1.8)	1 (0.4)
Weight decrease	7 (1.8)	1 (0.4)
Somnolence	85 (21.9)	21 (8.9)
Insomnia	66 (17)	27 (11.5)
Hallucination	35 (9)	6(2.6)
Confusion	16 (4.1)	3 (1.3)
Amnesia	14 (3.6)	4 (1.7)
Hypesthesia	11 (2.8)	2 (0.9)
Akathisia	6 (1.5)	0
Thinking Abnormal	6 (1.5)	1 (0.4)
Libido Decreased	5 (1.3)	0
Myoclonus	5 (1.3)	1 (0.4)
Vision Abnormality	10 (2.6)	0 (0.00)

Studies included M/2730/0001, M/2730/0004, and M/2730/0021

Somnolence (21.9%), constipation (13.7%), and hallucinations (9.0%) were reported in at least 5% of pramipexole patients and were twice as frequent as with placebo.

4.13.1.2 AT Patients

Appendix 4.13.1.2.1 lists AEs that were reported in ≥1% of AT patients assigned pramipexole in placebo controlled AT studies.

Table 4.13.1.2.1 lists the AEs that were reported at twice the rate of placebo and ≥1% (the rest of the AEs in appendix 4.13.1.2.1 were comparable to or less frequent than placebo):

Table 4.13.1.2.1
AT Patients
Adverse Events Occurring Twice as Frequently as Placebo

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	260	264
Chest Pain	8 (3.1)	4 (1.5)
Dry Mouth	17 (6.5)	7 (2.7)
Peripheral Edema	6 (2.3)	2 (0.8)
CPK Increase	3 (1.2)	1 (0.4)
Twitching	6 (2.3)	0
Bursitis	4 (1.5)	1 (0.4)
Myasthenia	3 (1.2)	0
Dyskinesia	123 (47.3)	83 (31.5)
Hallucination	43 (16.5)	10(3.8)
Paranoid Reaction	5 (1.9)	1 (0.4)
Delusions	3 (1.2)	1 (0.4)
Sleep Disorder	3 (1.2)	0
Rhinitis	7 (2.7)	3 (1.3)
Pneumonia	5 (1.9)	0
Diplopia	3 (1.2)	0
Urinary Frequency	15 (5.8)	7 (2.7)
Vision Abnormality	8 (3.1)	2 (0.8)

Studies included M/2730/0010, M/2730/0019, M/2730/0020 and M/2730/0022

Hallucinations (16.5%), urinary frequency (5.8%), and dry mouth (6.5%) were reported in at least 5% of pramipexole patients and were twice as frequent as with placebo.

4.13.2 Dose Response

4.13.2.1 Dose Response in ET Patients

Appendix 4.13.2.1.1 shows the effect of dose on AE risk for AEs that were reported in at least 10% of ET patients using pramipexole (irrespective of frequency in placebo). The sponsor's analysis was broken down not by individual doses but by phases: ascending, maintenance, and taper phases of the dosing cycles. The largest risk reported was during the ascending phase of the dosing. AEs shown are: asthenia, headache, infection, pain, constipation, nausea, dizziness, insomnia, and somnolence.

Since study 4 was designed as a specific dose response study, its dose-relatedness of adverse events was assessed separately. This study was performed in 264 patients with early Parkinson's disease. In this study patients were randomized equally to target dosages of 0, which was a placebo, 1.5mg; 3.0mg; 4.5mg or 6.0mg per day of pramipexole. (Doses given orally on a t.i.d. schedule with a six week dose escalation period and a four week maintenance period). With increasing dosages of pramipexole, there were more adverse events reported in the digestive system (nausea 15% (8/54), 17% (9/54), and 20% (11/55) for the 1.5 mg/day, 4.5mg/day, and 6.0mg/day doses, respectively) and the CNS (somnolence and insomnia) in the maintenance phase of the study. Vital signs were measured at each visit and time of last dose recorded, but the BP measurements were not timed to last dose.

4.13.2.2 Dose Response in AT Patients

Appendix 4.13.2.2.1 shows the effect of dose on selected AEs in AT patients following a similar approach as in ET patients. The sponsor's analysis was broken down not by individual doses but by phases: ascending, maintenance, and taper phases of the dosing cycles. The largest risk reported, here as well was during the ascending phase of the dosing. The AEs shown include dyskinesia, nausea, orthostatic hypotension, confusion, and hallucination.

No specific dose-response design studies were performed in the AT patients.

4.13.3 AE Occurrence and Plasma Concentration

Pramipexole plasma concentration was not measured at the time of AE occurrence in either ET or AT patients.

4.13.4 AE Risk by Time Since First Exposure

Appendix 4.13.4.1 shows risks for AEs reported in ≥ 10% of ET patient by time since first exposure.

Appendix 4.13.4.2 shows risks for AEs reported in ≥ 10% of AT patients by time since first exposure.

In general, the findings agree with those observed for dose response. The most frequently reported AEs, here as well occurred with the lower doses, which correspond with the ascending phase of the dosing.

4.13.5 AE Risk and Concurrent Medication Use

The sponsor examined the effect of concurrently used medications on AE risk that might be attributable to pramipexole for both ET and AT patients. AEs were selected if reported in at least 5% of a study population and concurrent medications were selected if their extent of use was at least 10%. The concurrent medications selected were selegiline, anticholinergic agents, amantadine, domperidone, beta blockers, thiazide diuretics, tricylic antidepressants, acetylsalicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and tocopherol.

4.13.5.1 AE Risk and Concurrent Medication Use In ET Patients

When examining the RRs (pramipexole compared to placebo), there were no differences of any consequence observed in the AE occurrence between the different concurrent medications analyzed. A search did not identify an RR that was two-fold greater than any comparison. Overall, no specific patterns were noted.

4.13.5.2 AE Risk and Concurrent Medication Use In AT Patients

When examining the RRs (pramipexole compared to placebo), there were no differences of any consequence observed in the AE occurrence between the different concurrent medications analyzed. A search did not identify an RR that was two-fold greater than any comparison. Overall, no specific patterns were noted.

4.13.6 AE Risk by Age, Gender and Race

Data from the pivotal trials were pooled in the ISS. For this review a subgroup analysis of AE risk by age and gender for the ET and AT trials was performed. Appendices 4.13.6.1-2 and 4.13.6.3-4 display the age (< 45, 45-55, 55-65, 65-75, and >75) and gender based analyses for AEs reported with a frequency of > 5% with analyses of relative risk (RR-relative rate for pramipexole/rate of placebo). A summary of findings in the appendices follows:

In the age analysis of the ET patients, when examining the RRs (pramipexole compared to placebo), there were no major differences observed in the AE occurrence between the different age groups analyzed. A search did not identify an RR that was two-fold greater than any comparison. However, there was a specific pattern of increasing RR with increasing age for the reported AE Hallucination.

In the age analysis of the AT patients, when examining the RRs (pramipexole compared to placebo), there were no major differences observed in the AE occurrence between the different age groups analyzed. A search did not identify an RR that was two-fold greater than any comparison. However, there was a specific pattern of increasing RR with increasing age for the reported AE Hallucination (even more prominent than with the ET patients).

In the gender analysis of the ET patients, depression was reported at a > two-fold higher RR in males than in females; and hallucination was reported at a > two-fold higher RR in females than in males. Other AEs were comparable.

In the gender analysis of the AT patients, dyspepsia was reported at a > two-fold higher RR in males than in females; and hallucination and urinary frequency were reported at a > two-fold higher RR in females than in males. Other AEs were comparable.

There were too few non-white patients exposed to pramipexole to examine variation in risk by race.

4.13.7 AE Risk for Selected Underlying Diseases

To describe any potential modification in pramipexole risk for patients with selected underlying (concurrent) diseases, The sponsor used a similar approach to that with concurrently used medications and for demographic subgroups. Concurrent disease was defined as illness present at baseline. Concurrent diseases that occurred in >=5% of pramipexole patients were used to calculate the relative risk. The concurrent diseases selected for study were arthritis, CV disease, constipation, depression, dizziness, hypercholesterolemia, hypertension, insomnia, and prostate disease.

When examining the RRs (pramipexole compared to placebo) in ET patients, there were no differences of any consequence observed in the AE occurrence between the different concurrent illnesses analyzed. A search did not identify an RR that was two-fold greater than any comparison. Overall, no specific patterns were noted.

When examining the RRs (pramipexole compared to placebo) in AT patients, there were no differences of any consequence observed in the AE occurrence between the different concurrent illnesses analyzed. A search did not identify an RR that was two-fold greater than any comparison. Overall, no specific patterns were noted.

4.14 AE Risk During Tapering

There were no significant differences in the AEs reported during tapering. In protocols where dose reduction was followed, no AEs could be attrbuted to drug withdrawal. There seemed to be more AEs (tremor, EPS, and hypokinesia) consistent with worsening of PD.

4.15 Changes in Laboratory Parameters Associated with Pramipexole Use

Here again, the sponsor primarily presented pooled analysis of the "adequate and well-controlled studies", 0001, 0004 (the studies in early PD patients) and 0010 (the study in advanced PD patients), without disregarding the other 6 PD studies. This portion of the review will follow the sponsor's approach. However, it should be noted that the individual ET and AT study reports were reviewed. Appendix 4.15.1 displays the laboratory criteria used by the sponsor as normal values; values outside these predefined limits were flagged. Appendix 4.15.2 summarizes the data of laboratory values with abnormal shifts (outside these predefined limits) in the 3 pivotal trials.

Hematology

Except for lymphocytes, the incidence of hematologic laboratory values exceeding predefined limits for pramipexole-treated patients was less than that of placebo patients and/or was lower than 1%. Approximately 3% of the pramipexole-treated patients (16/547) vs approximately 2% of placebo-treated patients (7/394) had lymphocyte values lower than the predefined limits. There was no statistically significant differences between the groups (Sponsor's Fishers' Exact Test, p=0.292).

There were no statistically significant changes in mean hematologic values for the pramipexole and placebo groups separately and when compared to each other across the baseline values. There was no evidence of dose-relatedness (1.5mg/day to 6.0mg/day in protocol 0004) for the hematologic analytes measured: HgB, WBC, and platelets.

For the other PD studies there were 2 pramipexole-treated patients (1.5%) who had spurious low lymphocyte values outside the predefined limits during treatment compared with 3 (2.2%) of the 137 placebo-treated patients.

In the PD studies one patient (patient #130, protocol 0004) out of 702 of the pramipexole-treated patients discontinued due to thrombocytopenia (case discussed in section 4.11). One placebo-treated patient (0.3%) discontinued because of leukopenia. In the completed schizophrenia studies, as well as the ongoing studies in Parkinson's disease, there were no reports of discontinuations because of hematologic laboratory values. In the review of deaths and serious AEs, no cases of aplastic anemia or agranulocytosis were found.

Blood Chemistry Parameters

Appendix table 4.15.2 summarizes all patients with laboratory data exceeding predefined limits in the pooled adequate and well-controlled studies. The proportion of patients which moved from a predefined normal GGT and CPK value to a higher abnormal value were 2% and 3.5%, respectively, in the pramipexole treated patients. These shifts were similar in the placebo treated patients. About 1% of the pramipexole treated patients had shifts to

abnormal values for AST and ALT. This was not observed for placebo. The incidence of shifts in other analytes (both for placebo and pramipexole treated patients) were less than 1% and clinically not significant.

A summary of patients with elevated CPKs is located in Appendix table 4.15.3. It enables one to appreciate the wide range of dispersion in values for both treatment groups. In the pooled database 19 (3.5%) of the pramipexole treated patients compared with 9 (2.3%) of the placebo treated patients had CPK values which exceeded predefined limits. There was no statistically significant difference between the two groups, (sponsor's Fishers' Exact Test, p=0.335).

Of the 19 pramipexole treated patients with elevated CPKs, 13 were reported in the 2 early Parkinson's studies and 6 in the advanced Parkinson's study 0010. In the placebo group, there were 5 reports in the early and 4 reports in the advanced. The AT study 0010, reported a statistically significant mean change elevation from baseline in total CPKs in the pramipexole group compared to the placebo group (+21.31 vs -1.28, $p<0.003$). The ET dose-response study (protocol 0004), also reported a mean change from baseline greater in the pramipexole than placebo group for both the ascending and maintenance phases at all doses other than the 4.5mg/day dose. Table 4.15.1, which displays the mean changes from baseline to endpoints for CPKs during the dosing periods for protocol 0001, can be considered representative of all PD studies:

Table 4.15.1. Mean changes from baseline to endpoints for CPKs

Group	WEEKS Ascending*		Maintenance		Reduction
	4	7	8	16	24
Pramipexole	+24	+27	+32	+31	+30
Placebo	+9.5	+1.0	+8.0	+6.0	+13

+ = Dosing phases

In the 6 studies designated other controlled studies, only the laboratory analyte CPK exceeded predefined limits (shifts to abnormal). Five (7%) of the 76 pramipexole patients exceeded predefined limits compared with none of the 83 placebo patients evaluated. For three of the five pramipexole patients, the abnormal values were spurious. For the other two patients their endpoint values remained elevated: one patient started with a high baseline CPK value of 257 u/L (normal range: 0-120 u/L) and at endpoint it was 336 u/L. The remaining patient (No. 20, Protocol 0020) was a 58-year old man with a CPK value of 86 u/L at baseline, at day-22 value of 219, and an endpoint value (day 48) of 3498 u/L. The patient was discontinued because of this elevated CPK. Although the patient had many other adverse events, a cause for the elevated CPK could not be identified by the investigator. Myopathy was not reported. After drug discontinuation, the CPK had returned to within the normal range.

As discussed in previous sections (serious and dropouts), a careful assessment for rhabdomyolysis was performed (by examining individual CRFs) and one patient was found that experienced rhabdomyolysis. The case is discussed in the serious AEs section.

Patients with increased GGTs are summarized in Appendix table 4.15.3. Of the 11 patients with GGT values outside the predefined limits during treatment, 5 had baseline elevations and 6 had post baseline elevations. Four pramipexole treated patients, from protocol 10, (number 1061, 1118, 1171, and 1226) had GGT values which ranged from 206 to 898 u/L (NR: 0-65 u/L). In all cases patients had clinically significant elevations of other liver enzymes as well (either AST or ALT values). In the placebo group one patient (number 1242) was identified with clinically significant elevations in GGT (value was 268 u/L). Mean changes in GGT levels from baseline were examined and there were no statistically significant differences between pramipexole and placebo.

Four patients (#s 182, 1171, 1021, 1092) had elevated ASTs and 4 patients (#s 1171, 1061, 1226, 1118) had elevated ALTs. Data are summarized in appendix table 4.15.3. The following patients reported values which were > =2.5 x ULN: patient #171 in protocol 0010 (AST, ALT and GGT); patient #1118, (ALT and GGT) and patient #1226, (ALT and GGT).

In protocol 10 (AT trial), there were statistically significant mean change elevations of ALT and AST from baseline in the pramipexole treated patients. Table 4.15.2 displays these differences:

Table 4.15.2. ALT and AST mean change from baseline

		Mean change from Baseline		
Visit number	Laboratory analyte	Pramipexole	Placebo	p-value
18	ALT IU/L	+5.14	0.28	0.005
	AST IU/L	+2.43	0.02	0.02
19	ALT IU/L	+4.3	-0.9	0.001
	AST IU/L	+1.8	-0.7	0.01

There were no differences in mean changes from baseline to designated endpoints between the treatment groups with respect to AST and ALT values in protocols 1 or 4 (ET trials).

One patient in protocol 0010 (patient #1226, CRF in volume 610) withdrew from pramipexole treatment because of the adverse event hepatitis and abdominal pain. He had elevated hepatic enzymes and is discussed in this section. Patient #1226 was a 67-year old white male with a past medical history significant for a cholecystectomy, kidney stones and removal of skin cancer. The patient had Parkinson's disease since 1964 treated with

antiparkinsonian medication including benztropine emsylate and carbidopa-levodopa. When the patient was seen for visit 5, the liver tests were noted to be markedly elevated with GGT at 3630 u/L (upper normal 75 u/L) as well as elevated AST, ALT, and alkaline phosphatase (values could not be read from the CRF). Repeat liver function test at visit 6 showed further increases in AST and LDH (once again, the values were illegible). The dose level of study medication was increased as per protocol to dose level 5. At visit 7, a general hepatitis A screen was reported to be positive. However, further workup indicated patient did not have active hepatitis (only past exposure). Further additional workup for hepatitis B and C was reported to be negative. At visit 8, additional LFTs were done demonstrating continuing elevations and these values were noted to be as follows: AST value on visit 8 was 205 u/L (NR: 0-65 u/L), ALT was 205 u/L on visit 8 (NR: 0-55 u/L) and GGT value on visit 8 was 1301 u/L (NR: 0-65 u/L). Study medication was discontinued. Patient was referred to a gastroenterologist who felt that the patient's elevated LFTs were drug-related. Within 30 days of discontinuing medication, normalization of LDH, AST and ALT occurred. Throughout the total time period that LFTs were elevated total bilirubin levels remained within the normal range. Based upon the patient's course and normalization of laboratory abnormalities following discontinuation of study drug, the abnormal LFTs appeared to be possibly related to the pramipexole. The patient did enter the open-label pramipexole study five months later. There were no reports of elevated LFTs.

As mentioned in the dropouts section, in the PD trials 3 pramipexole-treated patients and 1 placebo-treated patient discontinued because of chemistry AEs. These patients (pramipexole and placebo) discontinued because of increases in CPK, and were discussed earlier. In the completed schizophrenia studies, 1 out of 177 pramipexole-treated patients discontinued because of chemistry values considered abnormal (CPK increase--information on this patient is not available at this time) and 1 placebo-treated patient out of 95 discontinued due to an elevation in ALT. In the ongoing studies in Parkinson's disease, 1 out of 1,056 pramipexole-treated patients, discontinued (elevation in CPK). Patient #049 (protocol 0012 CRF in vol 667) discontinued because of increased CPK, pain in arm and back and dyskinesia.

Urine Analysis

Appendix table 4.15.2 lists the incidence of clinically significant urinalysis laboratory values exceeding predefined limits in the adequate and well-controlled studies. With the exception of urinary protein, the incidence of abnormalities for pramipexole-treated patients was less than that of placebo patients and/or was lower than 1%. In the pramipexole-treated patients 2.2% of the patients (8/364) vs 1% of the placebo-treated patients (2/219) had an abnormal laboratory urinary protein value which was abnormally high. Seven of the 8 pramipexole patients with urine protein values outside predefined limits also had protein in their urine at baseline.

There were no statistically significant changes in mean urinalysis analytes values for the pramipexole and placebo groups compared with baseline values.

In the other conrolled studies, the only value that was higher in the pramipexole-treated group compared to the placebo-treated group was the WBC in the urine where 25% of the pramipexole-treated patients (13/53) vs 10% of the placebo-treated patients (5/50) had values outside exceeding the predefined limits. There were no discontinuations reported.

There was no reporting in the ISS of urinary crystals. However, a review of numerous CRFs revealed that uric acid and calcium oxalate crystals were reported in pramipexole treated patients.

4.16 Changes in Vital Signs Associated with Pramipexole Use

Special attention was focused upon vital sign monitoring as a result of a clinical hold placed on the original IND 34,851 because of reports of hypotension (see letter of June 20, 1990, IND 34,851). In the phase 2/3 studies BP measurement was not timed relative to the time of dosing, but vital signs were checked at every visit.

As displayed in appendices 4.13.1.1.1 and 4.13.1.2.1, although there was little difference between pramipexole groups and placebo groups in the incidence of orthostatic hypotension, there was a great disparity between the ET and AT groups: 7.7% of ET patients taking pramipexole reported orthostatic hypotension and 52.7% of AT patients reported the same AE. A similar disparity between ET and AT placebo groups was noted.

A total of six (1%) of the pramipexole treated patients compared with 1 (0.3%) of the placebo treated patients discontinued treatment due to vital signs. Five (1 ET and 4 AT) of the six events were due to orthostatic hypotension.

4.17 Changes in ECG Parameters Associated with Pramipexole Use

Across the development program, there were no consistent changes in ECG or AEs that suggested that pramipexole had deleterious effects on cardiac function. Most studies had extensive ECG monitoring, and these did not reveal differences in incidence of any changes in ECG between pramipexole and placebo.

In the 3 adequate and well-controlled studies 0.5% (3/558) of the pramipexole treated patients compared with 0.2% (1/400) of placebo treated patients discontinued because of ECG abnormalities. Overall in the completed controlled studies in Parkinson's disease, 0.4% (3/702) of the pramipexole compared with 1% (4/551) of placebo treated patients discontinued because of ECG abnormalities.

The 3 pramipexole treated patients (patient numbers 114, 98 and 91) who discontinued from

protocol 0004 reported ECG abnormalities of palpitations, tachycardia, and an irregular heart rate (arrhythmia) that were not causally related to pramipexole. The 1 placebo patient (patient # 1399) was from protocol 10.

4.18 Dyskinesia

The Parkinson's Dyskinesia Scale (PDS) was used by investigators to characterize the severity of abnormal movements in patients. There was no difference in the PDS over time between treatment groups.

4.19 Review of Special Studies

4.19.1 Withdrawal Potential

Pramipexole is not a controlled substance. Pramipexole has not been systemically studied in animals or humans for its potential for abuse, tolerance or physical dependence; and receptor binding studies for the opiate receptors were not performed.

In protocols where dose reduction for one week was followed, no AEs could be attributed to drug withdrawal. Symptoms such as tremor, EPS, asthenia, hypertonia, gait abnormality, and hypokinesia during dose reduction were attributed to the underlying PD. In the clinical trials and in the labelling, the sponsor recommends that patients discontinue treatment gradually over a one-week period, despite instances of patients discontinuing abruptly or tapered at a rate faster than recommended exhibiting no withdrawal symptoms.

4.19.2 Interaction Studies

Four phase I studies were conducted to evaluate drug interactions of pramipexole with other drugs.

The potential interactions between probenecid, pramipexole, and cimetidine were investigated in six male and six female volunteers according to a three treatment crossover design (study 0061). This study demonstrated that concomitant therapy with drugs secreted by the cationic-transport system of the renal tubules may necessitate dose reduction of pramipexole.

In a modified and crossover design study (study 0063) of five male and four female volunteers, the pharmacokinetics of pramipexole and levodopa administration were examined. Pramipexole did not alter the extent of levodopa absorption, but there were differences in levodopa Cmax (42% increase) and Tmax (71% decrease) suggesting a faster rate of absorption, although the small number of subjects and the high degree of variability produced precluded a definitive estimate of the magnitude of this change. Titration of the levodopa dose to the individual patients optimum therapeutic response may be required

during concomitant treatment with pramipexole.

The sponsor did not perform drug metabolism studies. The rationale was that the high bioavailability (>90%) indicates no first pass effect and hence no phase 1 oxidative metabolism of the drug.

4.20 Human Reproduction Data

No pregnancy exposures were observed with pramipexole. Preclinical studies with high doses (1.5 mg/Kg/day) revealed embryo toxicity demonstrated by post-implantation loss, late embryonic deaths, and decreased fetal weights). No teratogenic effects were observed at any dose.

4.21 Human Carcinogenicity Potential

Pramipexole was not carcinogenic in the drug safety studies except for a 2 year study in rats, in which Leydig cell adenomas were found. The sponsor attributes the Leydig cell hyperplasia and increased number of adenomas to pramipexole-induced hypoprolactinemia. Because of the common occurrence of Leydig cell tumors in rats, the agency's cancer assessment committee (CAC) no longer requires mentioning of such tumors in the labelling.

4.22 Overdose Experience

There were no reports of intentional overdoses. There was only one report of an unintentional overdose in a patient with a 10-year history of schizophrenia. He took 11mg/day of pramipexole. No adverse events were reported.

5 Summary of the Safety Experience in the Pramipexole Development Program

5.1 General Comments

Overall, the pramipexole development program has included adequate short and long-term pramipexole use to evaluate its safety separately in ET and AT patients. There appears to have been enough experience at 4.5 mg per day, the maximum recommended dose, to evaluate the relative safety of that dose.

Follow-up of patients was good with few patients lost to follow-up. The clinical data provided was sufficient in most cases to describe the general character of most treatment emergent AEs.

On balance, there was little difference between pramipexole and placebo in the ET and AT patient populations. All cause study dropout risk for the ET patients was reported to be 14.4% in the pramipexole treated patients and 16.2% in the placebo, while 15.4% and 20.4%, respectively for the AT pateints. Dropout risk due to AEs for the ET patients was reported to be 11.9% in the pramipexole treated patients and 10.6% in the placebo, while 11.5% and 15.8%, respectively for the AT pateints. Dropout risk due to serious AEs for the ET patients was reported to be 2.1% in the pramipexole treated patients and 1.3% in the placebo, while 3.1% and 2.3%, respectively for the AT pateints. Serious AEs for the ET patients was reported at 5.1% in the pramipexole treated patients and 5.5% in the placebo, while 7.0% and 7.5%, respectively for the AT pateints. Mortality rate for the ET patients was reported at 0.34 in the pramipexole treated patients and 0.34 in the placebo, while 1.1% and 0.4, respectively for the AT pateints.

The events that were reported in more than 5% of pramipexole ET patients that were at least 2 times more frequent than in placebo were hallucinations and somnolence, while hallucinations and dry mouth in AT patients.

As a point of interest the OSH risk in the ET patients was reported at 7.7% in the pramipexole treated patients and 8.9% in the placebo, while 52.7% and 48.1%, respectively for the AT pateints. Risk for syncope in the ET patients was reported at 1.3% in the pramipexole treated patients and 0.9% in the placebo, while 1.5% and 2.7%, respectively for the AT pateints.

5.2 Cardiovascular System

In the preclinical studies, pramipexole lowered blood pressure and heart rate, especially in anesthetized animals. Results of experiments with antagonists indicated that the cardiovascular effects are related to the compound's main mechanism of action, (i.e., agonist at dopamine D2 receptors). This seems to be, however, primarily a first-dose effect. No (in rats) or little (in rhesus monkeys, especially after repeated doses) hypotensive

activity was found after oral administration to conscious animals. No interaction with l-deprenyl or L-dopa plus carbidopa could be observed on cardiovascular parameters.

In clinical pharmacology studies, pramipexole was associated with dose-related symptomatic orthostatic hypotension (OSH) in normal subjects beginning at the 0.2 mg dose and a dose-limiting phenomenon at a 0.4 mg/day dose in some studies. OSH occurred after the first dose in some volunteers and as early as 30 minutes at the highest doses. The duration of OSH varied from 1 hour or less to 8 hours, postural syncope occurred in some subjects. The magnitude of the drug-induced changes in standing blood pressure and pulse rate could not always be assessed because subjects were unable to stand for vital sign measurements. There were no clinically significant changes in ECG measurements during the evaluation periods.

In the phase 2/3 trials, there were exclusion criteria of not enrolling patients with active CV disease. The CV events that were most strongly associated with pramipexole use in the phase 1 trials were not consistent with findings in the phase 2/3 trials. In the ET studies, study dropouts and AE dropouts were similar in the pramipexole and placebo groups. Only one of the serious AE dropouts was CV in nature. There were 20 serious AEs reported in patients exposed to pramipexole and 7 were CV in nature, but none reported syncope or orthostatic hypotension. There were 5 syncopes reported in patients exposed to pramipexole and 2 in patients exposed to placebo.

In the AT studies, pramipexole was not associated with increases in study dropouts either overall or that associated with AEs. There was no clear pattern of AEs associated with dropouts. None of the 18 patients with serious AEs and exposed to pramipexole had syncope or orthostatic hypotension. There were 4 syncopes reported in patients exposed to pramipexole and 7 in patients exposed to placebo.

Overall, irrespective of severity there were 7 reports of dropouts due to the AE orthostatic hypotension in pramipexole treated patients in the combined ET, AT studies (1 and 6, respectively) compared with 3 reports in the placebo group in the combined ET, AT studies (0 and 3, respectively). Overall, there were few reports of symptomatic orthostatic hypotension, but two placebo and one pramipexole treated patients reported syncope as an AE and were discontinued. Of special interest is an ongoing double-blind, placebo-controlled study (protocol 55), where the CV effects of pramipexole in PD is being evaluated by performing the valsalva maneuver and tilt table testing.

ECG recordings in animals revealed bradycardia with a corresponding increase in the R-R interval. Other than bradycardia, there was no evidence in animals or humans that pramipexole affected cardiac conduction or was associated with dysrhythmias.

The 8 deaths that were potentially CV in nature, none could be attributed to any CV effect that pramipexole may have had.

In summary, the CV effects of OSH in healthy normal volunteers appear to result from the dopaminergic activity of pramipexole. Despite the benign clinical picture observed for pramipexole, we must keep in perspective its reported pharmacologic mechanism of action as a D_2 and alpha$_2$ agonist as well as the fact that in the studies, patients with significant underlying CV disease were excluded from participation. The CV effects of pramipexole may be detrimental in patients with advanced Parkinson's disease who may have impaired autonomic nervous system (Shy Drager Syndrome), impaired cardiovascular function, cardiovascular diseases which could be exacerbated by hypotension, in conditions such as hypovolemia and dehydration, and in conditions associated with abnormal early diastolic ventricular filling. Moreover, many elderly patients have resting cerebral blood flow that is close to the threshold for cerebral ischemia and thus, relatively small acute blood pressure reductions may produce cerebral ischemic symptoms such as dizziness, syncope, or falls.

5.3 Central Nervous System

In the animal studies, aside from behavioral changes, there were few significant CNS effects induced by acute treatment with pramipexole. The animal models demonstrated the sedating properties of pramipexole. At various ranges of dosing, ataxia was not reported. Pramipexole did not lower the threshold for seizures. Animal pharmacology studies to determine opiate-like activity for pramipexole were not performed, but there was no evidence of withdrawal.

Adverse events reported from the phase 1 studies were frequently related to the CNS (most frequently dizziness) and did not include any event not seen in phase 2/3 studies.

Reports of CNS AEs were more frequent in the AT group than in the ET group. The following events were considered drug-related in patients with early Parkinson's disease: hallucinations, somnolence, insomnia, and confusion. In the patients with advanced Parkinson's disease the following were considered drug-related: hallucinations, dyskinesia, and confusion. Parenthetically, M.V.A.s occurred in some patients treated with pramipexole and was attributed to somnolence.

There was no evidence of opiate - type withdrawal during the dose-reduction phase in the phase 2/3 studies.

In summary, the CNS adverse effects are known side effects of dopamine agonists. Pramipexole may exacerbate preexisting dyskinesia and potentiate the dopaminergic side effects of such drugs as levodopa.

5.4 Dermatological

There was no increase in the risk for rash. There were no hospitalizations for serious skin reactions in the pramipexole-treated patients.

5.5 Gastrointestinal

Preclinically, like other dopamine agonists, pramipexole induced emesis and the effect was blocked with a dopamine antagonist. Pramipexole inhibited gastrointestinal transit time, which in individuals older than 70 years of age may exacerbate an already existing situation. Nausea and vomiting were frequently reported in the Phase 1 studies. Two patients dropped out because of these events.

In phase 2/3, the AEs nausea and constipation featured prominently in the ET studies, but not in the AT. Other common causes of nausea, M.I.s and hepatitis were not reported in the patients who discontinued pramipexole use.

In summary, nausea as an AE should not be minimized. The potent influence of nausea on vasopressin release and subsequent antidiuretic effect is well established and may have important clinical consequences, particularly in the elderly P.D. patient.

5.6 Genitourinary/Renal

In animal studies, conflicting results were obtained in assessments of the renal effects of pramipexole in rats with respect to effect on urinary volume and electrolyte excretion. Contrasting effects were reported for pramipexole in conscious and anesthetized animals and may have been due to the anesthesia, dose, or strain of rats. The effectiveness of the D_1 antagonist against pramipexole suggest that the renal effects of pramipexole may be mediated by D_1 receptors. Noteworthy is the fact that both D_1 and D_2 receptors are associated with the renal vascular and tubular systems in humans. Moreover, $alpha_1$ receptors are found in the collecting tublules of humans.

In the Phase 1 studies, one pramipexole-treated patient dropped out because of renal colic. There were no reports of hyperuricemia or urinary crystals.

In the Phase 2/3 studies, twice as many AT pramipexole-treated patients reported genitourinary AEs than ET pramipexole-treated patients. There were no differences between the placebo groups. In the AT group, urinary frequency was reported by four times as many pramipexole-treated patients as ET pramipexole-treated patients. The placebo AT and the placebo ET groups were similar. A review of CRFs indicated the presence of calcium oxalate and uric acid crystals in some of the pramipexole treated patients, but these were not analyzed in the data presented by the sponsor and hence difficult to quantitate.

In summary, pramipexole is eliminated through the kidney and patients with renal insufficiency should be cautioned about dosing. Moreover, a normal serum creatinine level may mask renal dysfunction in frail older persons with low muscle mass. Creatinine clearance estimations may be a more useful measure of renal function in this age group of PD patients.

5.7 Hematologic

In animal studies, pramipexole was associated with thrombocytopenia in 20 to 40 percent of female rats.

In phase 2/3 studies, there was one case of severe thrombocytopenia which appeared to have been caused by an immune mechanism possibly associated with pramipexole. Of note is the fact that other sulfa-containing drugs also have been implicated in acute thrombocytopenia.

5.8 Metabolic Endocrine

Serum prolactin was decreased in both animals and humans in the preclinical and Phase 1-3 studies during exposure to pramipexole. Dopamine agonists are known to influence the lactotrope and prolactin secretion.

Overall, in the ET and AT studies, dropouts were infrequent. Most of the dropouts were due to elevated CPK levels and occurred more frequently in the pramipexole than the placebo groups.

As discussed previously, more pramipexole-treated patients than placebo-treated patients had reports of CPK levels exceeding predefined limits. The fractionation of CPK was not usually carried out in the studies. Of the 19 reports of elevated CPKs in pramipexole-treated patients, 13 occurred in the ET protocols and 6 in the AT protocols. In the placebo groups, the distribution was 5 and 4, respectively for the above protocols. Dyskinesia did not appear to be a contributing factor to elevated CPKs in all cases.

In summary, CPK increases above baseline occurred in pramipexole and placebo-treated patients. Exposure adjusted rates (per 100 patient-years) were more than twice as high for pramipexole-treated patients compared with placebo. The increases in CPK levels were often preceded by changes in blood pressure and not always preceded by reports of physical over activity and/or excessive muscular exertion. In at least one pramipexole-treated patient, increases in CPK were associated with rhabdomyolysis.

5.9 Musculoskeletal

There was one case of rhabdomyolysis associated with pramipexole. Preclinically, there

were no reports of adverse events associated with this system.

5.10 Respiratory

Preclinically, there were no respiratory effects noted with pramipexole. In Phase 2/3 studies, there was no evidence of pulmonary fibrosis with pramipexole. Pulmonary fibrosis has been reported infrequently with dopamine agonists of different chemical structures. The present database had limited power to have detected any pulmonary fibrosis cases even assuming this condition can be diagnosed accurately.

There was an increase in respiratory AEs in the pramipexole AT patients compared with placebo, whereas the reverse was true in the ET patients. More AT pramipexole- treated patients reported respiratory AEs than ET pramipexole-treated patients. Once again, the reverse was true for the placebo-treated patients. AT pramipexole-treated patients may have been at greater risk for pneumonia. There were no reports of pneumonia in placebo or ET patients. Similarly, there were no reports of pneumonia in the preclinical data base.

5.11 Special Senses

Preclinically, retinal degeneration occurred in albino rats. There were no reports of similar ocular findings in humans. In the phase 2/3 trials a higher incidence of "vision abnormalities" were reported in the pramipexole treated patients. The investigator verbatims of these abnormalities included flashing light in eyes, visual disturbance, seeing spots, visual flickering, floaters, trouble reading small print, white comet shooting forward in front of eye and decreased visual acuity. Some of the reported AEs are possibly related to visual hallucinations. No special eye examinations were conducted on these patients.

6 Conclusion

Since, the overall tolerance and safety profile for pramipexole is good, from the safety point of view pramipexole is approvable. The adverse event profile for pramipexole was similar to that frequently seen with dopamine agonists. In the completed controlled studies in Parkinson's disease, adverse events in the nervous, digestive and cardiovascular systems were most common. Patients with advanced Parkinson's disease who were older and on concomitant levodopa therapy often had higher reporting frequencies of adverse events than the patients with early Parkinson's disease. The adverse events emerged more often during the dose-ascending phase. Overall, there were no distinguishing pattern of adverse events by age except for hallucinations (more frequently in pramipexole patients over 65 years of age). Overall, there were no distinguishing pattern of adverse events to separate males and females except of hallucinations (more frequent in females).

In the cardiovascular system reports of adverse events were 3-4 times more frequent in the AT placebo and pramipexole-treated patients than in the ET placebo and pramipexole-treated

patients. Orthostatic hypotension was the most frequently reported CV adverse event in both the ET and AT groups and it was reported with several orders of magnitude more frequently in the AT patients than in the ET. It is important to note that, most of the reports of orthostatic hypotension in phase 2/3 were asymptomatic in contradistinction to the phase 1 trials. Pramipexole was not associated with an increased risk of syncope in either the ET or AT patients.

Across the ISS, the overall pramipexole mortality was 5 fold greater in AT compared to ET patients and 3 fold greater in AT compared to ET placebo treated patients. Five of 8 CV deaths occurred in the AT group. CV deaths might be expected from the advanced age of the patient population.

Significant, usually transient, elevations of serum enzymes such as CPK, GGT, AST and ALT occurred in pramipexole-treated patients. The laboratory abnormalities were rarely associated with clinical symptoms; however, rhabdomyolysis was reported in one pramipexole-treated patient who had markedly elevated CPKs. The relationship to pramipexole therapy is uncertain; the patient may have suffered from acute exertional rhabdomyolysis.

In conclusion,when the dose of pramipexole is slowly titrated and individualized to obtain optimum response, pramipexole is a safe treatment for patients with Parkinson's disease.

6.1 Suggested Follow-up Issues

(1) The sponsor should perform in vitro studies to determine the absence of phase I oxidative metabolism. Even in the absence of a P450 pathway, inhibition studies should be performed to evaluate potential drug-drug interactions.

(2) Explore the ET and AT database for the incidence of urinary crystals such as uric acid and calcium oxalate.

7 Labeling Recommendations

Clinical Pharmacology section:

(1) The sponsor should mention that pramipexole possesses alpha-two agonist activity.

(2) The claim that pramipexole reduces dopamine-induced neuronal degeneration is not based on scientific data and should be deleted.

Warnings section:

(1) The sponsor's claim in labeling that tolerance to the AE of orthostatic hypotension develops is not based on scientific evidence and should be deleted.

(2) The sponsor should mention that postural hypotension has been observed after the first dose of pramipexole in a few patients.

(3) The mention of hallucinations is appropriate, but it should be stressed that the elderly and possibly females seem to be at a higher risk.

Adverse Events section:

(1) The 1% table should be redone and two tables reflecting the ET and AT patient populations.

Other Adverse Events section:

(1) The sponsor should note the occurrence of rhabdomyolysis and thrombocytopenia under Rare events.

John D. Balian, M.D. — 11/13/96 Date

James F. Knudsen, M.D., PhD — 11/13/96 Date

Clinical Reviewers, Safety Group
Div. of Neuropharmacologic Drug Products

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Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
Phase I - Clinical Pharmacology (Basic Pharmacokinetic Studies, Studies in Factors Affecting Pharmacokinetics, and Safety & Tolerance Studies)								
M/2730/0003 Phase I	United States: 1	8/93-10/93	Dose escalation of pramipexole in healthy volunteers: Evaluation of tolerance development to blood pressure and hormone effects	PPX PBO	0.375 - 4.5	q8h	7-15 days	24 PPX 12 PBO
M/2730/0023 Phase I	Switzerland: 1	8/90-8/91	A case control study to investigate the influence of varying single doses of pramipexole (SND 919 CL 2Y) measuring Parkinsonian symptoms with a tracking device in patients with advanced PD	PPX	1-4.0	Single dose	Single dose	3 PPX
M/2730/0025 Phase I	Germany: 1	1/88-3/88	Phase I tolerance and preliminary PK: single-dose, dose-escalating, placebo-controlled, double-blind, healthy volunteers	PPX PBO	0.025-0.4 solution	Single dose	Single dose 2 doses per volunteer	15 PPX 9 PBO
M/2730/0026 Phase I	Germany: 1	5/88-6/88	Phase I tolerance and preliminary PK: multiple-dose, placebo-controlled, double-blind, healthy volunteers	PPX PBO	0.3	TID (q8h)	7 days	8 PPX 4 PBO

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M/2730/0027 Phase I	Germany: 1	8/88-11/88	Phase I tolerance and preliminary PK: single-dose, placebo-controlled, double-blind, pharmacological effects (ie, hormone levels, psychopharmacological evaluations) healthy volunteers	PPX PBO	0.010-0.3 (IV)	Single dose	Single dose 2-3 dose/volunteer	15 PPX 9 PBO

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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M/2730/0028 Phase I	Germany: 1	6/88-7/88	A four-way crossover dose and time pharmacodynamic response study of pramipexole given orally as a single dose to healthy male volunteers	PPX PBO	0.1-0.3	Single dose	Single dose 4-way crossover	12 total
M/2730/0029 Phase I	Germany: 1	4/89-4/89	Phase I PK and bioavailability study: single-dose, open-label, 3-way crossover, healthy volunteers	PPX PPX PPX	0.1 (IV) 0.3 tablet 0.3 solution	Single dose	Single dose 3-way crossover	12 total
M/2730/0030 Phase I	Germany: 1	10/90-12/90	Phase I PK and metabolism of radiolabeled [^{14}C] PPX, single-dose, open-label, 2-way crossover, healthy volunteers	PPX PPX	0.1 (IV) 0.3 (oral solution)	Single dose	Single dose 2-way crossover	6 total
M/2730/0031 Phase I	Germany: 1	7/90-9/90	Phase I tolerability and PK study of transdermal PPX in healthy volunteers	PPX PBO Patch Study	0.3-2.0	Continuous transdermal application	14 days	10 PPX 6 PBO
M/2730/0047 Phase I	United States: 1	3/94-4/94	Phase I steady state PK study: multiple-dose, dose-escalating, open-label, healthy volunteers	PPX	0.375-4.5	Q8h	22 days	16

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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M/2730/0051 Phase I	England: 1	6/94-11/94	Cardiovascular affects of pramipexole in healthy volunteers and for 0051 their antagonism by domperidone. Randomized, double-blind, four-way crossover, placebo-controlled study	PPX + PBO DOM + PBO PPX + DOM PBO + PBO	0.25 30 0.25 PPX + 30 DOM	Single dose	Single dose 4-way crossover	14 total
M/2730/0060 Phase I	United States: 1	11/94-ongoing	Phase I PK study in volunteers with impaired renal function: single-dose, open-label, parallel	PPX	0.25	Single dose	Single dose	26
M/2730/0061 Phase I	United States: 1	1/95-2/95	Phase I PK study: influence of probenecid and cimetidine on PPX PK, single-dose, 3-way crossover, healthy volunteers	PPX PPX + Probenecid PPX + Cimetidine	0.25 0.25 PPX + 2000 Probenecid 0.25 PPX + 1200 Cimetidine	Single dose PPX 1000 then 500 q6h 300 q6h	Single dose 3-way crossover 4 days 4 days	13 total
M/2730/0062 Phase I	Germany: 1	1/95-4/95	Phase I bioavailability study of clinical and final tablet formulations: 2 x 2 crossover, open-label, multiple-dose, healthy volunteers	PPX	0.375 excalating to 4.5	q8h	30 days	24 total

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M/2730/0063 Phase I	United States: 1	2/95-3/95	Phase I PK study of PPX and carbidopa/levodopa: open-label, modified crossover, multiple-dose PPX, single-dose carbidopa/levodopa, healthy volunteers	PPX carbidopa / levodopa	0.75-4.5 25/250	q8h Single dose	20 days Single dose	10 total

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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M/2730/0064 Phase I	United States: 1	3/95-3/95	Phase I PK evaluation of co-administration with selegiline: single-dose PPX, multiple-dose selegiline, 2-way crossover, open-label, healthy volunteers	PPX Selegiline	0.25 5	Single dose BID	Single dose 3 days	12 total
M/2730/0065 Phase I	England: 1	6/95-6/95	Phase I PK food interaction study; single-dose, open-label, 2-way crossover, healthy volunteers	PPX	0.25	Single dose	Single dose	12 total
M/2730/0069 Phase I	United States: 1	1/95-1/95	Phase I PK influence of age and gender on PPX PK: single-dose, open-label, healthy volunteers	PPX	0.25	Single dose	Single dose	38
M/2730/0073 Phase I Innovex: F=061 Basotherm GmbH No: IP-Nr 211.1)	Germany: 2	6/93-6/93	Study to investigate the tolerability of SND 919 CL eye drops (0.00625, 0.02, and 0.05%) in ascending order after single instillation into the eye of healthy volunteers	PPX PPX PPX PBO	1.8 µg 6 µg 15 µg	Single dose eye drops	Single dose	3 3 3 3
Parkinson's Disease Studies/Early								

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M/2730/0001 Phase III	United States: 26	7/93-1/95	Double-blind, placebo-controlled, parallel-group comparison to assess the safety, tolerance, and efficacy of pramipexole in early Parkinson's disease (Part I) and to assess long term safety with open-label pramipexole (Part II)	PPX PBO	0.375-4.5	TID	up to 32 weeks	164 PPX 171 PBO
M/2730/0002 Phase III	United States: 26	1/94-ongoing	Multicenter, open-label study in pts with early PD	PPX	0.375-4.5	TID	up to 27 months	281 PPX

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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M/2730/0004 Phase III	Canada: 5 United States: 15	3/94-12/94	Parallel group, placebo controlled, dose-response tolerability, safety and efficacy study of pramipexole in early Parkinson's disease	PPX PBO	1.5, 3, 4.5, 6	TID	11 weeks	213 PPX 51 PBO
M/2730/0005 Phase III	Austria: 2 Belgium: 2 Denmark: 3 Germany: 3 Italy: 9 Spain: 5 Sweden: 3 United Kingdom: 3	9/93-ongoing	A European double-blind, placebo-controlled, parallel-group comparison to assess the safety, tolerance, and efficacy of pramipexole in early Parkinson's disease (Part I) and to assess long term safety with open-label pramipexole (Part II)	PPX PBO	0.375-4.5	TID	up to 9 months	176 blinded
M/2730/0006 Phase III	Austria: 2 Belgium: 2 Denmark: 3 Germany: 3 Italy: 9 Spain: 5 Sweden: 3 United Kingdom: 3	2/94-ongoing	Open-label study (Follow-up to M/2730/0005)	PPX	0.375-4.5	TID	up to 29 months	41 PPX
M/2730/0016 Phase III	Canada: 5 United States: 15	6/94 - ongoing	Long term safety study of open-label pramipexole in early Parkinson's disease (extension of M/2730/0004 and M/2730/0017)	PPX	0.375-4.5	TID	up to 38 months	223 PPX
M/2730/0017 Phase II	United States: 4	3/91-7/92	An ascending dose tolerance and efficacy study of SND 919 in early Parkinson's disease	PPX PBO	0.3-4.5	TID	up to 11 weeks	28 PPX 27 PBO

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Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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M/2730/0021 Phase II	England: 6	1/92-6/93	A study to assess the efficacy and safety of the maximally tolerated oral dose of SND 919 (pramipexole) in patients with early Parkinson's disease	PPX PBO	0.1-4.5	TID	up to 12 weeks	11 PPX 13 PBO
Parkinson's Disease Studies/Advanced								
M/2730/0010 Phase III	Canada: 4 United States: 22	6/93-1/95	Double-blind, placebo-controlled, parallel-group comparison to assess the safety, tolerance, and efficacy of pramipexole in advanced Parkinson's disease (0679) and to assess long-term safety with open-label pramipexole (0979)	PPX PBO	0.375-4.5	TID	up to 32 weeks	181 PPX 179 PBO
M/2730/0011 Phase III	Canada: 4 United States: 22	6/93 - ongoing	Long-term safety open-label study (Follow-up to M/2730/0010)	PPX	0.375-4.5	TID	up to 29 months	305 PPX
M/2730/0012 Phase III	Austria: 4 Denmark: 3 England: 8 France: 14 Germany: 18 Italy: 6 Scotland: 1	9/93 - ongoing	Double-blind, placebo-controlled, parallel-group comparison to assess the safety, tolerance, and efficacy of pramipexole in advanced Parkinson's disease (838.021) and to assess long-term safety with open-label pramipexole (838.022)	PPX PBO	0.375-4.5	TID	up to 32 weeks	236 blinded

Appendix 4.1.1 Table of All Pramipexole Studies

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M/2730/0013 Phase III	Austria: 4 Denmark: 3 England: 8 France: 14 Germany: 16 Italy: 6 Scotland: 1	6/94 - ongoing	Long-term safety open-label study (Follow-up to M/2730/0012)	PPX	0.375-4.5	TID	up to 29 months	88 PPX

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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M/2730/0022 Phase II	Denmark: 9	9/90-6/92	A double-blind, placebo-controlled, randomized, multi-center study to assess the effects, safety and tolerance of SND 919 in advanced Parkinson's disease	PPX PBO	0.2-5	QID	up to 12 weeks	36 PPX 33 PBO
M/2730/0036 Phase III	Austria: 2 Canada: 12 Germany: 8 Netherlands: 4 Slovakia: 2 United Kingdom: 9	5/94-ongoing	A double-blind, placebo-controlled, randomized, multicenter trial to compare the safety, tolerance and efficacy of oral administration of pramipexole up to 4.5 mg and bromocriptine up to 30 mg in advanced Parkinson's disease	PPX PBO	0.375-4.5	TID	up to 9 months	124 blinded
M/2730/0055 Phase II	Italy: 1	9//94-12/95	A double-blind, placebo-controlled parallel-group study of the evaluation of some cardiovascular and biochemical effects of pramipexole in L-dopa stable responders in Parkinson's disease patients	PPX/PBO PPX + DOM PBO + DOM	0.25 0.25 + 20 0 + 20	Single dose TID	Single dose then 7-day repeated dose interval	6 blinded
Depression Studies								
M/2730/0037 Phase II	Germany: 2	12/93-ongoing	Tolerability of pramipexole in patients hospitalized for major depressive disorder. An open study to assess the maximum tolerated dose of pramipexole with repeated dosing	PPX	0.125-10.5	TID	up to 28 days	23 PPX

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M/2730/0014 Phase II	Denmark: 8 Germany: 4 New Zealand: 1 Switzerland: 2	11/91-ongoing	An open, uncontrolled, multi-center study to assess the effects, safety and tolerability of SND 919 in advanced Parkinson's disease (1st follow-up study of study no. 838.033 in Switzerland, Austria, Germany; study no. 383.008 in Denmark; study no. 838.005 in New Zealand)	PPX	0.4-5	QID	up to 3 years	89
M/2730/0018 Phase II	United States: 6	5/91-11/92	An ascending dose tolerance and efficacy study of SND 919 in advanced Parkinson's disease	PPX PBO	0.3-4.5	TID	up to 11 weeks	26 PPX 24 PBO
M/2730/0019 Phase II	Austria: 1 Germany: 7 Switzerland: 2	2/91-8/92	A double-blind, placebo-controlled, randomized, multi-center study to assess the effects, safety and tolerance of SND 919 with concomitant treatment of levodopa (and decarboxylase-inhibitor) in advanced Parkinson's disease	PPX PBO	0.2-5	QID	up to 12 weeks	34 PPX 43 PBO
M/2730/0020 Phase II	New Zealand: 1	8/91-9/92	A double-blind, placebo-controlled, randomized, parallel-group study to assess the efficacy and safety of SND 919 in patients with advanced Parkinson's disease	PPX PBO	0.3-4.5	TID	up to 16 weeks	9 PPX 10 PBO

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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M/2730/0022 Phase II	Denmark: 9	9/90-6/92	A double-blind, placebo-controlled, randomized, multi-center study to assess the effects, safety and tolerance of SND 919 in advanced Parkinson's disease	PPX PBO	0.2-5	QID	up to 12 weeks	36 PPX 33 PBO
M/2730/0036 Phase III	Austria: 2 Canada: 12 Germany: 8 Netherlands: 4 Slovakia: 2 United Kingdom: 9	5/94-ongoing	A double-blind, placebo-controlled, randomized, multicenter trial to compare the safety, tolerance and efficacy of oral administration of pramipexole up to 4.5 mg and bromocriptine up to 30 mg in advanced Parkinson's disease	PPX PBO	0.375-4.5	TID	up to 9 months	124 blinded
M/2730/0055 Phase II	Italy: 1	9//94-12/95	A double-blind, placebo-controlled parallel-group study of the evaluation of some cardiovascular and biochemical effects of pramipexole in L-dopa stable responders in Parkinson's disease patients	PPX/PBO PPX + DOM PBO + DOM	0.25 0.25 + 20 0 + 20	Single dose TID	Single dose then 7-day repeated dose interval	6 blinded
Depression Studies								
M/2730/0037 Phase II	Germany: 2	12/93-ongoing	Tolerability of pramipexole in patients hospitalized for major depressive disorder. An open study to assess the maximum tolerated dose of pramipexole with repeated dosing	PPX	0.125-10.5	TID	up to 28 days	23 PPX

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M/2730/0043 Phase II	United States: 2	11/94-ongoing	Pramipexole in the treatment of outpatients with major depression: a dose response study	PPX PBO	0.375-5	BID	up to 9 weeks	30 blin

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

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TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
Schizophrenia Studies, Phase II								
M/2730/0007 Phase II	United States: 3	1/94-ongoing	Pilot trial of pramipexole in the treatment of tardive dyskinesia; single-blind	PPX	0.125-5	BID	up to 12 weeks	5 PPX
M/2730/0015 Phase II	Hungary: 4	1990-1992	Double-blind, randomized, PBO-controlled, preliminary safety and efficacy study in pts with schizophrenia (negative symptoms)	PPX PBO	0.3-5	TID	11 weeks	28 PPX 30 PBO
M/2730/0024 Phase II	France: 17	1991-1992	Double-blind, randomized, multicenter, clinical trial to explore the effects of pramipexole in three doses in patients with acute schizophrenia: a haloperidol-treated group control study	PPX HAL	0.3-3 15	TID	6 weeks	79 PPX 22 HAL
M/2730/0033 Phase II	Germany: 4	1989-1991	Efficacy and safety of pramipexole in patients with acute schizophrenic psychoses in an open, randomized study controlled by the usual antipsychotic treatment of the participating centers	PPX HAL PER FLU	0.2-4.5 30 600 15	TID	4 weeks	34 PPX 18 HAL 10 PER 1 FLU

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	S S Tr
M/2730/0034 Phase II	Czechia: 2 Slovakia: 1	9/91-11/92	Double-blind, placebo- and haloperidol-controlled clinical study to determine the tolerability and effectiveness of pramipexole in acute exacerbations of schizophrenia (Protocol 837.009) Czech and Slovak Republics, M/2730/0034, Boehringer Ingelheim, Investigators: Vinar, Svestka, and Konikova)	PPX HAL PBO	0.25-5.25 1-20	TID	4 weeks	22 22 22
M/2730/0048 Phase II	Germany: 1	1990-1992	Double-blind, controlled clinical study to compare the safety and efficacy of pramipexole, haloperidol, and placebo in schizophrenic patients (Protocol 837.001 Germany, M/2730/0048, Boehringer Ingelheim, Investigators: Heinrich and Klieser)	PPX HAL PBO	0.5-5 2-20	TID	4 weeks	8 P 6 H 6 P
M/2730/0049 Phase II	Germany: 2	1991-1992	Double-blind, randomized multicenter clinical trial to compare the efficacy and tolerance of pramipexole in patients with schizophrenia characterized by a placebo-treated group	PPX PBO	0.3-5	TID	up to 12 weeks	5 P 4 P
M/2730/0050 Phase II	United States: 20	11/94-ongoing	Dose-response study in the treatment of negative symptoms of schizophrenia with pramipexole	PPX HAL	0.25-5 10	BID	up to 13 weeks	4 b

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	S Si Tre

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	S S Tr
M/2730/0067 Phase II	Austria: 2 Germany: 3	1/94-ongoing	An open-label, dose escalation study in schizophrenia in patients treated orally with pramipexole added to a maintenance therapy with haloperidol	PPX + HAL	0.25-10.25PPX + 5-20 HAL	BID	up to 28 days	5
M/2730/0079	Austria: 3	10/91-2/92	Double-blind, randomized, parallel-group, multicenter study to assess the efficacy and safety of three fixed doses of pramipexole and one dose of haloperidol in patients with acute exacerbations of schizophrenia.	PPX HAL	0.3-3 15	TID	up to 47 days	2 H 1 H

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placeb (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

Appendix 4.3.1

Demographics ET patiens (Protocols 1 and 4)			
Characteristic		Pramipexole	Placebo
Age (years)	N	377	222
	Mean +/- SD	62.6 +/- 10.49	61.6 +/- 11.61
	Range		
Weight (lbs)	N	364	220
	Mean +/- SD	170.8 +/- 34.17	166.8 +/- 35.18
	Range		
Sex	Male N (%)	243 (64)	130 (59)
	Female N (%)	134 (36)	92 (41)
Race	Caucasian N (%)	363 (96)	210 (95)
	Black N (%)	5 (1)	5 (2)
	Other N (%)	9 (2)	7 (3)

Demographics AT patiens (Protocol 10)			
Characteristic		Pramipexole	Placebo
Age (years)	N	181	178
	Mean +/- SD	63.4 +/- 9.70	63.2 +/- 9.60
	Range		
Weight (lbs)	N	181	178
	Mean +/- SD	162.6 +/- 31.43	160.6 +/- 36.13
	Range		
Sex	Male N (%)	119 (66)	115 (65)
	Female N (%)	62 (34)	63 (35)
Race	Caucasian N (%)	172 (95)	171 (96)
	Black N (%)	3 (2)	4 (2)
	Other N (%)	6 (3)	3 (2)

Demographics All Completed PD Studies (Protocols 1, 4, 10, and 17-22)			
Characteristic		Pramipexole	Placebo
Age (years)	N	701	550
	Mean +/- SD	62.8 +/- 9.99	62.2 +/- 10.25
	Range		
Weight (lbs)	N	687	546
	Mean +/- SD	166.4 +/- 32.78	163.5 +/- 34.9
	Range		
Sex	Male N (%)	452 (64)	348 (63)
	Female N (%)	250 (36)	203 (37)
Race	Caucasian N (%)	672 (96)	531 (96)
	Black N (%)	9 (1)	9 (2)
	Other N (%)	21 (3)	11 (2)

Appendix 4.6.1.1. Number of Patients and Estimated Person-Years in Patients with pramipexole Use up to 2 Years				
	Completed Trials		Completed + Ongoing Trials	
	N	Person-Years	N*	Person-Years
Phase I				
Healthy Volunteers+	250	--	276	--
PD Patients (0023)	3	--	3	--
Phase 2/3 (PD and Schizophrenia)				
All Patients@	879	274.37	1408	815.00**
0-24 Months	879	274.37	1349	662.32
>6-24 Months	286	175.87	543	488.84
>12-24 Months	0	--	178	223.96
All PD Patients#	702	258.78	1231	799.42**
0-24 Months	702	258.78	1172	646.74
>6-24 Months	286	175.87	543	488.84
>12-24 Months	0	--	178	223.96
ET Patients&	416	139.64	675	363.12
0-24 Months	416	139.64	675	363.12
>6-24 Months	137	84.66	312	269.98
>12-24 Months	0	--	91	113.82
AT Patients&&	286	119.14	556	436.30**
0-24 Months	286	119.14	497	283.62
>6-24 Months	149	91.21	231	218.86
>12-24 Months	0	--	87	110.14
Schizophrenia Patients!	177	15.59	177	15.59
0-24 Months	177	15.59	3	15.59
>6-24 Months	0	--	0	--
>12-24 Months	0	--	0	--

* Patients were counted only once

** Includes 59 AT pramipexole patients with continued use beyond 24 months (total of 34.68 additional PY)

+ All completed Studies are 3, 25, 26, 27, 28, 29, 30, 31, 47, 51, 61, 62,63, 64, 65, 69, and 73; one ongoing study (0060)

@ All completed studies are: 1,4, 10, 17, 18, 19, 20, 21, 22, 15, 24, 33, 34, 48, and 49; all open-label ongoing studies are: 2, 6, 11, 13, 14, and 16.

All AT + All ET studies

& All completed ET studies are 1, 4, 17, and 21; all open-label ongoing ET studies are 2, 6, and 16.

&& All completed AT studies are 10, 18, 19, 20, and 22; all open-label ongoing AT studies are 11, 13, and 14.

! All completed schizophrenia studies are 15, 24, 33, 34, 48, and 49.

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Appendix 4.6.2.1

Duration of Exposure by Mean Dose
ET Patients (Protocols 1 and 4)

Mean Daily Dose (mg)	Number (%) of Patients — Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	3 (<1)	3 (<1)	6 (2)	5 (1)	5 (1)	1 (<1)	3 (<1)	55 (15)	0	14 (4)	0	0	95 (25)
>1.5-3.0	0	0	0	0	1 (<1)	2 (<1)	6 (2)	95 (25)	2 (<1)	12 (3)	0	0	118 (31)
>3.0-4.5	0	0	0	0	0	0	1 (<1)	41 (11)	8 (2)	107 (28)	6 (2)	0	163 (43)
>4.5-6.0	0	0	0	0	0	0	0	1 (<1)	0	0	0	0	1 (<1)
Total	3 (<1)	3 (<1)	6 (2)	5 (1)	6 (2)	3 (<1)	10 (3)	192 (51)	10 (3)	133 (35)	6 (2)	0	377

Duration of Exposure by Mean Dose
AT patients (Protocol 10)

Mean Daily Dose (mg)	Number (%) of Patients — Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	1 (<1)	1 (<1)	3 (2)	1 (<1)	2 (1)	1 (<1)	0	1 (<1)	1 (<1)	19 (10)	0	0	30 (17)
>1.5-3.0	0	0	0	0	0	2 (1)	3 (2)	4 (2)	6 (3)	27 (15)	0	0	42 (23)
>3.0-4.5	0	0	0	0	0	0	0	1 (<1)	4 (2)	100 (55)	4 (2)	0	109 (60)
>4.5-6.0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	1 (<1)	1 (<1)	3 (2)	1 (<1)	2 (1)	3 (2)	3 (2)	6 (3)	11 (6)	146 (81)	4 (2)	0	181

Duration of Exposure by Mean Dose
All Completed PD Studies (Protocols 1, 4, 10, and 17-22)

Mean Daily Dose (mg)	Number (%) of Patients — Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	6 (<1)	8 (1)	9 (1)	8 (1)	8 (1)	5 (<1)	5 (<1)	66 (9)	1 (<1)	33 (5)	0	0	149 (21)
>1.5-3.0	0	0	0	0	1 (<1)	4 (<1)	15 (2)	117 (17)	27 (4)	39 (6)	0	0	203 (29)
>3.0-4.5	0	0	0	0	0	0	1 (<1)	106 (15)	25 (4)	207 (29)	10 (1)	0	349 (50)
>4.5-6.0	0	0	0	0	0	0	0	1 (<1)	0	0	0	0	1 (<1)
Total	6 (<1)	8 (1)	9 (1)	8 (1)	9 (1)	9 (1)	21 (3)	290 (41)	53 (8)	279 (40)	10 (1)	0	702

Appendix 4.6.2.2

Duration of Exposure by Maximum Dose
ET Patients (Protocols 1 and 4)

Maximum Daily Dose (mg)	Number (%) of Patients Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	3 (<1)	3 (<1)	6 (2)	4 (1)	3 (<1)	0	3 (<1)	50 (13)	0	7 (2)	0	0	79 (21)
>1.5-3.0	0	0	0	1 (<1)	2 (<1)	1 (<1)	2 (<1)	52 (14)	1 (<1)	14 (4)	0	0	73 (19)
>3.0-4.5	0	0	0	0	1 (<1)	1 (<1)	2 (<1)	49 (13)	9 (2)	112 (30)	6 (2)	0	180 (48)
>4.5-6.0	0	0	0	0	0	1 (<1)	3 (<1)	41 (11)	0	0	0	0	45 (12)
Total	3 (<1)	3 (<1)	6 (2)	5 (1)	6 (2)	3 (<1)	10 (3)	192 (51)	10 (3)	133 (35)	6 (2)	0	377

Duration of Exposure by Maximum Dose
AT Patients (Protocol 10)

Maximum Daily Dose (mg)	Number (%) of Patients Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	1 (<1)	1 (<1)	3 (2)	1 (<1)	1 (<1)	0	0	1 (<1)	0	13 (7)	0	0	21 (12)
>1.5-3.0	0	0	0	0	1 (<1)	2 (1)	1 (<1)	2 (1)	3 (2)	20 (11)	0	0	29 (16)
>3.0-4.5	0	0	0	0	0	1 (<1)	2 (1)	3 (2)	8 (4)	113 (62)	4 (2)	0	131 (72)
>4.5-6.0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	1 (<1)	1 (<1)	3 (2)	1 (<1)	2 (1)	3 (2)	3 (2)	6 (3)	11 (6)	146 (81)	4 (2)	0	181

Duration of Exposure by Maximum Dose
All Completed PD Studies (Protocols 1, 4, 10, and 17-22)

Maximum Daily Dose (mg)	Number (%) of Patients Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	6 (<1)	8 (1)	9 (1)	7 (<1)	5 (<1)	3 (<1)	3 (<1)	57 (8)	0	20 (3)	0	0	118 (17)
>1.5-3.0	0	0	0	1 (<1)	3 (<1)	3 (<1)	10 (1)	63 (9)	8 (1)	34 (5)	0	0	122 (17)
>3.0-4.5	0	0	0	0	1 (<1)	2 (<1)	5 (<1)	98 (14)	31 (4)	225 (32)	10 (1)	0	372 (53)
>4.5-6.0	0	0	0	0	0	1 (<1)	3 (<1)	72 (10)	14 (2)	0	0	0	90 (13)
Total	6 (<1)	8 (1)	9 (1)	8 (1)	9 (1)	9 (1)	21 (3)	290 (41)	53 (8)	279 (40)	10 (1)	0	702

Appendix 4.7.1
Number (%) of Healthy Volunteers with Adverse Events in the Phase I Studies
AEs for Pramipexole (Alone) and Placebo (Alone) Treatments
AEs Occurring ≥ 1%

Body System & Event	Pramipexole[a] (N=240)	Placebo[b] (N=69)
Body as a Whole		
Headache	63(26%)	6(9%)
Asthenia	62(26%)	14(20%)
Pain abdominal	18(8%)	2(3%)
Pain	11(5%)	0(0%)
Chills	7(3%)	2(3%)
Infection	5(2%)	0(0%)
Malaise	5(2%)	0(0%)
Pain back	5(2%)	0(0%)
Abdomen enlarged	4(2%)	0(0%)
Pain chest	3(1%)	0(0%)
Injection site reaction	3(1%)	0(0%)
Cardiovascular		
Pallor	15(6%)	1(1%)
Hypotension postural	8(3%)	2(3%)
Vasodilatation	8(3%)	2(3%)
Palpitations	3(1%)	0(0%)
Syncope	3(1%)	0(0%)
Digestive		
Nausea	63(26%)	5(7%)
Anorexia	20(8%)	1(1%)
Vomiting	15(6%)	0(0%)
Constipation	12(5%)	0(0%)
Dyspepsia	12(5%)	0(0%)
Flatulence	11(5%)	1(1%)
Diarrhea	8(3%)	0(0%)
Dry mouth	4(2%)	1(1%)

[a] Healthy Volunteers included from Protocols M/2730/0003, 0025, 0026, 0027, 0028, 0029, 0030, 0031, 0047, 0051, 0061, 0062, 0064, 0065, 0069, 0073. Protocols 0023 (PD patients), 0060 (ongoing study) and 0063 (concomitant L-dopa) not included. AEs counted once per patient during pramipexole treatment.

[b] Healthy Volunteers included from Protocols M/2730/0003, 0025, 0026, 0027, 0028, 0031, 0051, 0073. AEs counted once per patient during placebo treatment.

Appendix 4.7.1
Number (%) of Healthy Volunteers with Adverse Events in the Phase I Studies
AEs for Pramipexole (Alone) and Placebo (Alone) Treatments
AEs Occurring ≥ 1%

Body System & Event	Pramipexole[a] (N=240)	Placebo[b] (N=69)
Nervous		
Dizziness	50(21%)	3(4%)
Nervousness	11(5%)	0(0%)
Insomnia	10(4%)	3(4%)
Somnolence	7(3%)	1(1%)
Concentration impaired	6(3%)	0(0%)
Agitation	5(2%)	0(0%)
Tremor	4(2%)	0(0%)
Confusion	3(1%)	1(1%)
Respiratory		
Rhinitis	15(6%)	5(7%)
Pharyngitis	6(3%)	2(3%)
Hiccups	3(1%)	0(0%)
Skin		
Sweating	23(10%)	0(0%)
Pruritus	10(4%)	5(7%)
Rash	5(2%)	1(1%)
Special Senses		
Vision abnormal	3(1%)	1(1%)
Urogenital		
Creatinine clearance dec.	10(4%)	0(0%)

[a] Healthy Volunteers included from Protocols M/2730/0003, 0025, 0026, 0027, 0028, 0029, 0030, 0031, 0047, 0051, 0061, 0062, 0064, 0065, 0069, 0073. Protocols 0023 (PD patients), 0060 (ongoing study) and 0063 (concomitant L-dopa) not included. AEs counted once per patient during pramipexole treatment.
[b] Healthy Volunteers included from Protocols M/2730/0003, 0025, 0026, 0027, 0028, 0031, 0051, 0073. AEs counted once per patient during placebo treatment.

Appendix 4.11.1
All Serious Non-Fatal Adverse Experiences Reported up to Cut-off Date of 1/31/95
For the Phase II/III Pramipexole Studies

Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term
Body	M27300001	2040	67	Male	0	208	ALLERGIC REACTION	ALLERG REACT
		2056	59	Male	0	120	CHEST PRESSURE/PAIN	PAIN CHEST
		2141	41	Male	0	153	CHEST PAIN	PAIN CHEST
		2163	61	Male	4.5	102	CHEST PAIN	PAIN CHEST
		2397	73	Male	>	255	CHEST PAIN	PAIN CHEST
					>	259	LOW BACK PAIN	PAIN BACK
					>	259	MALAISE	MALAISE
		2406	56	Female	4.5	178	CHEST PAIN	PAIN CHEST
		2434	69	Male	0	14	INCREASED WEAKNESS	ASTHENIA
	M27300002	2017	72	Male	-	325	CHEST PAIN	PAIN CHEST
		2025	60	Male	-	-	BACK PAIN	PAIN BACK
		2109	75	Male	-	240	CONCUSSION	INJURY ACCID
					-	241	FEVER	FEVER
		2137	68	Female	-	28	BROKEN ANKLE	INJURY ACCID
		2285	64	Male	-	-	NAEVUS R PARIETAL AREA	ANOMALY CONGEN
		2391	64	Male	-	238	SWELLING ALL OVER	EDEMA GENERAL
		2394	69	Male	-	2	BACK STRAIN/PAIN	INJURY ACCID
					-	2	RIB CONTUSIONS	INJURY ACCID
					-	2	ROLLOVER MOTOR VEHICLE ACCIDENT	INJURY ACCID
		2441	79	Male	-	126	CHEST PAIN	PAIN CHEST
	M27300004	192	70	Male	6	36	FRACTURE RIGHT HIP	INJURY ACCID
		269	70	Male	4.5	30	FRACTURED RIGHT HIP	INJURY ACCID
	M27300006	927	69	Male	-	-	TRAUMATIC BURN	INJURY ACCID
					-	25	TRAUMATIC BURN ON THORAX, HANDS, FACE	INJURY ACCID
	M27300010	1046	70	Female	3.75	119	FALL-R WRIST FX	INJURY ACCID
		1047	57	Male	0.75	14	NECK PAIN	PAIN NECK
					0.75	14	NECK PAIN RADIATING IN L ARM	PAIN NECK
		1066	71	Female	0	113	BROKEN HIP	INJURY ACCID
		1073	73	Male	-	74	FALL	INJURY ACCID
					-	74	FALL IN HOME FRACTURED RIBS X3	INJURY ACCID
		1130	56	Male	4.5	58	DEEP LACERATION PIP JOINT LT INDEX FINGER	INJURY ACCID
		1160	54	Male	0	66	L LEG PAIN	PAIN
		1164	69	Male	4.5	158	BACK PAIN RADIATING TO LEFT EXTREMITY	PAIN BACK
					4.5	158	BK PN RAD TO LFT EXTR WITH LFT FT WEAKNESS	PAIN BACK
		1169	59	Male	0	80	BACK PAIN	PAIN BACK
					0	198	CHEST PAIN	PAIN CHEST
					0	138	GROIN PAIN	PAIN
		1173	46	Male	0	60	CELLULITIS RLE	CELLULITIS

Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term
Body	M27300010	1175	60	Male	-	223	ABDOMINAL PAIN	PAIN ABDO
		1315	66	Male	0	49	BACKPAIN	PAIN BACK
		1397	59	Male	0	44	HERNIA RT INGUINAL	HERNIA
					0	44	HERNIA,RT INGUINAL	HERNIA
		1399	63	Male	0	43	CHEST PAIN	PAIN CHEST
	M27300011	1037	62	Male	-	109	ACCIDENT	INJURY ACCID
		1039	75	Male	-	230	FALL	INJURY ACCID
		1047	57	Male	-	66	INFECTION AT SURGICAL WOUND	INFECT
					-	-3	INGUINAL HERNIA	HERNIA
		1078	65	Female	-	37	FALL	INJURY ACCID
		1091	67	Male	-	124	FALL	INJURY ACCID
		1103	63	Female	-	41	FRACTURE RIGHT FOREARM	INJURY ACCID
		1134	65	Female	-	167	OVERDOSE	OVERDOSE
		1174	69	Male	-	176	BACK PAIN	PAIN BACK
		1211	69	Male	-	104	FALL	INJURY ACCID
		1218	74	Male	-	178	CHEST PAIN	PAIN CHEST
		1254	77	Male	-	5	CHEST PAIN	PAIN CHEST
	M27300013	85	60	Female	-	113	BROKE LEFT ARM	INJURY ACCID
		138	74	Male	-	89	FALL	INJURY ACCID
		570	53	Male	-	-	LUMBAGO	PAIN BACK
	M27300014	7	59	Male	-	281	SEVERE CHEST PAIN	PAIN CHEST
		9	64	Male	-	-	BACK PAIN	PAIN BACK
		18	64	Female	-	-	PAINS IN THE LEFT INGUINAL REGION	PAIN ABDO
		31	75	Female	-	624	FRACT. COLLI FEM. DXT	INJURY ACCID
					-	624	FRACT. COLLISI DXT	INJURY ACCID
		35	58	Female	-	38	INTRA-ARTICULAR RADIUS-FRACTURE TROCHANTER MAJOR	INJURY ACCID
					-	19	INTRAARTIKUL. FRACTURE DISTAL RADIUS LEFT 200792	INJURY ACCID
		45	54	Male	-	-	PAIN IN THE BACK	PAIN BACK
		100	74	Female	-	204	FEVER	FEVER
					-	214	PAIN	PAIN
		129	69	Female	-	802	ACCIDENT HOUSEHOLD*	INJURY ACCID
					-	747	PAIN	PAIN
		137	59	Female	-	282	PAIN	PAIN
	M27300016	16042	67	Male	-	119	CHEST PAIN	PAIN CHEST
		16178	76	Male	-	106	BRACHIAL PLEXUS INJURY LEFT ARM	INJURY ACCID
					-	-	CELLULITIS R LEG	CELLULITIS
					-	97	CELLULITIS RIGHT LEG	CELLULITIS
		16703	74	Female	-	254	PERIPELVIC CYST ON SKIN	CYST

Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term
Body	M27300018	102	68	Male	0	17	CHEST TIGHTNESS	PAIN CHEST
	M27300024	39	39	Male	-	12	ATTEMPT OF SUICIDE BY STRANGULATION	SUICIDE ATTEMPT
		42	37	Male	-	2	ATTEMPT OF SUICIDE	SUICIDE ATTEMPT
		109	41	Female	-	30	SUICIDE ATTEMPT	SUICIDE ATTEMPT
		112	54	Female	-	8	BP COLLAPSED	SHOCK
Cardiovascular	M27300001	2038	75	Male	0	89	ATRIAL FLUTTER	FLUTTER ATR
		2056	59	Male	0	120	CORONARY ARTERY DISEASE	CORONARY ART DIS
					0	120	SINUS ARRHYTHMIA	ARRHYTHMIA ATR
					0	120	UNSTABLE ANGINA	ANGINA PECTORIS
		2114	67	Male	0	10	ATRIAL FIBRILLATION	FIBRILLAT ATR
					0	10	INTERMITTENT TACHYCARDIA	TACHYCARDIA
		2174	72	Male	0	183	DEEP VEIN THROMBOSIS	THROMBOPHLEB DEEP
		2250	77	Female	4.5	114	ACUTE MYOCARDIAL INFARCT	INFARCT MYOCARD
		2405	59	Male	0	202	BRADYCARDIA	BRADYCARDIA
					0	202	HYPOTENSION	HYPOTENS
	M27300002	2010	67	Male	-	94	ATRIAL FIB.	FIBRILLAT ATR
		2017	72	Male	-	30	ABDOMINAL AORTIC ANEURYSM	ANOMALY VASCUL
		2056	59	Male	-	-	CORONARY ARTERY DISEASE	CORONARY ART DIS
		2086	68	Male	-	214	ANGINA	ANGINA PECTORIS
		2109	75	Male	-	241	ATRIAL FIBRILLATION	FIBRILLAT ATR
					-	241	IRREGULAR HEART RATE	ARRHYTHMIA
		2371	60	Female	-	118	ANGINA	ANGINA PECTORIS
		2391	64	Male	-	238	CONGESTIVE HEART FAILURE	HEART FAIL
		2441	79	Male	-	126	ATRIAL FIBRILLATION	FIBRILLAT ATR
	M27300004	30	77	Male	4.5	36	LEFT VENTRICULER DYSFUNCTION	HEART FAIL LEFT
		182	60	Male	0	9	MYOCARDIAL INFARCTION	INFARCT MYOCARD
		269	70	Male	6	42	BILATERAL PULMONARY EMBOLUS	EMB PULM
	M27300010	1399	63	Male	0	43	PALPITATIONS	PALPITAT
		1411	75	Female	0	21	SYNCOPE X2	SYNCOPE
	M27300011	1171	67	Female	-	77	LEFT PONTIVE INFARCT	CEREBROVASC ACCID
		1195	66	Male	-	190	DVT	THROMBOPHLEB DEEP
		1218	74	Male	-	178	ATRIAL FIB	FIBRILLAT ATR
	M27300013	329	70	Male	-	50	ATRIAL FIBRILLATION	ARRHYTHMIA ATR
		570	53	Male	-	33	LIPOTHYMIA	SYNCOPE
	M27300014	7	59	Male	-	270	SEVERE M.I.	INFARCT MYOCARD
					-	566	UNSTABLE ANGINA	ANGINA PECTORIS
		52	65	Male	-	150	ARRHYTHMIA	ARRHYTHMIA
					-	-	MYOCARDIAL DECOMPENSATION	HEART FAIL
					-	170	MYOCARDIAL DECOMPENSATION	HEART FAIL
					-	-	TACHYCARDIA	TACHYCARDIA
		53	63	Male	-	664	EMBOLISM CEREBRAL	EMB CEREBR
					-	665	HEART BLOCK AV	AV BLOCK
					-	662	INTERMITTENT AURICULAR FLUTTER WITH 2:1 VENTRICULAR ACTIVATION	ARRHYTHMIA ATR

Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term
Cardiovascular	M27300014	53	63	Male	-	662	INTERMITTENT AURICULAR FLUTTER WITH 2:1-VENTRICULAR ACTIVATION	ARRHYTHMIA ATR
					-	665	SUSPICION OF AV-BLOCK 2.3 DEGREE UNDER THERAPY WITH ISOPTIN AND DIGOXIN	AV BLOCK
		78	71	Female	-	182	MYOCARDIAL INFARCTION	INFARCT MYOCARD
		98	69	Female	-	-	ANGINA PECTORIS	ANGINA PECTORIS
		102	70	Male	-	-	MB. CARDIS INCOMP	HEART FAIL
	M27300015	58	52	Male	1.5	28	MYOCARDIAL INFARCTION	INFARCT MYOCARD
	M27300016	16042	67	Male	-	119	MYOCARDIAL INFARCTION	INFARCT MYOCARD
		16236	69	Male	-	10	SYNCOPAL SPELL	SYNCOPE
	M27300018	102	68	Male	0	17	PALPITATIONS	PALPITAT
					0	17	PREMATURE VENTRICULAR CONTRACTIONS(PVCS)	ARRHYTHMIA VENT
		309	73	Male	>	74	MI	INFARCT MYOCARD
	M27300019	30	65	Male	5	43	STENOCARDIA	ANGINA PECTORIS
					4	42	STENOCARDIA DSYPNOEA	ANGINA PECTORIS
	M27300020	18	67	Male	4.5	75	INFECTED HAEMATOMA ON (R) HAND	HEM
	M27300022	39	70	Female	+	-	ANGINA PECTORIS	ANGINA PECTORIS
	M27300024	112	54	Female	-	8	SYNCOPE	SYNCOPE
Digestive	M27300001	2113	69	Male	>	236	EARLY RECTAL CANCER	CARCINOMA GI
					>	236	WORSENING OF POLYPS-COLON	GI DIS
		2251	50	Female	0	69	BOWEL OBSTRUCTION	OBSTRUCT INTEST
					0	69	DIARRHEA	DIARRHEA
					0	90	SMALL BOWEL OBSTRUCTION	OBSTRUCT INTEST
		2397	73	Male	>	259	DYSPEPSIA	DYSPEPSIA
					>	259	PANCREATIC CANCER	CARCINOMA GI
		2434	69	Male	0	15	DECREASED APPETITE	ANOREXIA
	M27300010	1046	70	Female	3.75	119	NAUSEA	NAUSEA
		1122	55	Male	0	87	ESOPHAGEAL SPASM	CARDIOSPASM
		1155	74	Male	0	51	GI BLEED(PROB GASTIC ULCER)	HEM GI
		1175	60	Male	-	223	NAUSEA	NAUSEA
		1221	81	Male	0	101	COLITIS	COLITIS
					0	100	CONSTIPATION	CONSTIP
					0	101	DIARRHEA	DIARRHEA
		1263	63	Male	0	53	CONSTIPATION(WORSENED)	CONSTIP
		1332	69	Male	0	120	COLLITIS	COLITIS
	M27300011	1047	57	Male	-	157	BOWEL IMPACTION	IMPACT FECAL
	M27300018	909	60	Male	<	-10	GI BLEEDING	ULCER DUODEN HEM

Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term
Endocrine	M27300001	2002	45	Female	1.5	72	THYROID NODULE	NEOPL THYR
Hemic and Lymphatic	M27300004	130	72	Male	4.5	40	DECREASED PLATELETS	THROMBOCYTOPENIA
	M27300010	1326	77	Male	3.75	118	LUMBAR RADICULOPATHY(MULTIPLE MYELOMA)	MYELOMA
Metabolic and Nutritional	M27300001	2397	73	Male	>	255	WEIGHT LOSS	WEIGHT DEC
		2434	69	Male	0	16	DECREASED POTASSIUM	HYPOKALEM
	M27300002	2109	75	Male	-	241	DEHYDRATION	DEHYDRAT
					-	241	ELEVATED CPK	CREATINE PK INC
	M27300010	1092	49	Male	-	22	ELEVATED CPK	CREATINE PK INC
					-	22	HOSPITALIZATION DUE TO ELEVATED CK(CPK)	CREATINE PK INC
	M27300020	20	58	Male	4.5	47	ELEVATED SERUM CK	CREATINE PK INC
Musculo-Skeletal	M27300002	2025	60	Male	-	177	MRSA INFECTION OF T10-T11,T12	OSTEOMYELITIS
	M27300010	1164	69	Male	4.5	158	LEFT FOOT WEAKNESS	MYASTHENIA
	M27300011	1171	67	Female	-	229	INCREASED RT SIDE WEAKNESS	MYASTHENIA
		1245	77	Female	-	-75	ARTHRITIC PAIN(SPINAL STENOSIS)	ARTHRITIS
	M27300014	53	63	Male	-	-	OSTEOPOROSIS	OSTEOPOROSIS
		135	62	Male	-	-	DEG. MENISKOPATH	JOINT DIS

Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term
Nervous	M27300001	2078	59	Male	0.75	14	DROWSINESS	SOMNOLENCE
					1.5	16	DROWSINESS	SOMNOLENCE
		2405	59	Male	0	202	DIZZINESS	DIZZINESS
					0	202	LIGHTHEADEDNESS	DIZZINESS
		2434	69	Male	0	14	WORSENING PARKINSON'S DISEASE	EXTRAPYR SYND
	M27300002	2010	67	Male	-	93	ACUTE SEIZURE ACTIVITY	CONVULS
		2011	65	Male	-	70	INCREASED VISUAL HALLUCINATION	HALLUCIN
					-	70	WORSENING OF PARKINSON'S DISEASE	EXTRAPYR SYND
		2408	67	Male	-	95	LEFT HEMISPHERIC INFARCT (INSULAR CORTEX)	INFARCT CEREBR
	M27300004	158	62	Female	3	28	SEVERE SOMNOLENCE RAN OFF ROAD IN HER CAR	SOMNOLENCE
		199	71	Male	1.5	61	CONFUSION	CONFUS
					1.5	61	HALLUCINATIONS	HALLUCIN
	M27300010	1035	65	Male	+	-	NUMB TINGL ACHE WEAK(CER RADICULOPATHY)	NEUROPATHY
		1038	68	Female	-	15	PARANOIA	PARANOID REACT
					-	15	VISUAL HALLUCINATIONS	HALLUCIN
		1066	71	Female	0	113	DIZZINESS	DIZZINESS
		1110	75	Female	0	51	CONFUSION	CONFUS
					0	51	PARANOIA	PARANOID REACT
		1129	74	Male	4.5	123	INCREASED OFF PERIODS	EXTRAPYR SYND
		1168	75	Male	0	108	RIGHT CEREBRAL INFARCT(BET 7-15-94 + 7-22-94)	INFARCT CEREBR
		1191	72	Male	0.75	74	CONFUSION	CONFUS
	M27300011	1016	75	Male	-	136	PSYCHOSIS	PSYCHOSIS
					-	106	TIA	ISCHEMIA CEREBR
		1019	36	Male	-	5	AKINETIC	AKINESIA
		1068	65	Female	-	101	INCR DYSKINESIAS	DYSKINESIA
		1186	71	Male	-	119	CONFUSION	CONFUS
	M27300013	115	52	Male	-	-6	PARANOIA	PARANOID REACT
		141	79	Female	-	-	INCREASE OF PARKINSON SYNDR.	EXTRAPYR SYND
					-	-	INCREASE OF PARKINSON SYNDROM	EXTRAPYR SYND
					-	1	INCREASE OF PARKINSON SYNDROMS	EXTRAPYR SYND
	M27300014	1	63	Female	-	999	AGGRAVATION OF PARKINSON'S SYMPTOMS	EXTRAPYR SYND
		20	72	Male	-	460	AGGRAVATION OF PARKINSON'S SYMPTOMS	EXTRAPYR SYND
		41	64	Male	-	207	PAINFUL DYSKINESIA	DYSKINESIA
		50	55	Female	-	2	DIZZINESS, NAUSEA FAINTING	DIZZINESS

Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term
Nervous	M27300014	50	59	Male	-	-	PARKINSONISM AGGRAVATED	EXTRAPYR SYND
		52	65	Male	-	150	PARKINSONISM AGGRAVATED	EXTRAPYR SYND
		76	54	Female	-	337	INCREASED PARKINSONISM	EXTRAPYR SYND
		81	50	Male	-	106	ANXIETY	ANXIETY
		100	74	Female	-	32	WORSENING OF PARKINSON	EXTRAPYR SYND
		101	52	Male	-	597	LUMBAR NERVE ROOT COMPRESSION	NEURALGIA
					-	597	LUMBAR NERVE ROOT COMPRESSION RELAPSE OF	NEURALGIA
		102	70	Male	-	-	HALLUCINATIONS	HALLUCIN
					-	-	SEVERE "OFF-PERIODS"	EXTRAPYR SYND
		105	74	Female	-	-	LONG AND PAINFUL OFF-PERIODS, INNER RESTLESS	EXTRAPYR SYND
	M27300015	18	35	Male	+	-	ACUT PSYCHOTIC SYMPTOMS	SCHIZOPHRENIC REACT
					1.5	37	EXAC. OF PSYCHOSIS WITH HALLUCIN.	SCHIZOPHRENIC REACT
					2	33	REHOSPILIZ. BEC. OF PRAEPSY. SIGNS	SCHIZOPHRENIC REACT
					+	-	REHOSPITALISATION	SCHIZOPHRENIC REACT
		23	53	Male	0	34	EXACERBATION OF PSYCHOSIS	SCHIZOPHRENIC REACT
		49	49	Female	+	-	INCREASED HALLUCINATORY BEHAVIOR	HALLUCIN
					+	-	RESTLESSNESS, AGRESSIVITY	HOSTILITY
	M27300016	16280	74	Female	-	32	NEUROPATHY	NEUROPATHY
	M27300018	802	48	Male	<	-21	DYSTONIA	DYSTONIA
					<	-20	SEVERE OFF PERIOD(WORSENING OF DISEASE)	EXTRAPYR SYND
	M27300019	10	47	Male	+	-	INCREASE OF BLOCKAGES	EXTRAPYR SYND
					0	59	INCREASING OFF PERIODS	EXTRAPYR SYND
					+	-	WORSENING OF PARKINSON.-BLOCKAG.	EXTRAPYR SYND
	M27300020	18	67	Male	1.5	18	FALL WITH (R) HUMERUS	GAIT ABNORM
		20	58	Male	4.5	45	CONFUSION	CONFUS
					4.5	45	HYPERSOMNOLENCE	SOMNOLENCE
	M27300021	71	54	Male	-	58	HALLUCINATION (VISUAL/AUDITORY)	HALLUCIN
		73	72	Male	-	36	PARANOID PSYCHOSIS	PSYCHOSIS
	M27300022	77	62	Female	2	37	DYSKINESIA	DYSKINESIA
	M27300024	42	37	Male	-	-1	ACUTE ANGUISH	AGITATION
Nervous	M27300024	96	39	Male	-	40	EPILEPTIC CRISES	CONVULS
		109	41	Female	-	25	STATE OF DEPRESSION	DEPRESSION

Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term
Respiratory	M27300001	2019	42	Female	>	126	BILATERAL PNEUMONIA	PNEUMONIA
					-	106	R MIDDLE LOBE PNEUMONIA	PNEUMONIA
	M27300002	2149	77	Male	-	164	SHORTNESS OF BREATH	DYSPNEA
	M27300004	30	77	Male	3	32	DYSPNEA	DYSPNEA
	M27300010	1065	72	Male	3	30	PNEUMONIA	PNEUMONIA
		1191	72	Male	0.75	71	PNEUMONIA	PNEUMONIA
	M27300011	1186	71	Male	-	33	DYSPNEA	DYSPNEA
	M27300014	26	67	Male	-	6	PNEUMONIA	PNEUMONIA
		36	63	Male	-	-	BRONCHITIS	BRONCHITIS
					-	-	DYSPNEA	DYSPNEA
		52	65	Male	-	-	TACHYPNOEA	HYPERVENTIL
		53	63	Male	-	657	EXACERB. COPD WITH BRONCHIAL SUPERINFECTION	EMPHYSEMA
					-	443	EXACERB. COPD WITH BRONCHITIS	EMPHYSEMA
		55	73	Male	-	575	DYSPNOE	DYSPNEA
		102	70	Male	-	463	OEDEMA PULMONEUM	EDEMA LUNG
	M27300022	99	67	Female	4	71	ACUTE PNEUMONIA	PNEUMONIA
Skin	M27300001	2081	70	Male	0.375	1	BASAL CELL CARCINOMA OF L EAR	CARCINOMA SKIN
		2097	78	Female	0	106	SKIN CANCER-LEFT CHEEK	CARCINOMA SKIN
	M27300002	2097	78	Female	-	-	SKIN CANCER-LEFT CHEEK	CARCINOMA SKIN
		2342	73	Male	-	191	MELANOMA	MELANOMA SKIN
	M27300014	7	59	Male	-	0	EXCISION OF MELANOMA (R)FLANK, (L)THIGH	MELANOMA SKIN
Special Senses	M27300014	102	42	Female	-	-	BLEPHAROSPASM	EYE DIS

Body System	Study Number	Patient Number	Age	Gender	Dose mg/day	Time from First Dose to AE Onset (days)	Adverse Event Verbatim	COSTART Term
Urogenital	M27300001	2148	70	Male	4.5	222	PROSTATE CANCER	CARCINOMA PROSTATE
		2174	72	Male	0	174	ADVANCED BLADDER TRABECULAE	UG DIS
					0	197	BLADDER CANCER	CARCINOMA BLADDER
					+	-	CYSTITIS	CYSTITIS
					+	-	OBSTRUCTED PROSTATE	PROSTAT DIS
		2361	61	Male	4.5	215	CA OF PROSTATE	CARCINOMA PROSTATE
	M27300002	2074	67	Male	-	70	WORSENING BPH	PROSTAT DIS
		2148	70	Male	-	-	PROSTATE CANCER	CARCINOMA PROSTATE
		2361	61	Male	-	-	CA OF PROSTATE	CARCINOMA PROSTATE
	M27300004	105	68	Female	+	-	BREAST MALIGNANT NEOPLASM, FEMALE	CARCINOMA BREAST
	M27300010	1168	75	Male	0	83	ABNORMAL URINE COLOR	URIN ABNORM
					0	101	ACUTE URINARY RETENTION	URIN RETENT
		1242	72	Male	>	32	MASS R KIDNEY	CARCINOMA BLADDER
	M27300011	1045	68	Male	-	28	UTI	INFECT URIN TRACT
		1047	57	Male	-	97	ACUTE URINARY RETENTION	URIN RETENT
		1195	66	Male	-	209	HEMATURIA	HEMATURIA
		1253	77	Male	-	62	HEMATURIA	HEMATURIA
	M27300014	4	71	Male	-	-	PROSTATIC CARCINOMA*	CARCINOMA PROSTATE
		5	63	Male	-	463	PROSTATE CANCER	CARCINOMA PROSTATE
		113	46	Male	-	-	SPASTIC BLADDER / INCONTINENS	INCONTIN URIN
		131	66	Male	-	53	HYDROCELE	EPIDIDYMITIS
	M27300016	16050	43	Female	-	125	FIBROIDS	UTER FIBROID ENLARGE
					-	106	PRE-CANCER CELLS IN UTERUS	CARCINOMA ENDOMETR
					-	117	VAGINAL BLEEDING	HEM VAGINAL
		16236	69	Male	-	12	PROSTATIC HYPERTROPHY	PROSTAT DIS
		16703	74	Female	-	-	URINARY FREQUENCY	URIN FREQUENCY
					-	-	URINARY URGENCY	URIN URGENCY
					-	272	UTERINE DESCENSUS	UTER DIS
	M27300019	10	47	Male	+	-	BLADDER CARCINOMA	CARCINOMA BLADDER
					0	77	PAPILLARY BLADDER CARCINOMA	CARCINOMA BLADDER

Note: mglvl = '+' indicates onset date missing; '<' onset prior to date of first dose; '>' onset after date of last dose; '-' dose level not available

Appendix 4.13.1.1.1

% and 95% C.I. of Patients with Adverse Events (TES Reported in >= 1% of the Patients in the Pramipexole Group)
Group: All Double-Blind Placebo Controlled Studies for Early Parkinson's Disease (Early Controlled Studies: 1, 4, & 21)

Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
Total Patients (N)	388			235				
All Body Systems	344	88.7	(85.0, 91.6)	202	86.0	(80.7, 90.0)	2.7	(-3.1, 8.5)
BODY AS A WHOLE	205	52.8	(47.7, 57.8)	150	63.8	(57.3, 69.9)	-11.0	(-19.2, -2.8)
...INFECT	59	15.2	(11.9, 19.3)	52	22.1	(17.1, 28.1)	-6.9	(-13.6, -0.2)
...HEADACHE	55	14.2	(11.0, 18.2)	37	15.7	(11.4, 21.1)	-1.5	(-7.6, 4.6)
...ASTHENIA	54	13.9	(10.7, 17.8)	27	11.5	(7.8, 16.5)	2.4	(-3.3, 8.1)
...PAIN	51	13.1	(10.0, 17.0)	45	19.1	(14.4, 24.8)	-6.0	(-12.4, 0.4)
...INJURY ACCID	34	8.8	(6.3, 12.2)	20	8.5	(5.4, 13.0)	0.3	(-4.6, 5.2)
...PAIN BACK	31	8.0	(5.6, 11.3)	20	8.5	(5.4, 13.0)	-0.5	(-5.3, 4.3)
...PAIN ABDO	20	5.2	(3.3, 8.0)	15	6.4	(3.8, 10.5)	-1.2	(-5.4, 3.0)
...EDEMA GENERAL	19	4.9	(3.1, 7.7)	7	3.0	(1.3, 6.3)	1.9	(-1.5, 5.3)
...FLU SYND	10	2.6	(1.3, 4.9)	6	2.6	(1.1, 5.8)	0.0	(-2.9, 2.9)
...MALAISE	7	1.8	(0.8, 3.8)	2	0.9	(0.2, 3.4)	0.9	(-1.2, 3.0)
...ALLERG REACT	6	1.5	(0.6, 3.4)	4	1.7	(0.5, 4.6)	-0.2	(-2.6, 2.2)
...REACT UNEVAL	6	1.5	(0.6, 3.4)	2	0.9	(0.2, 3.4)	0.6	(-1.5, 2.7)
...PAIN CHEST	5	1.3	(0.5, 3.2)	11	4.7	(2.5, 8.5)	-3.4	(-6.7, -0.1)
...PAIN NECK	5	1.3	(0.5, 3.2)	5	2.1	(0.8, 5.1)	-0.8	(-3.3, 1.7)
...FEVER	4	1.0	(0.3, 2.8)	1	0.4	(0.0, 2.7)	0.6	(-1.0, 2.2)
CARDIOVASCULAR SYSTEM	50	12.9	(9.8, 16.7)	38	16.2	(11.9, 21.7)	-3.3	(-9.4, 2.8)
...HYPOTENS POST	30	7.7	(5.3, 10.9)	21	8.9	(5.7, 13.5)	-1.2	(-6.0, 3.6)
...VASODILAT	11	2.8	(1.5, 5.1)	10	4.3	(2.2, 8.0)	-1.5	(-4.9, 1.9)

(CONTINUED)

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
...HYPERTENS	6	1.5	(0.6, 3.4)	4	1.7	(0.5, 4.6)	-0.2	(-2.6, 2.2
...SYNCOPE	5	1.3	(0.5, 3.2)	2	0.9	(0.2, 3.4)	0.4	(-1.6, 2.4
...TACHYCARDIA	5	1.3	(0.5, 3.2)	3	1.3	(0.3, 4.0)	0.0	(-2.2, 2.2
DIGESTIVE SYSTEM	181	46.6	(41.6, 51.7)	94	40.0	(33.7, 46.6)	6.6	(-1.7, 14.9
...NAUSEA	107	27.6	(23.3, 32.4)	42	17.9	(13.3, 23.5)	9.7	(2.7, 16.7
...CONSTIP	53	13.7	(10.5, 17.6)	14	6.0	(3.5, 10.1)	7.7	(2.8, 12.6
...DYSPEPSIA	28	7.2	(4.9, 10.4)	16	6.8	(4.1, 11.0)	0.4	(-4.1, 4.9
...ANOREXIA	17	4.4	(2.7, 7.1)	5	2.1	(0.8, 5.1)	2.3	(-0.8, 5.4
...DIARRHEA	17	4.4	(2.7, 7.1)	18	7.7	(4.8, 12.1)	-3.3	(-7.6, 1.0
...DRY MOUTH	13	3.4	(1.9, 5.9)	16	6.8	(4.1, 11.0)	-3.4	(-7.4, 0.6
...SALIVA INC	10	2.6	(1.3, 4.9)	7	3.0	(1.3, 6.3)	-0.4	(-3.4, 2.6
...DYSPHAGIA	7	1.8	(0.8, 3.8)	1	0.4	(0.0, 2.7)	1.4	(-0.5, 3.3
...FLATUL	7	1.8	(0.8, 3.8)	4	1.7	(0.5, 4.6)	0.1	(-2.4, 2.6
...TOOTH DIS	7	1.8	(0.8, 3.8)	4	1.7	(0.5, 4.6)	0.1	(-2.4, 2.6
...VOMIT	7	1.8	(0.8, 3.8)	8	3.4	(1.6, 6.8)	-1.6	(-4.6, 1.4
METABOLIC & NUTRITIONAL SYSTEM	31	8.0	(5.6, 11.3)	14	6.0	(3.5, 10.1)	2.0	(-2.4, 6.4
...EDEMA PERIPH	19	4.9	(3.1, 7.7)	10	4.3	(2.2, 8.0)	0.6	(-3.1, 4.3
...WEIGHT DEC	7	1.8	(0.8, 3.8)	1	0.4	(0.0, 2.7)	1.4	(-0.5, 3.3
...CREATINE PK INC	5	1.3	(0.5, 3.2)	3	1.3	(0.3, 4.0)	0.0	(-2.2, 2.2
MUSCULO SKELETAL SYSTEM	22	5.7	(3.7, 8.6)	12	5.1	(2.8, 9.0)	0.6	(-3.4, 4.6
...CRAMPS LEG	17	4.4	(2.7, 7.1)	9	3.8	(1.9, 7.3)	0.6	(-2.9, 4.1

(CONTINUED)

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
...TWITCH	6	1.5	(0.6, 3.4)	3	1.3	(0.3, 4.0)	0.2	(-2.0, 2.4)
NERVOUS SYSTEM	258	66.5	(61.5, 71.1)	138	58.7	(52.1, 65.0)	7.8	(-0.4, 16.0)
...DIZZINESS	97	25.0	(20.8, 29.7)	57	24.3	(19.1, 30.4)	0.7	(-6.6, 8.0)
...SOMNOLENCE	85	21.9	(18.0, 26.4)	21	8.9	(5.7, 13.5)	13.0	(7.2, 18.8)
...INSOMNIA	66	17.0	(13.5, 21.2)	27	11.5	(7.8, 16.5)	5.5	(-0.4, 11.4)
...TREMOR	37	9.5	(6.9, 13.0)	39	16.6	(12.2, 22.1)	-7.1	(-13.0, -1.2)
...HALLUCIN	35	9.0	(6.4, 12.4)	6	2.6	(1.1, 5.8)	6.4	(2.6, 10.2)
...HYPERTONIA	23	5.9	(3.9, 8.9)	18	7.7	(4.8, 12.1)	-1.8	(-6.3, 2.7)
...DEPRESSION	22	5.7	(3.7, 8.6)	17	7.2	(4.4, 11.5)	-1.5	(-5.9, 2.9)
...ANXIETY	18	4.6	(2.8, 7.3)	11	4.7	(2.5, 8.5)	-0.1	(-3.9, 3.7)
...DREAM ABNORM	17	4.4	(2.7, 7.1)	10	4.3	(2.2, 8.0)	0.1	(-3.5, 3.7)
...CONFUS	16	4.1	(2.4, 6.7)	3	1.3	(0.3, 4.0)	2.8	(0.0, 5.6)
...AMNESIA	14	3.6	(2.1, 6.1)	4	1.7	(0.5, 4.6)	1.9	(-0.9, 4.7)
...ATAXIA	13	3.4	(1.9, 5.9)	19	8.1	(5.1, 12.5)	-4.7	(-9.0, -0.4)
...EXTRAPYR SYND	13	3.4	(1.9, 5.9)	24	10.2	(6.8, 15.0)	-6.8	(-11.4, -2.2)
...HYPESTHESIA	11	2.8	(1.5, 5.1)	2	0.9	(0.2, 3.4)	1.9	(-0.5, 4.3)
...GAIT ABNORM	8	2.1	(1.0, 4.2)	6	2.6	(1.1, 5.8)	-0.5	(-3.3, 2.3)
...DYSTONIA	7	1.8	(0.8, 3.8)	3	1.3	(0.3, 4.0)	0.5	(-1.8, 2.8)
...AKATHISIA	6	1.5	(0.6, 3.4)	0	0.0	(0.0, 2.0)	1.5	(-0.1, 3.1)
...HYPOKINESIA	6	1.5	(0.6, 3.4)	12	5.1	(2.8, 9.0)	-3.6	(-7.0, -0.2)
...THINKING ABNORM	6	1.5	(0.6, 3.4)	1	0.4	(0.0, 2.7)	1.1	(-0.7, 2.9)

(CONTINUED)

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
...LIBIDO DEC	5	1.3	(0.5, 3.2)	0	0.0	(0.0, 2.0)	1.3	(-0.2, 2.6
...MYOCLONUS	5	1.3	(0.5, 3.2)	1	0.4	(0.0, 2.7)	0.9	(-0.8, 2.6
...NERVOUSNESS	5	1.3	(0.5, 3.2)	5	2.1	(0.8, 5.1)	-0.8	(-3.3, 1.7
...PARESTHESIA	5	1.3	(0.5, 3.2)	7	3.0	(1.3, 6.3)	-1.7	(-4.5, 1.1
...VERTIGO	5	1.3	(0.5, 3.2)	13	5.5	(3.1, 9.5)	-4.2	(-7.7, -0.7
...PARALYSIS	4	1.0	(0.3, 2.8)	4	1.7	(0.5, 4.6)	-0.7	(-3.0, 1.6
RESPIRATORY SYSTEM	48	12.4	(9.4, 16.2)	37	15.7	(11.4, 21.1)	-3.3	(-9.3, 2.7
...PHARYNGITIS	13	3.4	(1.9, 5.9)	8	3.4	(1.6, 6.8)	0.0	(-3.3, 3.3
...SINUSITIS	13	3.4	(1.9, 5.9)	9	3.8	(1.9, 7.3)	-0.4	(-3.8, 3.0
...RHINITIS	12	3.1	(1.7, 5.5)	8	3.4	(1.6, 6.8)	-0.3	(-3.5, 2.9
...DYSPNEA	9	2.3	(1.1, 4.5)	6	2.6	(1.1, 5.8)	-0.3	(-3.2, 2.6
...COUGH INC	8	2.1	(1.0, 4.2)	7	3.0	(1.3, 6.3)	-0.9	(-3.8, 2.0
...VOICE ALTERAT	5	1.3	(0.5, 3.2)	7	3.0	(1.3, 6.3)	-1.7	(-4.5, 1.1
SKIN & APPENDAGES	30	7.7	(5.3, 10.9)	27	11.5	(7.8, 16.5)	-3.8	(-9.0, 1.4
...RASH	15	3.9	(2.3, 6.5)	12	5.1	(2.8, 9.0)	-1.2	(-5.0, 2.6
...SWEAT	13	3.4	(1.9, 5.9)	14	6.0	(3.5, 10.1)	-2.6	(-6.5, 1.3
...PRURITUS	5	1.3	(0.5, 3.2)	2	0.9	(0.2, 3.4)	0.4	(-1.6, 2.4
SPECIAL SENSES	37	9.5	(6.9, 13.0)	14	6.0	(3.5, 10.1)	3.5	(-1.1, 8.1
...ACCOMMODATION ABNORM	11	2.8	(1.5, 5.1)	6	2.6	(1.1, 5.8)	0.2	(-2.8, 3.2
...VISION ABNORM	10	2.6	(1.3, 4.9)	0	0.0	(0.0, 2.0)	2.6	(0.7, 4.5
...TINNITUS	5	1.3	(0.5, 3.2)	2	0.9	(0.2, 3.4)	0.4	(-1.6, 2.4

(CONTINUED)

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
...CONJUNCTIVITIS	4	1.0	(0.3, 2.8)	3	1.3	(0.3, 4.0)	-0.3	(-2.4, 1.8)
...DIPLOPIA	4	1.0	(0.3, 2.8)	2	0.9	(0.2, 3.4)	0.1	(-1.8, 2.0)
...TASTE PERVERS	4	1.0	(0.3, 2.8)	2	0.9	(0.2, 3.4)	0.1	(-1.8, 2.0)
UROGENITAL SYSTEM	24	6.2	(4.1, 9.2)	24	10.2	(6.8, 15.0)	-4.0	(-8.9, 0.9)
...INFECT URIN TRACT	11	2.8	(1.5, 5.1)	12	5.1	(2.8, 9.0)	-2.3	(-5.9, 1.3)
...URIN FREQUENCY	8	2.1	(1.0, 4.2)	10	4.3	(2.2, 8.0)	-2.2	(-5.5, 1.1)
...IMPOTENCE	7	1.8	(0.8, 3.8)	3	1.3	(0.3, 4.0)	0.5	(-1.8, 2.8)

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

Appendix 4.13.1.2.1

% and 95% C.I. of Patients with Adverse Events (TES Reported in > = 1% of the Patients in the Pramipexole Group)
Group: All Double-Blind Placebo Controlled Studies for Advanced Parkinson's Disease (Advanced Controlled Studies: 10, 19, 20 & 22)

Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
Total Patients (N)	260			264				
All Body Systems	245	94.2	(90.4, 96.6)	237	89.8	(85.3, 93.1)	4.4	(-0.6, 9.4)
BODY AS A WHOLE	137	52.7	(46.4, 58.9)	133	50.4	(44.2, 56.6)	2.3	(-6.6, 11.2)
...INJURY ACCID	43	16.5	(12.3, 21.7)	39	14.8	(10.9, 19.8)	1.7	(-4.9, 8.3)
...PAIN	31	11.9	(8.3, 16.6)	43	16.3	(12.2, 21.4)	-4.4	(-10.7, 1.9)
...ASTHENIA	26	10.0	(6.8, 14.5)	21	8.0	(5.1, 12.1)	2.0	(-3.3, 7.3)
...INFECT	26	10.0	(6.8, 14.5)	36	13.6	(9.8, 18.5)	-3.6	(-9.5, 2.3)
...HEADACHE	23	8.8	(5.8, 13.1)	38	14.4	(10.5, 19.4)	-5.6	(-11.4, 0.2)
...PAIN BACK	14	5.4	(3.1, 9.1)	18	6.8	(4.2, 10.7)	-1.4	(-5.9, 3.1)
...FLU SYND	12	4.6	(2.5, 8.1)	18	6.8	(4.2, 10.7)	-2.2	(-6.5, 2.1)
...EDEMA GENERAL	10	3.8	(1.9, 7.1)	7	2.7	(1.2, 5.7)	1.1	(-2.3, 4.5)
...PAIN ABDO	10	3.8	(1.9, 7.1)	10	3.8	(1.9, 7.1)	0.0	(-3.7, 3.7)
...PAIN CHEST	8	3.1	(1.5, 6.2)	4	1.5	(0.5, 4.1)	1.6	(-1.3, 4.5)
...MALAISE	7	2.7	(1.2, 5.7)	5	1.9	(0.7, 4.6)	0.8	(-2.1, 3.7)
...PAIN NECK	4	1.5	(0.5, 4.1)	4	1.5	(0.5, 4.1)	0.0	(-2.5, 2.5)
CARDIOVASCULAR SYSTEM	148	56.9	(50.6, 63.0)	144	54.5	(48.3, 60.6)	2.4	(-6.5, 11.3)
...HYPOTENS POST	137	52.7	(46.4, 58.9)	127	48.1	(42.0, 54.3)	4.6	(-4.3, 13.5)
...HYPERTENS	7	2.7	(1.2, 5.7)	7	2.7	(1.2, 5.7)	0.0	(-3.2, 3.2)
...HYPOTENS	6	2.3	(0.9, 5.2)	8	3.0	(1.4, 6.1)	-0.7	(-3.8, 2.4)
...VASODILAT	5	1.9	(0.7, 4.7)	7	2.7	(1.2, 5.7)	-0.8	(-3.7, 2.1)
...SYNCOPE	4	1.5	(0.5, 4.1)	7	2.7	(1.2, 5.7)	-1.2	(-4.0, 1.6)

(CONTINUED)

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
...PALPITAT	3	1.2	(0.3, 3.7)	4	1.5	(0.5, 4.1)	-0.3	(-2.7, 2.
DIGESTIVE SYSTEM	110	42.3	(36.3, 48.6)	110	41.7	(35.7, 47.9)	0.6	(-8.2, 9.
...NAUSEA	58	22.3	(17.5, 27.9)	61	23.1	(18.3, 28.7)	-0.8	(-8.4, 6.
...CONSTIP	26	10.0	(6.8, 14.5)	23	8.7	(5.7, 12.9)	1.3	(-4.1, 6.
...DRY MOUTH	17	6.5	(3.9, 10.4)	7	2.7	(1.2, 5.7)	3.8	(-0.2, 7.
...ANOREXIA	14	5.4	(3.1, 9.1)	18	6.8	(4.2, 10.7)	-1.4	(-5.9, 3.
...DYSPEPSIA	13	5.0	(2.8, 8.6)	17	6.4	(3.9, 10.2)	-1.4	(-5.7, 2.
...DIARRHEA	10	3.8	(1.9, 7.1)	11	4.2	(2.2, 7.6)	-0.4	(-4.1, 3.
...SALIVA INC	7	2.7	(1.2, 5.7)	11	4.2	(2.2, 7.6)	-1.5	(-5.0, 2.
...TOOTH DIS	7	2.7	(1.2, 5.7)	8	3.0	(1.4, 6.1)	-0.3	(-3.5, 2.
...VOMIT	5	1.9	(0.7, 4.7)	12	4.5	(2.4, 8.0)	-2.6	(-6.0, 0.
...DYSPHAGIA	3	1.2	(0.3, 3.7)	5	1.9	(0.7, 4.6)	-0.7	(-3.2, 1.
...FLATUL	3	1.2	(0.3, 3.7)	2	0.8	(0.1, 3.1)	0.4	(-1.7, 2.
METABOLIC & NUTRITIONAL SYSTEM	9	3.5	(1.7, 6.7)	3	1.1	(0.3, 3.5)	2.4	(-0.5, 5.
...EDEMA PERIPH	6	2.3	(0.9, 5.2)	2	0.8	(0.1, 3.1)	1.5	(-1.0, 4.
...CREATINE PK INC	3	1.2	(0.3, 3.7)	1	0.4	(0.0, 2.5)	0.8	(-1.1, 2.
MUSCULO SKELETAL SYSTEM	43	16.5	(12.3, 21.7)	28	10.6	(7.3, 15.1)	5.9	(-0.3, 12.
...CRAMPS LEG	14	5.4	(3.1, 9.1)	12	4.5	(2.4, 8.0)	0.9	(-3.2, 5.
...MYALGIA	10	3.8	(1.9, 7.1)	13	4.9	(2.7, 8.4)	-1.1	(-5.0, 2.
...ARTHRITIS	7	2.7	(1.2, 5.7)	3	1.1	(0.3, 3.5)	1.6	(-1.1, 4.
...TWITCH	6	2.3	(0.9, 5.2)	0	0.0	(0.0, 1.8)	2.3	(0.1, 4.

(CONTINUED)

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

Body System	Number (%) of Patients						% difference	95% C.I. fo % differenc
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
...BURSITIS	4	1.5	(0.5, 4.1)	1	0.4	(0.0, 2.5)	1.1	(-0.9, 3.
...ARTHRALGIA	3	1.2	(0.3, 3.7)	5	1.9	(0.7, 4.6)	-0.7	(-3.2, 1.
...MYASTHENIA	3	1.2	(0.3, 3.7)	0	0.0	(0.0, 1.8)	1.2	(-0.5, 2.
NERVOUS SYSTEM	213	81.9	(76.6, 86.3)	199	75.4	(69.7, 80.4)	6.5	(-0.9, 13.
...DYSKINESIA	123	47.3	(41.1, 53.6)	83	31.4	(25.9, 37.4)	15.9	(7.3, 24.
...EXTRAPYR SYND	72	27.7	(22.4, 33.6)	68	25.8	(20.7, 31.6)	1.9	(-6.1, 9.
...INSOMNIA	70	26.9	(21.7, 32.8)	57	21.6	(16.9, 27.2)	5.3	(-2.4, 13.
...DIZZINESS	67	25.8	(20.7, 31.6)	66	25.0	(20.0, 30.8)	0.8	(-7.0, 8.
...HALLUCIN	43	16.5	(12.3, 21.7)	10	3.8	(1.9, 7.1)	12.7	(7.3, 18.
...DREAM ABNORM	28	10.8	(7.4, 15.4)	25	9.5	(6.4, 13.9)	1.3	(-4.3, 6.
...CONFUS	26	10.0	(6.8, 14.5)	19	7.2	(4.5, 11.2)	2.8	(-2.4, 8.
...SOMNOLENCE	23	8.8	(5.8, 13.1)	16	6.1	(3.6, 9.9)	2.7	(-2.2, 7.
...DEPRESSION	22	8.5	(5.5, 12.7)	44	16.7	(12.5, 21.9)	-8.2	(-14.2, -2.
...DYSTONIA	21	8.1	(5.2, 12.3)	19	7.2	(4.5, 11.2)	0.9	(-4.0, 5.
...TREMOR	19	7.3	(4.6, 11.3)	38	14.4	(10.5, 19.4)	-7.1	(-12.8, -1.
...GAIT ABNORM	18	6.9	(4.3, 10.9)	13	4.9	(2.7, 8.4)	2.0	(-2.4, 6.
...HYPERTONIA	17	6.5	(3.9, 10.4)	16	6.1	(3.6, 9.9)	0.4	(-4.1, 4.
...AMNESIA	15	5.8	(3.4, 9.6)	11	4.2	(2.2, 7.6)	1.6	(-2.5, 5.
...HYPOKINESIA	15	5.8	(3.4, 9.6)	22	8.3	(5.4, 12.5)	-2.5	(-7.3, 2.
...ATAXIA	12	4.6	(2.5, 8.1)	13	4.9	(2.7, 8.4)	-0.3	(-4.3, 3.
...ANXIETY	9	3.5	(1.7, 6.7)	12	4.5	(2.4, 8.0)	-1.0	(-4.7, 2.

(CONTINUED)

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
...PARESTHESIA	8	3.1	(1.5, 6.2)	9	3.4	(1.7, 6.6)	-0.3	(-3.7, 3.1)
...AKATHISIA	7	2.7	(1.2, 5.7)	6	2.3	(0.9, 5.2)	0.4	(-2.7, 3.5)
...THINKING ABNORM	7	2.7	(1.2, 5.7)	4	1.5	(0.5, 4.1)	1.2	(-1.6, 4.0)
...APATHY	6	2.3	(0.9, 5.2)	12	4.5	(2.4, 8.0)	-2.2	(-5.7, 1.3)
...HYPESTHESIA	5	1.9	(0.7, 4.7)	4	1.5	(0.5, 4.1)	0.4	(-2.2, 3.0)
...PARANOID REACT	5	1.9	(0.7, 4.7)	1	0.4	(0.0, 2.5)	1.5	(-0.7, 3.7)
...NERVOUSNESS	4	1.5	(0.5, 4.1)	7	2.7	(1.2, .5.7)	-1.2	(-4.0, 1.6)
...DELUSIONS	3	1.2	(0.3, 3.7)	1	0.4	(0.0, 2.5)	0.8	(-1.1, 2.7)
...SLEEP DIS	3	1.2	(0.3, 3.7)	0	0.0	(0.0, 1.8)	1.2	(-0.5, 2.9)
...VERTIGO	3	1.2	(0.3, 3.7)	4	1.5	(0.5, 4.1)	-0.3	(-2.7, 2.1)
RESPIRATORY SYSTEM	29	11.2	(7.8, 15.8)	19	7.2	(4.5, 11.2)	4.0	(-1.3, 9.3)
...DYSPNEA	10	3.8	(1.9, 7.1)	8	3.0	(1.4, 6.1)	0.8	(-2.7, 4.3)
...RHINITIS	7	2.7	(1.2, 5.7)	3	1.1	(0.3, 3.5)	1.6	(-1.1, 4.3)
...SINUSITIS	6	2.3	(0.9, 5.2)	4	1.5	(0.5, 4.1)	0.8	(-1.9, 3.5)
...PNEUMONIA	5	1.9	(0.7, 4.7)	0	0.0	(0.0, 1.8)	1.9	(-0.1, 3.9)
...COUGH INC	4	1.5	(0.5, 4.1)	4	1.5	(0.5, 4.1)	0.0	(-2.5, 2.5)
...PHARYNGITIS	3	1.2	(0.3, 3.7)	5	1.9	(0.7, 4.6)	-0.7	(-3.2, 1.8)
SKIN & APPENDAGES	24	9.2	(6.1, 13.6)	22	8.3	(5.4, 12.5)	0.9	(-4.3, 6.1)
...RASH	9	3.5	(1.7, 6.7)	10	3.8	(1.9, 7.1)	-0.3	(-3.9, 3.3)
...SWEAT	9	3.5	(1.7, 6.7)	9	3.4	(1.7, 6.6)	0.1	(-3.4, 3.6)
...SKIN DIS	5	1.9	(0.7, 4.7)	3	1.1	(0.3, 3.5)	0.8	(-1.7, 3.3)

(CONTINUED)

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

Body System	Number (%) of Patients						% difference	95% C.I. for % difference
	Pramipexole			Placebo				
	n	%	95% C.I.	n	%	95% C.I.		
...PRURITUS	3	1.2	(0.3, 3.7)	2	0.8	(0.1, 3.1)	0.4	(-1.7, 2.5)
SPECIAL SENSES	24	9.2	(6.1, 13.6)	12	4.5	(2.4, 8.0)	4.7	(0.0, 9.4)
...ACCOMMODATION ABNORM	10	3.8	(1.9, 7.1)	6	2.3	(0.9, 5.2)	1.5	(-1.8, 4.8)
...VISION ABNORM	8	3.1	(1.5, 6.2)	2	0.8	(0.1, 3.1)	2.3	(-0.4, 5.0)
...CONJUNCTIVITIS	3	1.2	(0.3, 3.7)	3	1.1	(0.3, 3.5)	0.1	(-2.1, 2.3)
...DIPLOPIA	3	1.2	(0.3, 3.7)	0	0.0	(0.0, 1.8)	1.2	(-0.5, 2.9)
...LACRIMATION DIS	3	1.2	(0.3, 3.7)	2	0.8	(0.1, 3.1)	0.4	(-1.7, 2.5)
UROGENITAL SYSTEM	25	9.6	(6.4, 14.0)	17	6.4	(3.9, 10.2)	3.2	(-1.8, 8.2)
...URIN FREQUENCY	15	5.8	(3.4, 9.6)	7	2.7	(1.2, 5.7)	3.1	(-0.7, 6.9)
...INFECT URIN TRACT	10	3.8	(1.9, 7.1)	9	3.4	(1.7, 6.6)	0.4	(-3.2, 4.0)
...INCONTIN URIN	5	1.9	(0.7, 4.7)	3	1.1	(0.3, 3.5)	0.8	(-1.7, 3.3)

n = Number of patients reporting an adverse event during treatment
N = Intent-to-treat population
Note: Difference refers to p(Pramipexole) - p(Placebo).

Appendix 4.13.2.1.1
ET Patients In Completed Adequate And Well-Controlled Studies:
Adverse Events Occurring With Frequency Greater Than Or Equal to 10%
By Study Phase Where Event Was First Reported
Date Produced: 10/30/96

Body System	Costart	Pramipexole				Placebo			
		Ascend N(%)	Maint N(%)	Taper N(%)	Total N(%)	Ascend N(%)	Maint N(%)	Taper N(%)	Total N(%)
Total Patients		377(100.00)	346(100.00)	332(100.00)	377(100.00)	222(100.00)	212(100.00)	200(100.00)	222(100.00)
BODY AS A WHOLE	ASTHENIA	36(9.55)	11(3.18)	6(1.81)	53(14.06)	16(7.21)	7(3.30)	4(2.00)	27(12.16)
	HEADACHE	43(11.41)	9(2.60)	1(0.30)	53(14.06)	24(10.81)	12(5.66)		36(16.22)
	INFECT	20(5.31)	34(9.83)	4(1.20)	58(15.38)	20(9.01)	27(12.74)	3(1.50)	50(22.52)
	PAIN	21(5.57)	27(7.80)	3(0.90)	51(13.53)	25(11.26)	18(8.49)	2(1.00)	45(20.27)
DIGESTIVE SYSTEM	CONSTIP	42(11.14)	9(2.60)	2(0.60)	53(14.06)	8(3.60)	6(2.83)		14(6.31)
	NAUSEA	88(23.34)	17(4.91)	1(0.30)	106(28.12)	25(11.26)	15(7.08)	1(0.50)	41(18.47)
NERVOUS SYSTEM	DIZZINESS	69(18.30)	25(7.23)	2(0.60)	96(25.46)	44(19.82)	12(5.66)		56(25.23)
	INSOMNIA	42(11.14)	13(3.76)	10(3.01)	65(17.24)	21(9.46)	6(2.83)		27(12.16)
	SOMNOLENCE	70(18.57)	15(4.34)		85(22.55)	18(8.11)	2(0.94)	1(0.50)	21(9.46)

Includes Studies M/2730/0001 and M/2730/0004

Appendix 4.13.2.2.1

AT Patients In Completed Adequate And Well-Controlled Studies:
Adverse Events Occurring With Frequency Greater Than Or Equal to 10%
By Study Phase Where Event Was First Reported

Body System	Costart	Pramipexole				Placebo			
		Ascend N(%)	Maint N(%)	Taper N(%)	Total N(%)	Ascend N(%)	Maint N(%)	Taper N(%)	Total N(%)
Total Patients		181(100.00)	169(100.00)	177(100.00)	181(100.00)	178(100.00)	157(100.00)	165(100.00)	178(100.00)
BODY AS A WHOLE	INFECT	8(4.42)	15(8.88)		23(12.71)	12(6.74)	19(12.10)	2(1.21)	33(18.54)
	INJURY ACCID	16(8.84)	24(14.20)	2(1.13)	42(23.20)	17(9.55)	18(11.46)	3(1.82)	39(21.91)
	PAIN	9(4.97)	15(8.88)	1(0.56)	25(13.81)	10(5.62)	20(12.74)	3(1.82)	33(18.54)
CARDIOVASCULAR SYSTEM	HYPOTENS POST	92(50.83)	26(15.38)	5(2.82)	123(67.96)	93(52.25)	16(10.19)	9(5.45)	118(66.29)
DIGESTIVE SYSTEM	CONSTIP	11(6.08)	12(7.10)		23(12.71)	12(6.74)	9(5.73)	1(0.61)	22(12.36)
	NAUSEA	35(19.34)	7(4.14)	2(1.13)	44(24.31)	35(19.66)	13(8.28)	2(1.21)	50(28.09)
NERVOUS SYSTEM	CONFUS	14(7.73)	8(4.73)	1(0.56)	23(12.71)	10(5.62)	6(3.82)	2(1.21)	18(10.11)
	DIZZINESS	43(23.76)	8(4.73)	3(1.69)	54(29.83)	33(18.54)	16(10.19)	2(1.21)	51(28.65)
	DREAM ABNORM	14(7.73)	6(3.55)	1(0.56)	21(11.60)	15(8.43)	5(3.18)		20(11.24)
	DYSKINESIA	99(54.70)	12(7.10)	2(1.13)	113(62.43)	59(33.15)	17(10.83)	1(0.61)	77(43.26)
	EXTRAPYR SYND	12(6.63)	39(23.08)	14(7.91)	65(35.91)	26(14.61)	29(18.47)	6(3.64)	61(34.27)
	HALLUCIN	28(15.47)	6(3.55)	4(2.26)	38(20.99)	6(3.37)	3(1.91)	1(0.61)	10(5.62)
	INSOMNIA	27(14.92)	17(10.06)	7(3.95)	51(28.18)	32(17.98)	16(10.19)	1(0.61)	49(27.53)

Includes Study M/2730/0010

Appendix 4.13.4.1
Adverse Events By Dose At First Occurrence
ET Patients; Studies 1, 4, & 21

	Dose at First Occurrence									
	0 - 0.75		>0.75 - 1.5		>1.5 - 3.0		>3.0 - 4.5		>4.5	
	n	%	n	%	n	%	n	%	n	%
Total Patients (N)	387		372		308		234		45	
ASTHENIA	21	5.43	7	1.88	7	2.27	9	3.85	2	4.44
CONSTIP	18	4.65	10	2.69	9	2.92	12	5.13	2	4.44
DIZZINESS	30	7.75	16	4.30	19	6.17	28	11.97	1	2.22
HEADACHE	33	8.53	5	1.34	7	2.27	7	2.99	1	2.22
INFECT	6	1.55	8	2.15	8	2.60	30	12.82	1	2.22
INSOMNIA	21	5.43	15	4.03	8	2.60	11	4.70	0	0.00
NAUSEA	42	10.85	21	5.65	22	7.17	21	8.97	0	0.00
PAIN	11	2.84	4	1.08	9	2.92	21	8.97	3	6.67
SOMNOLENCE	29	7.49	17	4.57	16	5.19	23	9.83	0	0.00

Events with first occurrence during the dose reduction phase have been excluded

Appendix 4.13.4.2
Adverse Events By Dose At First Occurrence
AT Patients; Studies 10, 19, 20, & 22

	Dose at First Occurrence									
	0 - 0.75		>0.75 - 1.5		>1.5 - 3.0		>3.0 - 4.5		>4.5	
	n	%	n	%	n	%	n	%	n	%
Total Patients (N)	260		246		226		183		45	
DIZZINESS	26	10.00	7	2.85	14	6.19	15	3.54	1	2.22
DREAM ABNORM	12	4.62	6	2.44	4	1.77	5	2.73	0	0.00
DYSKINESIA	41	15.77	35	14.23	27	11.95	18	9.84	0	0.00
EXTRAPYR SYND	5	1.92	5	2.03	11	4.87	30	16.39	0	0.00
HALLUCIN	8	3.08	6	2.44	13	5.75	8	4.37	3	6.67
HYPOTENS POST	57	21.92	18	7.32	26	11.50	27	14.75	4	8.89
INJURY ACCID	8	3.08	5	2.03	10	4.42	18	9.84	0	0.00
INSOMNIA	20	7.69	7	2.85	11	4.87	23	12.57	1	2.22
NAUSEA	26	10.00	14	5.69	9	3.98	6	3.28	1	2.22
PAIN	3	1.15	5	2.03	8	3.54	12	6.56	0	0.00

Events with first occurrence during the dose reduction phase have been excluded

Appendix 4.13.6.1
ET Patients Studies 1, 4, & 21
Adverse Events By Age

		Pramipexole (Total Patients = 388)			Placebo (Total Patients = 235)					
		n	N*	Rate	n	N*	Rate	RR**	Lower 95% CI	Upper 95% CI
Age	Costart									
<= 45	ASTHENIA	8	30	0.267	4	23	0.174	1.53	0.53	4.47
	CONSTIP	3	30	0.100	1	23	0.043	2.30	0.26	20.70
	DEPRESSION	4	30	0.133	3	23	0.130	1.02	0.25	4.12
	DIZZINESS	5	30	0.167	5	23	0.217	0.77	0.25	2.34
	DYSPEPSIA	3	30	0.100	1	23	0.043	2.30	0.26	20.70
	HALLUCIN	3	30	0.100	.	.	.	.	.	.
	HEADACHE	6	30	0.200	3	23	0.130	1.53	0.43	5.49
	HYPERTONIA	1	30	0.033	5	23	0.217	0.15	0.02	1.22
	HYPOTENS POST	3	30	0.100	.	.	.	.	.	.
	INFECT	.	.	.	9	23	0.391	.	.	.
	INJURY ACCID	2	30	0.067	2	23	0.087	0.77	0.12	5.04
	INSOMNIA	10	30	0.333	2	23	0.087	3.83	0.93	15.82
	NAUSEA	6	30	0.200	5	23	0.217	0.92	0.32	2.64
	PAIN	6	30	0.200	1	23	0.043	4.60	0.59	35.60
	PAIN ABDO	.	.	.	2	23	0.087	.	.	.
	PAIN BACK	1	30	0.033	.	.	.	.	.	.
	SOMNOLENCE	7	30	0.233	1	23	0.043	5.37	0.71	40.61
	TREMOR	4	30	0.133	4	23	0.174	0.77	0.21	2.74
45-55	ASTHENIA	8	63	0.127	2	41	0.049	2.60	0.58	11.65
	CONSTIP	9	63	0.143	3	41	0.073	1.95	0.56	6.79

(CONTINUED)

Includes Studies M/2730/0001, M/2730/0004, and M/2730/0021
* N is the number of patients in each age group
** Relative risk computed as rate of PPX / rate of Placebo

		Pramipexole (Total Patients = 388)			Placebo (Total Patients = 235)			RR**	Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate			
Age	Costart									
45-55	DEPRESSION	4	63	0.063	1	41	0.024	2.60	0.30	22.48
	DIZZINESS	11	63	0.175	7	41	0.171	1.02	0.43	2.42
	DYSPEPSIA	5	63	0.079	1	41	0.024	3.25	0.39	26.86
	HALLUCIN	2	63	0.032	1	41	0.024	1.30	0.12	13.90
	HEADACHE	12	63	0.190	9	41	0.220	0.87	0.40	1.87
	HYPERTONIA	4	63	0.063	3	41	0.073	0.87	0.20	3.68
	HYPOTENS POST	3	63	0.048	2	41	0.049	0.98	0.17	5.59
	INFECT	8	63	0.127	6	41	0.146	0.87	0.32	2.32
	INJURY ACCID	4	63	0.063	2	41	0.049	1.30	0.25	6.79
	INSOMNIA	13	63	0.206	4	41	0.098	2.12	0.74	6.04
	NAUSEA	15	63	0.238	10	41	0.244	0.98	0.49	1.96
	PAIN	8	63	0.127	11	41	0.268	0.47	0.21	1.08
	PAIN ABDO	3	63	0.048	1	41	0.024	1.95	0.21	18.13
	PAIN BACK	4	63	0.063	4	41	0.098	0.65	0.17	2.46
	SOMNOLENCE	10	63	0.159	1	41	0.024	6.51	0.87	48.95
	TREMOR	7	63	0.111	5	41	0.122	0.91	0.31	2.68
56-65	ASTHENIA	19	120	0.158	9	68	0.132	1.20	0.57	2.50
	CONSTIP	16	120	0.133	6	68	0.088	1.51	0.62	3.68
	DEPRESSION	9	120	0.075	7	68	0.103	0.73	0.28	1.87
	DIZZINESS	26	120	0.217	20	68	0.294	0.74	0.45	1.22

(CONTINUED)

Includes Studies M/2730/0001, M/2730/0004, and M/2730/0021
* N is the number of patients in each age group
** Relative risk computed as rate of PPX / rate of Placebo

		Pramipexole (Total Patients = 388)			Placebo (Total Patients = 235)					
		n	N°	Rate	n	N°	Rate	RR°°	Lower 95% CI	Upper 95% CI
Age	Costart									
56-65	DYSPEPSIA	13	120	0.108	4	68	0.059	1.84	0.63	5.43
	HALLUCIN	7	120	0.058	3	68	0.044	1.32	0.35	4.95
	HEADACHE	20	120	0.167	10	68	0.147	1.13	0.56	2.28
	HYPERTONIA	9	120	0.075	6	68	0.088	0.85	0.32	2.29
	HYPOTENS POST	8	120	0.067	9	68	0.132	0.50	0.20	1.24
	INFECT	23	120	0.192	15	68	0.221	0.87	0.49	1.55
	INJURY ACCID	11	120	0.092	6	68	0.088	1.04	0.40	2.68
	INSOMNIA	22	120	0.183	10	68	0.147	1.25	0.63	2.47
	NAUSEA	33	120	0.275	12	68	0.176	1.56	0.86	2.81
	PAIN	12	120	0.100	15	68	0.221	0.45	0.23	0.91
	PAIN ABDO	8	120	0.067	4	68	0.059	1.13	0.35	3.63
	PAIN BACK	14	120	0.117	4	68	0.059	1.98	0.68	5.79
	SOMNOLENCE	24	120	0.200	7	68	0.103	1.94	0.88	4.27
	TREMOR	19	120	0.158	13	68	0.191	0.83	0.44	1.57
66-75	ASTHENIA	11	144	0.076	11	83	0.133	0.58	0.26	1.27
	CONSTIP	21	144	0.146	3	83	0.036	4.03	1.24	13.12
	DEPRESSION	4	144	0.028	4	83	0.048	0.58	0.15	2.24
	DIZZINESS	46	144	0.319	19	83	0.229	1.40	0.88	2.21
	DYSPEPSIA	6	144	0.042	8	83	0.096	0.43	0.16	1.20
	HALLUCIN	16	144	0.111	2	83	0.024	4.61	1.09	19.56

(CONTINUED)

Includes Studies M/2730/0001, M/2730/0004, and M/2730/0021
° N is the number of patients in each age group
°° Relative risk computed as rate of PPX / rate of Placebo

		Pramipexole (Total Patients = 388)			Placebo (Total Patients = 235)				Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate	RR**		
Age	Costart									
66-75	HEADACHE	17	144	0.118	13	83	0.157	0.75	0.39	1.47
	HYPERTONIA	7	144	0.049	3	83	0.036	1.34	0.36	5.06
	HYPOTENS POST	15	144	0.104	9	83	0.108	0.96	0.44	2.10
	INFECT	25	144	0.174	18	83	0.217	0.80	0.47	1.38
	INJURY ACCID	14	144	0.097	8	83	0.096	1.01	0.44	2.30
	INSOMNIA	20	144	0.139	9	83	0.108	1.28	0.61	2.68
	NAUSEA	43	144	0.299	12	83	0.145	2.07	1.16	3.69
	PAIN	21	144	0.146	16	83	0.193	0.76	0.42	1.37
	PAIN ABDO	9	144	0.063	5	83	0.060	1.04	0.36	2.99
	PAIN BACK	7	144	0.049	10	83	0.120	0.40	0.16	1.02
	SOMNOLENCE	38	144	0.264	10	83	0.120	2.19	1.15	4.16
	TREMOR	6	144	0.042	15	83	0.181	0.23	0.09	0.57
> 75	ASTHENIA	8	31	0.258	1	20	0.050	5.16	0.70	38.19
	CONSTIP	4	31	0.129	1	20	0.050	2.58	0.31	21.46
	DEPRESSION	1	31	0.032	2	20	0.100	0.32	0.03	3.33
	DIZZINESS	9	31	0.290	6	20	0.300	0.97	0.41	2.30
	DYSPEPSIA	1	31	0.032	2	20	0.100	0.32	0.03	3.33
	HALLUCIN	7	31	0.226	.	.	.	.	.	.
	HEADACHE	.	.	.	2	20	0.100	.	.	.
	HYPERTONIA	2	31	0.065	1	20	0.050	1.29	0.13	13.31

(CONTINUED)

Includes Studies M/2730/0001, M/2730/0004, and M/2730/0021
* N is the number of patients in each age group
** Relative risk computed as rate of PPX / rate of Placebo

		Pramipexole (Total Patients = 388)			Placebo (Total Patients = 235)				Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate	RR**		
Age	Costart									
> 75	HYPOTENS POST	1	31	0.032	1	20	0.050	0.65	0.04	9.74
	INFECT	3	31	0.097	4	20	0.200	0.48	0.12	1.94
	INJURY ACCID	3	31	0.097	2	20	0.100	0.97	0.18	5.29
	INSOMNIA	1	31	0.032	2	20	0.100	0.32	0.03	3.33
	NAUSEA	10	31	0.323	3	20	0.150	2.15	0.67	6.87
	PAIN	4	31	0.129	2	20	0.100	1.29	0.26	6.40
	PAIN ABDO	.	.	.	3	20	0.150	.	.	.
	PAIN BACK	5	31	0.161	2	20	0.100	1.61	0.35	7.53
	SOMNOLENCE	6	31	0.194	2	20	0.100	1.94	0.43	8.66
	TREMOR	1	31	0.032	2	20	0.100	0.32	0.03	3.33

* N is the number of patients in each age group
** Relative risk computed as rate of PPX / rate of Placebo

Appendix 4.13.6.2
AT Patients Studies 10, 19, 20, & 22
Adverse Events By Age

		Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)				Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate	RR**		
Age	Costart									
<= 45	AMNESIA	.	.	.	1	11	0.091	.	.	.
	ANOREXIA	.	.	.	2	11	0.182	.	.	.
	ASTHENIA	1	10	0.100	1	11	0.091	1.10	0.08	15.36
	CONFUS	1	10	0.100	.	.	.	.	.	.
	CONSTIP	1	10	0.100	.	.	.	.	.	.
	CRAMPS LEG	1	10	0.100	.	.	.	.	.	.
	DEPRESSION	2	10	0.200	5	11	0.455	0.44	0.11	1.78
	DIZZINESS	3	10	0.300	3	11	0.273	1.10	0.28	4.25
	DREAM ABNORM	1	10	0.100	2	11	0.182	0.55	0.06	5.18
	DRY MOUTH	.	.	.	1	11	0.091	.	.	.
	DYSKINESIA	8	10	0.800	5	11	0.455	1.76	0.86	3.61
	DYSPEPSIA	1	10	0.100	1	11	0.091	1.10	0.08	15.36
	DYSTONIA	.	.	.	1	11	0.091	.	.	.
	EXTRAPYR SYND	3	10	0.300	4	11	0.364	0.82	0.24	2.82
	HEADACHE	.	.	.	2	11	0.182	.	.	.
	HYPERTONIA	.	.	.	1	11	0.091	.	.	.
	HYPOKINESIA	2	10	0.200	1	11	0.091	2.20	0.23	20.72
	HYPOTENS POST	6	10	0.600	3	11	0.273	2.20	0.74	6.54
	INFECT	2	10	0.200	2	11	0.182	1.10	0.19	6.41
	INJURY ACCID	1	10	0.100	1	11	0.091	1.10	0.08	15.36

(CONTINUED)

		Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)				Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate	RR**		
Age	Costart									
<= 45	INSOMNIA	2	10	0.200	5	11	0.455	0.44	0.11	1.78
	NAUSEA	3	10	0.300	3	11	0.273	1.10	0.28	4.25
	PAIN	2	10	0.200	1	11	0.091	2.20	0.23	20.72
	PAIN BACK	.	.	.	1	11	0.091	.	.	.
	SOMNOLENCE	1	10	0.100	1	11	0.091	1.10	0.08	15.36
	TREMOR	1	10	0.100	2	11	0.182	0.55	0.06	5.18
45-55	AMNESIA	4	48	0.083	4	51	0.078	1.06	0.28	4.01
	ANOREXIA	4	48	0.083	2	51	0.039	2.12	0.41	11.08
	ASTHENIA	7	48	0.146	2	51	0.039	3.72	0.81	17.02
	CONFUS	5	48	0.104	3	51	0.059	1.77	0.45	7.01
	CONSTIP	5	48	0.104	1	51	0.020	5.31	0.64	43.84
	CRAMPS LEG	4	48	0.083	3	51	0.059	1.42	0.33	6.00
	DEPRESSION	6	48	0.125	6	51	0.118	1.06	0.37	3.07
	DIZZINESS	8	48	0.167	10	51	0.196	0.85	0.37	1.97
	DREAM ABNORM	4	48	0.083	3	51	0.059	1.42	0.33	6.00
	DRY MOUTH	5	48	0.104	.	.	.	.	.	.
	DYSKINESIA	25	48	0.521	22	51	0.431	1.21	0.80	1.83
	DYSPEPSIA	2	48	0.042	3	51	0.059	0.71	0.12	4.06
	DYSTONIA	4	48	0.083	4	51	0.078	1.06	0.28	4.01
	EXTRAPYR SYND	21	48	0.438	13	51	0.255	1.72	0.97	3.03

(CONTINUED)

		Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)				Lower 95% CI	Upper 95% CI
Age	Costart	n	N*	Rate	n	N*	Rate	RR**		
45-55	GAIT ABNORM	2	48	0.042	2	51	0.039	1.06	0.16	7.25
	HALLUCIN	2	48	0.042	1	51	0.020	2.13	0.20	22.68
	HEADACHE	5	48	0.104	10	51	0.196	0.53	0.20	1.44
	HYPERTONIA	3	48	0.063	4	51	0.078	0.80	0.19	3.38
	HYPOKINESIA	5	48	0.104	5	51	0.098	1.06	0.33	3.44
	HYPOTENS POST	20	48	0.417	23	51	0.451	0.92	0.59	1.45
	INFECT	5	48	0.104	14	51	0.275	0.38	0.15	0.97
	INJURY ACCID	5	48	0.104	8	51	0.157	0.66	0.23	1.89
	INSOMNIA	19	48	0.396	12	51	0.235	1.68	0.92	3.08
	NAUSEA	11	48	0.229	14	51	0.275	0.83	0.42	1.65
	PAIN	4	48	0.083	7	51	0.137	0.61	0.19	1.94
	PAIN BACK	4	48	0.083	6	51	0.118	0.71	0.21	2.36
	SOMNOLENCE	4	48	0.083	3	51	0.059	1.42	0.33	6.00
	TREMOR	1	48	0.021	5	51	0.098	0.21	0.03	1.75
	URIN FREQUENCY	3	48	0.063	2	51	0.039	1.59	0.28	9.13
56-65	AMNESIA	3	91	0.033	4	90	0.044	0.74	0.17	3.22
	ANOREXIA	3	91	0.033	8	90	0.089	0.37	0.10	1.35
	ASTHENIA	12	91	0.132	10	90	0.111	1.19	0.54	2.61
	CONFUS	3	91	0.033	7	90	0.078	0.42	0.11	1.59
	CONSTIP	8	91	0.088	10	90	0.111	0.79	0.33	1.91

(CONTINUED)

		Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)				Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate	RR**		
Age	Costart									
56-65	CRAMPS LEG	4	91	0.044	6	90	0.067	0.66	0.19	2.26
	DEPRESSION	9	91	0.099	17	90	0.189	0.52	0.25	1.11
	DIZZINESS	22	91	0.242	23	90	0.256	0.95	0.57	1.57
	DREAM ABNORM	12	91	0.132	12	90	0.133	0.99	0.47	2.08
	DRY MOUTH	6	91	0.066	2	90	0.022	2.97	0.62	14.31
	DYSKINESIA	43	91	0.473	33	90	0.367	1.29	0.91	1.82
	DYSPEPSIA	4	91	0.044	8	90	0.089	0.49	0.15	1.58
	DYSTONIA	8	91	0.088	8	90	0.089	0.99	0.39	2.52
	EXTRAPYR SYND	19	91	0.209	22	90	0.244	0.85	0.50	1.47
	GAIT ABNORM	7	91	0.077	5	90	0.056	1.38	0.46	4.20
	HALLUCIN	15	91	0.165	4	90	0.044	3.71	1.28	10.75
	HEADACHE	10	91	0.110	16	90	0.178	0.62	0.30	1.29
	HYPERTONIA	7	91	0.077	8	90	0.089	0.87	0.33	2.29
	HYPOKINESIA	5	91	0.055	8	90	0.089	0.62	0.21	1.82
	HYPOTENS POST	47	91	0.516	45	90	0.500	1.03	0.78	1.38
	INFECT	10	91	0.110	7	90	0.078	1.41	0.56	3.55
	INJURY ACCID	14	91	0.154	17	90	0.189	0.81	0.43	1.55
	INSOMNIA	21	91	0.231	25	90	0.278	0.83	0.50	1.37
	NAUSEA	23	91	0.253	21	90	0.233	1.08	0.65	1.81
	PAIN	10	91	0.110	19	90	0.211	0.52	0.26	1.06

(CONTINUED)

		Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)				Lower 95% CI	Upper 95% CI
Age	Costart	n	N*	Rate	n	N*	Rate	RR**		
56-65	PAIN BACK	1	91	0.011	6	90	0.067	0.16	0.02	1.34
	SOMNOLENCE	8	91	0.088	5	90	0.056	1.58	0.54	4.65
	TREMOR	8	91	0.088	20	90	0.222	0.40	0.18	0.85
	URIN FREQUENCY	3	91	0.033	3	90	0.033	0.99	0.21	4.77
66-75	AMNESIA	7	96	0.073	2	98	0.020	3.57	0.76	16.77
	ANOREXIA	6	96	0.063	2	98	0.020	3.06	0.63	14.80
	ASTHENIA	5	96	0.052	6	98	0.061	0.85	0.27	2.69
	CONFUS	13	96	0.135	7	98	0.071	1.90	0.79	4.55
	CONSTIP	11	96	0.115	10	98	0.102	1.12	0.50	2.52
	CRAMPS LEG	4	96	0.042	3	98	0.031	1.36	0.31	5.92
	DEPRESSION	4	96	0.042	14	98	0.143	0.29	0.10	0.85
	DIZZINESS	28	96	0.292	25	98	0.255	1.14	0.72	1.81
	DREAM ABNORM	9	96	0.094	8	98	0.082	1.15	0.46	2.85
	DRY MOUTH	6	96	0.063	4	98	0.041	1.53	0.45	5.26
	DYSKINESIA	41	96	0.427	19	98	0.194	2.20	1.38	3.51
	DYSPEPSIA	5	96	0.052	5	98	0.051	1.02	0.31	3.41
	DYSTONIA	6	96	0.063	5	98	0.051	1.23	0.39	3.88
	EXTRAPYR SYND	23	96	0.240	23	98	0.235	1.02	0.62	1.69
	GAIT ABNORM	7	96	0.073	6	98	0.061	1.19	0.42	3.42
	HALLUCIN	22	96	0.229	4	98	0.041	5.61	2.01	15.69

(CONTINUED)

		Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)				Lower 95% CI	Upper 95% CI
Age	Costart	n	N*	Rate	n	N*	Rate	RR**		
66-75	HEADACHE	7	96	0.073	9	98	0.092	0.79	0.31	2.05
	HYPERTONIA	6	96	0.063	3	98	0.031	2.04	0.53	7.93
	HYPOKINESIA	3	96	0.031	7	98	0.071	0.44	0.12	1.64
	HYPOTENS POST	52	96	0.542	48	98	0.490	1.11	0.84	1.45
	INFECT	7	96	0.073	12	98	0.122	0.60	0.24	1.45
	INJURY ACCID	17	96	0.177	11	98	0.112	1.58	0.78	3.19
	INSOMNIA	24	96	0.250	13	98	0.133	1.88	1.02	3.48
	NAUSEA	19	96	0.198	20	98	0.204	0.97	0.55	1.70
	PAIN	11	96	0.115	14	98	0.143	0.80	0.38	1.68
	PAIN BACK	6	96	0.063	4	98	0.041	1.53	0.45	5.26
	SOMNOLENCE	10	96	0.104	6	98	0.061	1.70	0.64	4.50
	TREMOR	8	96	0.083	9	98	0.092	0.91	0.37	2.25
	URIN FREQUENCY	9	96	0.094	1	98	0.010	9.19	1.19	71.14
> 75	AMNESIA	1	15	0.067	.	.	.	.	.	.
	ANOREXIA	1	15	0.067	4	14	0.286	0.23	0.03	1.84
	ASTHENIA	1	15	0.067	2	14	0.143	0.47	0.05	4.60
	CONFUS	4	15	0.267	2	14	0.143	1.87	0.40	8.65
	CONSTIP	1	15	0.067	2	14	0.143	0.47	0.05	4.60
	CRAMPS LEG	1	15	0.067	.	.	.	.	.	.
	DEPRESSION	1	15	0.067	2	14	0.143	0.47	0.05	4.60

(CONTINUED)

		Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)				Lower 95% CI	Upper 95% CI
Age	Costart	n	N*	Rate	n	N*	Rate	RR**		
> 75	DIZZINESS	6	15	0.400	5	14	0.357	1.12	0.44	2.86
	DREAM ABNORM	2	15	0.133	.	.	.	.	.	.
	DYSKINESIA	6	15	0.400	4	14	0.286	1.40	0.50	3.94
	DYSPEPSIA	1	15	0.067	.	.	.	.	.	.
	DYSTONIA	3	15	0.200	1	14	0.071	2.80	0.33	23.87
	EXTRAPYR SYND	6	15	0.400	6	14	0.429	0.93	0.39	2.22
	GAIT ABNORM	2	15	0.133	.	.	.	.	.	.
	HALLUCIN	4	15	0.267	1	14	0.071	3.73	0.47	29.49
	HEADACHE	1	15	0.067	1	14	0.071	0.93	0.06	13.54
	HYPERTONIA	1	15	0.067	.	.	.	.	.	.
	HYPOKINESIA	.	.	.	1	14	0.071	.	.	.
	HYPOTENS POST	12	15	0.800	8	14	0.571	1.40	0.83	2.35
	INFECT	2	15	0.133	1	14	0.071	1.87	0.19	18.38
	INJURY ACCID	6	15	0.400	2	14	0.143	2.80	0.67	11.64
	INSOMNIA	4	15	0.267	2	14	0.143	1.87	0.40	8.65
	NAUSEA	2	15	0.133	3	14	0.214	0.62	0.12	3.19
	PAIN	4	15	0.267	2	14	0.143	1.87	0.40	8.65
	PAIN BACK	3	15	0.200	1	14	0.071	2.80	0.33	23.87
	SOMNOLENCE	.	.	.	1	14	0.071	.	.	.
	TREMOR	1	15	0.067	2	14	0.143	0.47	0.05	4.60
	URIN FREQUENCY	.	.	.	1	14	0.071	.	.	.

* N is the number of patients in each gender
** Relative risk computed as rate of PPX / rate of Placebo

Appendix 4.13.6.3
ET Patients Studies 1, 4, & 21
Adverse Events By Gender

		Pramipexole (Total Patients = 388)			Placebo (Total Patients = 235)				Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate	RR**		
Sex	Costart									
Male	ASTHENIA	32	251	0.127	10	141	0.071	1.80	0.91	3.55
	CONSTIP	36	251	0.143	7	141	0.050	2.89	1.32	6.32
	DEPRESSION	17	251	0.068	5	141	0.035	1.91	0.72	5.07
	DIZZINESS	57	251	0.227	29	141	0.206	1.10	0.74	1.64
	DYSPEPSIA	18	251	0.072	11	141	0.078	0.92	0.45	1.89
	HALLUCIN	24	251	0.096	5	141	0.035	2.70	1.05	6.91
	HEADACHE	27	251	0.108	16	141	0.113	0.95	0.53	1.70
	HYPERTONIA	15	251	0.060	10	141	0.071	0.84	0.39	1.83
	HYPOTENS POST	19	251	0.076	12	141	0.085	0.89	0.44	1.78
	INFECT	39	251	0.155	33	141	0.234	0.66	0.44	1.01
	INJURY ACCID	25	251	0.100	9	141	0.064	1.56	0.75	3.25
	INSOMNIA	45	251	0.179	17	141	0.121	1.49	0.89	2.50
	NAUSEA	47	251	0.187	16	141	0.113	1.65	0.97	2.80
	PAIN	29	251	0.116	24	141	0.170	0.68	0.41	1.12
	PAIN ABDO	12	251	0.048	7	141	0.050	0.96	0.39	2.39
	PAIN BACK	16	251	0.064	10	141	0.071	0.90	0.42	1.93
	SOMNOLENCE	60	251	0.239	9	141	0.064	3.75	1.92	7.32
	TREMOR	27	251	0.108	22	141	0.156	0.69	0.41	1.16
Female	ASTHENIA	22	137	0.161	17	94	0.181	0.89	0.50	1.58
	CONSTIP	17	137	0.124	7	94	0.074	1.67	0.72	3.86

(CONTINUED)

		Pramipexole (Total Patients = 388)			Placebo (Total Patients = 235)				Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate	RR**		
Sex	Costart									
Female	DEPRESSION	5	137	0.036	12	94	0.128	0.29	0.10	0.78
	DIZZINESS	40	137	0.292	28	94	0.298	0.98	0.65	1.47
	DYSPEPSIA	10	137	0.073	5	94	0.053	1.37	0.48	3.89
	HALLUCIN	11	137	0.080	1	94	0.011	7.55	0.99	57.48
	HEADACHE	28	137	0.204	21	94	0.223	0.91	0.55	1.51
	HYPERTONIA	8	137	0.058	8	94	0.085	0.69	0.27	1.76
	HYPOTENS POST	11	137	0.080	9	94	0.096	0.84	0.36	1.94
	INFECT	20	137	0.146	19	94	0.202	0.72	0.41	1.28
	INJURY ACCID	9	137	0.066	11	94	0.117	0.56	0.24	1.30
	INSOMNIA	21	137	0.153	10	94	0.106	1.44	0.71	2.92
	NAUSEA	60	137	0.438	26	94	0.277	1.58	1.08	2.31
	PAIN	22	137	0.161	21	94	0.223	0.72	0.42	1.23
	PAIN ABDO	8	137	0.058	8	94	0.085	0.69	0.27	1.76
	PAIN BACK	15	137	0.109	10	94	0.106	1.03	0.48	2.19
	SOMNOLENCE	25	137	0.182	12	94	0.128	1.43	0.76	2.70
	TREMOR	10	137	0.073	17	94	0.181	0.40	0.19	0.84

* N is the number of patients in each gender

** Relative risk computed as rate of PPX / rate of Placebo

Appendix 4.13.6.4
AT Patients Studies 10, 19, 20, & 22
Adverse Events By Gender

		Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)				Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate	RR**		
Sex	Costart									
Male	AMNESIA	9	164	0.055	8	173	0.046	1.19	0.47	3.00
	ANOREXIA	9	164	0.055	9	173	0.052	1.05	0.43	2.59
	ASTHENIA	17	164	0.104	11	173	0.064	1.63	0.79	3.38
	CONFUS	19	164	0.116	13	173	0.075	1.54	0.79	3.02
	CONSTIP	20	164	0.122	14	173	0.081	1.51	0.79	2.88
	CRAMPS LEG	6	164	0.037	9	173	0.052	0.70	0.26	1.93
	DEPRESSION	10	164	0.061	24	173	0.139	0.44	0.22	0.89
	DIZZINESS	42	164	0.256	34	173	0.197	1.30	0.87	1.94
	DREAM ABNORM	16	164	0.098	18	173	0.104	0.94	0.50	1.78
	DRY MOUTH	11	164	0.067	4	173	0.023	2.90	0.94	8.93
	DYSKINESIA	73	164	0.445	52	173	0.301	1.48	1.11	1.97
	DYSPEPSIA	10	164	0.061	8	173	0.046	1.32	0.53	3.26
	DYSTONIA	13	164	0.079	13	173	0.075	1.05	0.50	2.21
	EXTRAPYR SYND	44	164	0.268	40	173	0.231	1.16	0.80	1.68
	GAIT ABNORM	12	164	0.073	9	173	0.052	1.41	0.61	3.25
	HALLUCIN	31	164	0.189	9	173	0.052	3.63	1.79	7.40
	HEADACHE	10	164	0.061	22	173	0.127	0.48	0.23	0.98
	HYPERTONIA	11	164	0.067	8	173	0.046	1.45	0.60	3.52
	HYPOKINESIA	7	164	0.043	15	173	0.087	0.49	0.21	1.18
	HYPOTENS POST	86	164	0.524	78	173	0.451	1.16	0.93	1.45

(CONTINUED)

		Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)				Lower 95% CI	Upper 95% CI
Sex	Costart	n	N*	Rate	n	N*	Rate	RR**		
Male	INFECT	18	164	0.110	25	173	0.145	0.76	0.43	1.34
	INJURY ACCID	29	164	0.177	19	173	0.110	1.61	0.94	2.76
	INSOMNIA	41	164	0.250	35	173	0.202	1.24	0.83	1.84
	NAUSEA	34	164	0.207	34	173	0.197	1.05	0.69	1.61
	PAIN	19	164	0.116	27	173	0.156	0.74	0.43	1.28
	PAIN BACK	10	164	0.061	16	173	0.092	0.66	0.31	1.41
	SOMNOLENCE	17	164	0.104	11	173	0.064	1.63	0.79	3.38
	TREMOR	13	164	0.079	21	173	0.121	0.65	0.34	1.26
	URIN FREQUENCY	8	164	0.049	5	173	0.029	1.69	0.56	5.05
Female	AMNESIA	6	96	0.063	3	91	0.033	1.90	0.49	7.36
	ANOREXIA	5	96	0.052	9	91	0.099	0.53	0.18	1.51
	ASTHENIA	9	96	0.094	10	91	0.110	0.85	0.36	2.00
	CONFUS	7	96	0.073	6	91	0.066	1.11	0.39	3.17
	CONSTIP	6	96	0.063	9	91	0.099	0.63	0.23	1.70
	CRAMPS LEG	8	96	0.083	3	91	0.033	2.53	0.69	9.23
	DEPRESSION	12	96	0.125	20	91	0.220	0.57	0.30	1.10
	DIZZINESS	25	96	0.260	32	91	0.352	0.74	0.48	1.15
	DREAM ABNORM	12	96	0.125	7	91	0.077	1.63	0.67	3.95
	DRY MOUTH	6	96	0.063	3	91	0.033	1.90	0.49	7.36
	DYSKINESIA	50	96	0.521	31	91	0.341	1.53	1.08	2.16

(CONTINUED)

		Pramipexole (Total Patients = 260)			Placebo (Total Patients = 264)				Lower 95% CI	Upper 95% CI
		n	N*	Rate	n	N*	Rate	RR**		
Sex	Costart									
Female	DYSPEPSIA	3	96	0.031	9	91	0.099	0.32	0.09	1.13
	DYSTONIA	8	96	0.083	6	91	0.066	1.26	0.46	3.50
	EXTRAPYR SYND	28	96	0.292	28	91	0.308	0.95	0.61	1.47
	GAIT ABNORM	6	96	0.063	4	91	0.044	1.42	0.41	4.88
	HALLUCIN	12	96	0.125	1	91	0.011	11.38	1.51	85.73
	HEADACHE	13	96	0.135	16	91	0.176	0.77	0.39	1.51
	HYPERTONIA	6	96	0.063	8	91	0.088	0.71	0.26	1.97
	HYPOKINESIA	8	96	0.083	7	91	0.077	1.08	0.41	2.87
	HYPOTENS POST	51	96	0.531	49	91	0.538	0.99	0.76	1.29
	INFECT	8	96	0.083	11	91	0.121	0.69	0.29	1.64
	INJURY ACCID	14	96	0.146	20	91	0.220	0.66	0.36	1.23
	INSOMNIA	29	96	0.302	22	91	0.242	1.25	0.78	2.01
	NAUSEA	24	96	0.250	27	91	0.297	0.84	0.53	1.35
	PAIN	12	96	0.125	16	91	0.176	0.71	0.36	1.42
	PAIN BACK	4	96	0.042	2	91	0.022	1.90	0.36	10.10
	SOMNOLENCE	6	96	0.063	5	91	0.055	1.14	0.36	3.60
	TREMOR	6	96	0.063	17	91	0.187	0.33	0.14	0.81
	URIN FREQUENCY	7	96	0.073	2	91	0.022	3.32	0.71	15.56

* N is the number of patients in each gender
** Relative risk computed as rate of PPX / rate of Placebo

Predefined Limits for Laboratory Assays

Assay	Unit of Measure	Sex	Criterion Value
Hemoglobin	g/dL	M	<10, >18
		F	<9, >17
Hematocrit	%	M	<30, >54
		F	<27, >51
RBC	10^6/uL	M	<3, >7
		F	<2.5, >6.5
MCV	fL		<75, >110
MCH	pg		<24, >36
MCHC	%		<30, >38
Platelet Count	cells/mm^3		<80,000 >600,000
WBC Count	10^3/uL		<3, >13
Neutrophils	%		<=15
Lymphocytes	%		<=10, >=80
Monocytes	%		>=20
Eosinophil	%		>=10
Basophil	%		>=10
Bands	%		>=10
Glucose	mg/dL		<60, >200
BUN	mg/dL		>40
Creatinine	mg/dL		>2.5
Uric Acid	mg/dL		>10
Total Cholesterol	mg/dL		>50
Total Bilirubin	mg/dL		>2.5
Alkaline Phosphatase	U/L		2.5 x ULN*
LDH	U/L		2.5 x ULN
SGOT (AST)	U/L		2.5 x ULN
SGPT (ALT)	U/L		2.5 x ULN
Creatine Kinase	U/L		2.5 x ULN
Gamma-Glutamyl Transpeptidase (GGT)	U/L		2.5 x ULN
Total Protein	g/dL		<4.5, >9
Calcium	mg/dL		≤8, ≥12
Chloride	mEq/L		≤90, ≥115
Protein Globulin	G/DL		≤1.0, ≥4.0

(Continued)

Predefined Limits for Laboratory Assays

Assay	Unit of Measure	Sex	Criterion Value
Potassium	mEq/L		≤3.0, ≥6.0
Sodium	mEq/L		≤125, ≥160
Specific Gravity			≤1.005, ≥1.028
pH			≤4.0, ≥9.0
Urine Protein			> 1+
Urine Glucose			> 1+
Urine Ketone			> 2+
Urine RBC			> 5
Urine WBC	HPF	M	> 10
	HPF	F	> 20
Urine Casts			Present
Culture			Positive

* ULN = Upper Limit of Normal Range

Summary of All patients With Laboratory Values
Exceeding Predefined Limits
Group: Adequate and Well-Controlled Studies# for Parkinson's Disease

		Medication					
		Pramipexole			Placebo		
Laboratory Test		n	N	%	n	N	%
Hematology	Hemoglobin	5	547	0.91	5	394	1.27
	Hematocrit	4	547	0.73	5	394	1.27
	RBC Count	1	547	0.18	1	394	0.25
	MCV	3	547	0.55	2	394	0.51
	MCH	5	547	0.91	4	394	1.02
	MCHC	4	547	0.73	3	394	0.76
	WBC Count	13	547	2.38	15	394	3.81
	Neutrophils Segs	0	339	0	0	343	0
	Bands	0	209	0	0	51	0
	Lymphocytes	16	547	2.93	7	394	1.78
	Monocytes	0	547	0	0	394	0
	Eosinophils	19	547	3.47	24	394	6.09
	Basophils	0	547	0	0	394	0
	Platelet Count	3	546	0.55	1	394	0.25
Blood Chemistry	Glucose	30	547	5.48	25	394	6.35
	BUN	1	547	0.18	2	394	0.51
	Creatinine	1	547	0.18	0	394	0
	Uric Acid	3	547	0.55	4	394	1.02
	Cholesterol, Total	16	547	2.93	14	394	3.55
	Bilirubin, Total	0	547	0	1	394	0.25
	Alkaline Phosphatase	2	547	0.37	0	394	0
	LDH	1	547	0.18	0	394	0
	SGOT	4	547	0.73	0	394	0
	SGPT	4	547	0.73	2	394	0.51
	CPK	19	544	3.49	9	392	2.30
	GGT	11	547	2.01	4	394	1.02
	Protein, Total	1	547	0.18	0	394	0
Urinalysis	Urine Protein	8	364	2.20	2	219	0.91
	Urine Glucose	6	364	1.65	5	219	2.28
	Urine Micro WBC	12	364	3.30	14	219	6.39
	Urine Micro RBC	13	364	3.57	18	219	8.22
	Urine Ketone	0	364	0	0	219	0
	Urine Micro Casts	6	161	3.73	8	169	4.73
	Urine Culture	0	0	0	1	1	100.00

Source: Appendix C, Table 30.1
Protocols M/2730/0001, M/2730/0004, and M/2730/0010

Appendix 4.15.3

PLACEBO Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's at endpoint*).							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments-Relevant Info
0001	2302 Burch	46/F/W	-12 25 53 106 169 232 239	347 91 122 135 217 766 630	Angina - 1988; Hypertension; Bypass surgery (for weight control) - 1975; Hypothyroidism - 1968; Prostatism; Osteoarthritis; Back pain; Obesity; ECG NSR; Prominent anterior forces; may be artifact	Artane Eldepryl Flagyl Sulfamethoxazole Naproxen Tylenol with codeine Relafen Voltaren Amitriptyline Steroid injection	Increase fall or injury was not noted. All CPK were 100% CK-MM. Investigator judged elevations as not clinically significant.
0001	2058 Paulson	46/F/W	-14 28 71 136 196 260 267	408 777 427 399 650 582 566	Inferior Infarct - ?; Increased cholesterol; Increased CPK; Increased eosinophils; kidney stones ?; L. knee surgery - 1987 H/A; Tight muscle - scalp; ECG NSR; Inferior infarct age undet.	Kemidrin Benadryl ASA Eldepryl	The CPK was already slightly increased at baseline. On Day 71, the patient complained of chest pains for which stress test was ordered. All CPK fractionizations showed ≥ 98% CK-MM. Though not clinically significant patient was referred to cardiologist.

*Endpoint = end of study or dropout.

PLACEBO Protocol: M/2730			Laboratory Test: CPK (Pt's who had elevated CPK's at endpoint*).				
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments-Relevant Info
0001	2241 Weiner	71/F/W	-7 22 64 120 183 239 253	638 638 355 532 750 979 689	Ing hernia - 1983; Spinal fusion - 1970; R. Carpel tunnel Sx - 1993; Blood in semen - 1993; Increased CPK - etiology unknown; arthritis R. knee; ECG Abnormal R. Waves Q II III, F; old I WMI; ST-T changes I, AV, V6	Deprenyl-PD Naproxen Corticosteroid injection Tetracycline Dyazide	The patient's CPK was increased at baseline and remained elevated till end of study. Investigator's opinion: no evidence of skeletal muscle damage and elevation judged to be NCS. Fractionation showed ≥ 95% CK3=MM.
0010	1256 Lieberman	59/M/W	-7 25 37 67	80 109 393 1049	Gastric reaction - 1966; Vagotomy-partial- 1966; Periodic back pain; ECG = NSR	Pergolide Selegiline Norazepam Amantadine Trihexy-pheridil Sinemet	Patient had increasing dyskinesia. Investigator felt the elevated CPK was secondary to severe dyskinesia which necessitated visit to ER.

*Endpoint = end of study or dropout.

PLACEBO Protocol: M/2730			Laboratory Test: CPK (Pt's who had elevated CPK's and ret.to normal at endpoint*.)				
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	2343 Bennett	63/F/W	-11 25 32 53 109 170 221 228	235 511 160 142 105 141 538 236	Hypertension - 1992; Spinal stenosis surgery - 1992; L. Carpel tunnel syndrome surgery - 1992; ECG-NSR, LVH by voltage	terazosin	Day 25 CPK 511; CPK fractionated showed 98% CK-MM - Contused R. wrist 3 days prior to CPK; Day 221 CPK 538 CPK fractionated showed CK-MM 97%; investigator comment "physical exertion"

*Endpoint = end of study or dropout.

PLACEBO Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret.to normal at endpoint*.)

Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	2157 Fazzini	65/F/W	-12 24 52 115 175 233 245	157 485 158 184 165 118 134	Angina - ASHD-63 HTN - 91; Renal calculi 1963 (nephrolithasis); L. Knee surgery - 1990; R. Ing. hernia - 1941; Tonsillectomy - 30's; Ganglion cyst R. gr. toe - 1978; Skin cyst - neck - 1978; CXR - Screen; linear scarring in R. lung field; diaphragm flattened; Aorta elongated & tortuous. Heart size enlarged - some degree of COPD & old fibrosis @ R. base ASHD suggested. ECG - Sinus bradycardia; Early R. Wave progression; 1st degree AV block.	Eldynyl Cardizem Tenormin ASA - nitro-glycerin	Day 24 CPK 485; CPK fractionated; CK-MM 98%; Investigator comment: NCS

*Endpoint = end of study or dropout.

PLACEBO Protocol: M/2730			Laboratory Test: CPK (Pt's who had elevated CPK's and ret.to normal at endpoint*.)				
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0010	1173 Eidelman	46/M/W	-23 22 52 106 162 218 224	268 590 324 165 421 281 272	Diverticulitis - 1993; Back pain - 1973; Subarachnoid Cyst - 1990; ECG = NSR	Sinemet CR	1st elevation (590) was said to be due to prolonged tourniquet time; 2nd elevation (421) was due to patient shoveling driveway for 5 hours. Both fractionated CKB-MB= 99-100%
0010	1122 Perimutter	55/M/W	-7 29 43 99 155 213 218	71 80 143 72 101 857 140	Migraine - 1988; Tunnel Vision - 1990; Generalized choreiform movements (brady-kinesia R>L) ECG=NSR; L. anterior fascicular block	Persantine Amantadine Diphenhy-dramine Sinemet CR	Patient developed severe esophageal spasm for which he was hospitalized. He also experienced increased dyskinesia & nocturnal myoclonus. The patient had multiple needle sticks prior to this blood draw accounting for elevated CPK fractionation: CK3-MM = 99%; CK2-MB = 1%

*Endpoint = end of study or dropout.

PLACEBO Protocol: M/2730			Laboratory Test: CPK (Pt's who had elevated CPK's and ret.to normal at endpoint*.)				
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0010	1221 Richter	81/M/W	-12 20 106 175 234 241	625 691 387 112 369 326	Hypertension - 1991; L. Inguinal hernia - 1993; Back muscle spasm; Osgood-Schlatter Disease - 1993; ECG-NSR; Slight cardiomegaly on chest x-ray	Primivil Hydrochloro-thiazide Toradol	Patient had elevated CPK 6 weeks prior to baseline (4700) which the investigator related to muscle trauma. Fractionation: CK3-MM = 99%; Subsequently CPK came down and other fractionation also was CK3-MM = 98-99%

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)

Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	2048 Fazzini	33/F/W	-7 22 53 92 148 162	77 188 95 741 205 104	ECG - Sinus bradycardia; R. bundle intraventricular conduction delay	Eldepryl Permax	Day 92 CPK 741; CPK fractionated showed 98% CK-MM, Investigator comment: NCS; Day 162 dropped from study due to adverse event (paranoia & auditory hallucinations).
0001	2143 Friedman	60/F/W	-7 27 58 124 177 247 254	289 244 350 428 624 325 285	Hypertension, increased cholesterol; lobectomy (bronchiectasis), ulcer, IBS, hyperthyroidism; kidney stones; erectile dysfunction (due to hypertension meds); anxiety; ECG poor R Wave progression, L. axis-clockwise rotation - ST Wave Abnormality	Eldepryl Inderol Mevacor Zantac Imodium Allopurinol Klonopin	Day 177 CPK 624; CPK fractionated showed 97% CK-MM, Investigator comment: NCS

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)

Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	2039 Kurth	48/F/W	-16 22 50 101 154 224 230	270 641 116 346 209 163 160	Urinary urgency; head injury - 1984; ECG - NSR	Eldepryl Amantadine Elavil	Day 22 CPK 641; CPK fractionated showed 100% CK-MM, Investigator comment: NCS

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)

Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	2197 Olanow	66/F/W	-2 22 50 106 160 218 225	224 242 305 639 264 349 357	Stroke L. - 1989; Arthritis - 1990; Intermittent constipation -1993; Back cyst removed; Mortons neuroma - 1992; Memory difficulties - 1991; Intermittent light-headedness - 1991; ECG - Rapid early transition. Non Sp. ST-T Wave changes; Sm. non-pathological Q waves lead III. Cannot R/O old inferior posterior MI; borderline abnormalities may not indicate heart disease	Cogentin Eldepryl	Prior to Day 106, Patient reported freezing; blurry vision; & increased forget-fullness; Day 106 - CPK 639; fractionated showed CK-MM 100%, Investigator comment: NCS

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	2310 Richter	56/F/W	-5 51 107 170 247	222 215 258 522 285	Hematuria; erectile dysfunction; Rash - chest; ECG - Sinus bradycardia; L. possible Atrial enlargement - bigeminal PAC's with standing	No relevant concomitant medications.	Day 170 CPK 522; CPK fractionated; Shows 100% CK-MM; Muscle problem ongoing per investigator

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)

Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	2213 Watts	57/F/W	-13 27 58 111 125 169 220 232	90 221 163 507 516 148 180 160	PUD - 1972; occasional burning on urination - 1992; urinary frequency - 1992; partial amputation 5th digit R. hand - 1967; bilaterial hip pain - 1992; head trauma - 1955; ECG sinus bradycardia L. axis deviation - old findings; T-abnormality - old findings	Selegiline trinekyphe-nidyl non ASA analgesic ibuprofen Novacaine llysine	Day 111 CPK 507; CPK fractionated; showed 100% CK-MM, Investigator comment: "No chest pain, injury or flu, will recheck again with muscle specific enzyme"; Day 125 CPK 516; CPK fractionated showed 100% CK-MM, Investigator comment: "unknown clinical significant - asymptomatic; ? myositis; injury, without chest pain and fever; second high value will repeat and check aldolase and ESR at same time".

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)

Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0004	251 Grimes	59/M/W	-10 45 68	285 657 384	Impotence x 1; A-Fib x 15 yrs; hypertension (renal dysfunction); transient arthritis - wrists; gout - which was drug related in 1988; cholecystecomy in 1982; ECG Atrial Fibrilliation.	Deprenyl Doxycline Digoxin, ASA Novahy-diazide Novasen Vasotec Verapamil HCL Selegeline Isoptin Enalapril Maleate	Day 45 CPK 657 - CPK not fractionated, investigator comment: "all known before".
0004	192 Sethi	70/M/W	-10 43 68	115 519 41	Hiatal hernia - 1991; strained muscle mid back; benign cyst R. kidney - 1987.	Ibuprofen Tums Standback powder amoxicillin L-Deprenyl Amantidine Nubain Fentanyl Dxycodone & propexyphene	Day 43 CPK 519. CPK not fractionated. R. hip fx - patient fell 8/2/94 @ Day 42 - hospitalized for surgery. Not walking at end of study;.

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0010	1247 Guttman	52/M/O	-6 25 59 105 155 204 211	165 210 244 384 984 305 360	Kidney stone (1979) MVA back injury (1989) Knee effusion (1993) Slightly hypertensive intermittent (L) Knee pain Chronic sinus infection ECG: NSR Day 56: NSR with non-specific T-wave abnormality	Sinemet CR Naprosyn Steroid injection (for knee) on Visit 4 Amoxicillin (for sinus)	Per investigator, the elevated CPK (not fractionated) was skeletal, probably related to osteoarthropathy & was accompanied by slight ↑ LDH (not clinically significant level of 254; (N= 0-250) CPK levels came down at subsequent visits

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt's who had elevated CPK's and ret. to normal at endpoint.*)

Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0010	1295 Hubble	53/M/W	-8 21 49 105 162 218 225	103 238 248 722 494 232 229	Multiple fractures (1961, 1962, 199) ECG = NSR	Eldepryl Trazodine Restoril	Around Day 105, pt fell off a horse while riding. Investigator noted that pt. had rhabdomyolysis due to fall; fractionation was 100% CK3-MM. CPK subsequently returned to normal
0010	1120 Jankovic	62/M/W	-7 24 43 65	238 216 733 117	Occasional dizzy spells. ECG = NSR	Sinemet	Pt. had complained of increasing early morning dystonia. CPK fractionation = 95% CK3-MM, 3% CK2 - MB Pt. was discontinued from study; no work-up or diagnosis available. The CPK returned to normal on Day 65

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*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt.'s who had elevated CPK's at endpoint*).							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	2152 Factor	76/F/W	-7 22 29 85 141 204 211	170 195 157 137 202 158 537	Sm. ventral hernia midline; angina since 1975; CABG 1975; Enlarged prostate 1993; Arthritis (neck) - 1993; increased serum glucose -1989; hiatrial hernia - 1992; gall stones - 1992-93; circumcision - 1974 ECG; Sinus Rythymn borderline; 1st degree AV block; baseline artifact; systolic ejection murmur	Nitro disc Ecotrin Proscar Eldepryl	Day 211 CPK 537 - CPK fractionated showed 96% CK-MM; Investigator comment: NCS; No fall/injury reported.

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt.'s who had elevated CPK's at endpoint*).

Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	2127 Olanow	73/F/W	-13 22 50 103 163 219 227	236 171 166 178 172 143 555	Arthritis shoulder & hip - 1983; hyper-tension - 1989; anxiety - 1973; Surgeries: Hernia - 1983; rhinoplasty - 1968; plastic surgery ears - 1958 ECG - marked sinus arrythmia - premature supraventricular complexes - occasional PAC- freq. dropped beats	Ibuprofen Eldepryl Zestril Tranxene	Day 227 CPK 555; CPK fractionated; showed 100% CK-MM; Investigator comment: "minor injury?" No other information available.

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt.'s who had elevated CPK's at endpoint*).

Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0001	2309 Richter	62/F/W	-14 22 55 110 172 242 249	211 311 263 263 320 398 688	Angioplasty - 1988; histoplasmosis - 1947; appendectomy; hiatial hernia; frequency urination; enlarged prostate - 1978; mild depression; Hyper lipidemia, hypertension - 1993; anxiety - 1991; ECG NSR; possible L. atrial enlargement; ventricular hypertrophy; ST-T Wave Abnormality; consider lateral Ischemia	Cardizen CD Hytrin Valium Buspar Benadryl Tagament Prozac Xanax Ativan	Day 249 CPK 688; CPK fractionated showed 100% of CK-MM; Investigator comment: "muscle spasm ongoing". Minor fall - Day 249.

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt.'s who had elevated CPK's at endpoint*).							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0004	182 Kurlan	60/M/W	-7 9	56 1109	Borderline hypertension - 1992; Arthritis; anxiety x 3 months; mild depression; hyperflexia in legs L>R; ECG NSR movement artifact	Verapamil Tylenol Corimdin Nitro PRN Lopressor	On Day 7 patient was involved in a MVA; following syncope. While at clinic had ECG findings of ST-T wave elevations for which he was sent to ER. The diagnosis was myocardial infarction of anterior wall. Elevated CPK was not fractionated.
0004	137 Trosch	63/M/W	-9 43 71	310 638 971	COPD - 1990; PVC - 1990; Hypertension - 1992; Gout - 1992; Osteoarthritis - 1992; Asthma - childhood; ECG-NSR but possible left atrial enlargement & non-specific T-Wave Abnormality	Selegiline L-deprenyl Vasotec dilantin cyanoco-balamin naproxen terazosin bumetanide	Day 9 - Hypertonia; Day 28 onset of bilateral pedal edema (removed from open-label study due to ongoing symptoms); Day 43 & 71 CPK 638 & 971 CPKs not fractionated. Investigator comment: NCS.

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt.'s who had elevated CPK's at endpoint*).							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0010	1383 Eidelman	63/F/W	-14 24 46	67 47 1123	CABG (1990); AAA repair; Duodenal ulcer (1994); Fx - R shoulder (1992); knee replacement (1993); Obese; slightly hypertensive; ECG: Sinus tachycardia; L anterior fascicular block	Permax Parlodel Lasix Eldepryl K-Dor	Pt. fell several days prior to Day 46; CPK was not fractionated; pt. dropped from the study on Day 46 due to adverse event (visual hallucination)
0010	1021 Paulson	64/M/W	-12 23 92 148	72 73 63 790	Dementia (1987); Hallucination (1990) Leg cramps (1989) Thrombosed hemorroids ECG: NSR	Sinemet CR Symmetrel Florinef (started on Day 90)	Around Day 148 - the ECG showed "old inferoposterior infarction". According to investigator, the patient had silent infarct & family doctor notified. Pt. died unexpectedly in his sleep.

*Endpoint = end of study or dropout.

PRAMIPEXOLE Protocol: M/2730 Laboratory Test: CPK (Pt.'s who had elevated CPK's at endpoint*).							
Study #	Patient # Investigator	Age/Sex /Race	Day of Study	CPK Value U/L	Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
0010	1258 Tetrud	60/F/W	Baseline 20 51 107 163 191 212	Not done 225 235 156 218 680 828	Hypertension (1982) Hypothyroid (46 years) Arthritis (1982) Dystonia (foot, 1986) Depression (1993) ECG: NSR Chest X-ray: Mild scarring & atelectasis (Both bases - not clinically significant.)	Parlodel Triam/Hcz Synthroid Ecotrin Sinemet Flexeril (for dystonia)	Pt. had complained of increased shakiness, stiffness, tremor & worsening dystonia in spite of Flexeril; the dystonia was moderate to severe at times; CPK fractionated on Day 191 & 212. Showed 100% CK-MM

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*Endpoint = end of study or dropout.

Table 2 Placebo: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0001	*2218 Watts	58/F/W			-12 24 51 113 124 170 229 235	23 30 20 200 39 31 22 15	-12 24 51 113 124 170 229 235	23 24 21 464 160 28 28 27	borderline hypertension, bilateral ankle edema, gallstone, kidney stone, L. pyelolithotomy, R. knee pain, insomnia, dry mouth, voice hoarseness, H/As, urinary hesitation urgency, EKG - NSR with sinus arrhythmia - R. ventricular conduction delay - old findings, asymptomatic - sinus bradycardia	l-deprenyl, Rolaid, nizoral, ibuprofen, bufferin, Maalox	bilirubin wnl thru out study, SGPT & GGT increased at visit 13, inv. comment "clinically significant - was mildly symptomatic x 1 day with midline abd. pain, ? gallstone passed - recheck lab next wk, has had history of gallstones in past". GGT increased at visit 14 - inv. comment "NCS - prob. gallstone effect again"
0001	2391 Farmer	64/F/W					-7 23 51 107 163 219 226	183 164 145 113 97 86 104	old knee inj, L. traumatic pinoveal nerve (same as muscular), mild depression - occ. bouts, back surgery - disc, PX: L. foot drop, CXR - mild atherosclerotic CV changes, degenerative mid-thoracic spine changes, hilar promenence is considered to be due to pulmonary vessels	Sinemet, sulfamethoxazde, doxycycline, Hytrin, urispas, Motrin	bilirubin wnl thru out study, GGT increased at screen - inv. comment "NCS - other LFT is OK - will f/u during trial" prostatitis at visit 10

*Patients with ≥ 2 increased LFT abnormalities.

(Continued)

Table 2 Placebo: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0004	139 Trosch	56/M/W					-9 43 71	32 29 203	bladder infections, osteoarthritis/hands, muscular H/A, transient vocal cord paralysis, abd. umbilical hernia, occasional insomnia, depression, chemical pneumonia due to epoxy paint,1970 PX: umbilical hernia, high frequency hearing loss	l-deprenyl, Mylanta, fluoxetine, ibuprophen, diphendydramine, pseudoephidrine, excedrin x 2 days for H/A (day 42)	bilirubin wnl thru out study, GTT elevated day 71 - (203), inv. NCS
0010	1242 Karp	72/M/W					5 37 59 115 173 236	12 174 9 19 16 16	post nasal drip (hayfever), appendectomy, CXR - mild COPD	Symmetrel, Sinemet, ASA, chlortrimeton	bilirubin wnl thru out study, GGT increased at screen - labs repeated at visit 1, GGT increased - inv. comment "probably 2° to sinemet high-dose, visit 2 - hematuria - ref. to urologist & primary care phy., cystoscopy & IVP - mass R. kidney (no f/u req)

(Continued)

Table 2 Placebo: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0010	1204 Guttman	62/M/W			-14 23 49 94 141 206 212	98 91 82 93 117 158 117			atrial fibrillation - intermittent, congestive heart failure, seasonal asthma, hayfever, cholecystectomy, inguinal hernia repair, abn. liver function tests, diabetic, back pain, prostate surgery, bladder volume small - surgical expansion, hydronephrosis - partial; PX: R. arm mole (no change at end of study), EKG non-specific ST-T, changes possible old inferior infarct - incomplete R. bundle branch block	symmetrel, flexeril, glyburide, lanoxin, lasix, asprocream, instantine, prolopa, psyllium, nitropatch	bilirubin wnl thru out study, SGOT, SGPT increased - inv. states "chronic elevation flucuating abnormaly in past" - NCS, EKG changed from baseline at visit 19 - possible ischemia noted, f/u with FMD next day - on O_2 (1 liter) at noc for dyspnea, study drug D/C until cardiac evaluation is completed visit 19

(Continued)

Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0001	2392 Farmer	77/F/W					-9 22 50 79 89	75 60 58 135 102	hypertension, cholecystectomy, menopause, inguinal herniorrhaphy, multi infarct dementia with short term memory loss, cataract surgery, Px - mild thyroid enlargement, no mass, +1 ankle edema, occ. ecchymotic areas, EKG - marked sinus arrhythmia with sinus bradycardia, occ. supraventricular complexes	Trental, Norvasc, Kerlone, Darvocet	NCS, bilirubin wnl thru out study, GGT increased - NCS/inv.
0001	2024 Siemers	59/F/W					-14 22 43 92 148 204 211	267 482 180 221 342 221 331	peptic ulcer disease - melena approx. twice/year, cholecystectomy, intermittant H/A, mild L. ulnar neuropathy, bilateral foot pain/planter callouses, CXR abn. - calcified granuloma RUL,	l-deprenyl, Tagamet, Tylenol, v-cillin, Baclofen, mylanta, ASA - (Baby), gaviscon, Valium, Ex-lax, inderal, benadryl, Clariton	bilirubin wnl thru out study, SGPT & GGT increased at screen - inv. comment "prior common bile duct stint following transection during cholecystectomy, clinically aymptomatic for 20+ years NCS", onset of hypertension at visit 17

Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments-Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0001	2099 Siemers	67/F/W					-14 22 29 85 139 197 204	217 207 208 233 266 157 176	hypertension, CAD, allergy - voltarin, hayfever, colitis, bowel obstruction - surgery, diabetes, hypothyroidism, fibromyalgia, bursitis both shoulders, anxiety, idiopathic thrombocytopenic purpura, cataracts - bilateral, gastroesophageal reflex, CXR - abn. - area of atelectasis bi-apical pleural thickening, inv./NCS, EKG - L. atrial abn. NSR, PX: +1 pedal edema	l-deprenyl, premarin, Verelan, Provera, Xanax, Beconase AQ, Synthroid, Darvocet, Artane, Mylanta, titralac acid, carafate	bilirubin wnl thru out study, GGT increased - "Estrogen replacement" NCS per inv.
0004	182 Kurlan	60/M/W	-7 9	19 173					borderline hypertension, ragweed allergy, arthritis, anxiety x 3 months, mild depression, PX: hyper-reflexia in legs L>R, EKG - Abn Q waves V1 - V6 st. elevation V1 - V6, extensive acute anterior wall injury/MI	acetomenophen, Verapamil	bilirubin elevated day 70 but remained within predefined limits - pt. was having myocardial infarction - increased CPK at the time of lab draws day 70, pt. terminated from study week 10 (day 70)

(Continued)

Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0004	177 Hurtig	50/F/B					-16 53 76	414 474 480	hypertension, diabetes, sciatica - left, hepatitis (comment: GGT levels as high as 660 per FMD)	l-deprenyl, ibuprophen, insulin	bilirubin values normal thru out study, GGT values elevated thru out study - investigator indicates not significant due to history of hepatitis, episodic headaches during study-relieved with Motrin
0004	133 Trosch	67/M/W					-14 43 71	102 70 153	systolic murmur, episodic pulmonary inf, allergy - pcn, Ca Prostate - "93"/ Surgery 93, Fx R. wrist - 47; arthritis R & L shoulders, melanoma & surgery L. shoulder - 1991, head trauma - 1957, Fx L. ankle - 89, T&A, hemorrhoids & surgery, cataract & surgery - 1990, facial/plastic surgery, EKG - bradycardia - L. Axis deviation with occ PVC.	l-deprenyl, Tavist-D, clindamycin (prophylatic finger infection)	bilirubin wnl thru out study, GGTincreased - NCS by inv., URI - day 70

(Continued)

Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments-Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0010	*+1171 Eidelman	67/F/W	-6 23 51 94 148 204 209	14 14 207 17 16 22 14	-6 23 51 94 148 204 209	9 17 140 16 12 15 9	-6 23 51 94 148 204 209	43 38 207 40 35 34 30	cardiac cath - 50% blockage of L. decending artery, hypertension, PVC's (normal EKG), allergy - pcn, sulfa, hiatal hernia with esophageal reflux, cholecystectomy, hypothyroid, hypercholestendemia, c-section, ruptured ectopic preg, arthritis, sciatica, stapedectomy L. ear, deaf L., anxiety	Symmetrel, Synthroid, Maalox, Bentyl, Cogentin, Zantac, Ascriptin, eldepryl, Xanax, Sinemet, Cardizen, Senokot, tetracycline	bilirubin wnl thru out study, Dx of common bile stenosis by internist at visit 14, increased LFTs - inv. "referred to internist for flu", numbness across upper lip visit 10, carotid & transcranial doppler were ordered

*Patients with ≥ 2 increased LFT abnormalities.
+Patients with elevated LFT but returned to normal at endpoint.

(Continued)

Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0010	+1061 Golbe	74/F/W			-21 29 85 141 199 206	14 165 23 15 17 12			hypertension, hysterectomy, R. ankle pain, depression, insomnia, cataract removed - OD, Px - LUE numbness, loud S_4 RSB, EKG: NSR L. Axis deviation - possible anterior infarct age undetermined,non-specific T wave abnormality, non-specific ST abnormality anterior leads, CXR - small nodule L. upper lung field, no change from old films	Diazepam, trazodone, Ambien, temazepam, chlorthalidone, Sinemet, Tylenol	SGOT, SGPT, GGT increased - inv. comment "will watch - chronic & recurrent", bilirubin wnl thru out study
0010	+1092 Factor	49/M/W	-7 22 29	28 175 39					valve disease (aortic) replacement, hypertension, asthma, peptic ulcer, ruptured appendix - bowel resection, osteoarthritis, depression, herniorrhaphy, vein stripping/varicose veins, EKG - sinus tachycardia, CXR cardiomegaly - NCS	Klonopin, Motrin, Sinemet, Baclofen, Colace, Benadryl, Prozac, Ventolin spray, Permax, chloralhydrate	visit 5 increased SGOT inv. comment "Dx with rhabdomyolysis", hospitalized visit 9 due to increased CK mm, bilirubin wnl thru out study

+Patients with elevated LFT but returned to normal at endpoint.

(Continued)

Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments-Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0010	1021 Paulson	64/M/W	-12 23 36 92 148	23 26 37 29 176					shingles, dementia, hallucinations, old thrombosed hemorrhoid L. lateral quadrant, leg cramps, light headed, PX: dementia & hallucinations, CXR - plaque-like disease probably related to asbestos, EKG - sinus arrthymia & junctional ST depression old, inferoposterior infarction	Symmetrel, Florinef, Sinemet CR, thiamine, Zofran	bilirubin wnl thru out study, SGOT increased visit 16, inv. comment "He had, apparently, a heart attack". Pt. was asymptomatic - died unexpectedly at night.
0010	1034 Friedman	72/F/W					-7 24 57 108 162 218 225	124 106 104 109 106 111 137	hypertension, congestive heart failure, allergy to some medications, gallbladder out, low back strain, clinical myelopathy, depression, R. mastectomy, CA colon - resection, insomnia, hypotonic bladder, Px - +2 pedal edema, EKG NSR - possible anteroseptal infarct non-specific, ST-T wave abnormalities	lanoxin, Sinemet CR, Pamelor, Benadryl, Restoril, Valisone Cream, Tylenol, quinine, Lasix	GGT increased - NCS, bilirubin wnl thru out study, mod to severe bilateral leg pain visit 6 to end of study

(Continued)

Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0010	*1118 Jankovic	45/M/W			-7 24 78 136 194 204	101 96 73 122 216 225	-7 24 78 136 194 204	202 194 160 219 143 158	possible history of murmur, eczema, lumbar laminectomy, post traumatic stress inj, EKG L. axis deviation, early precardial R/S transition, sinus tachycardia, Px: eczema - face	e-ldepryl, Sinemet, amitriptyline, tums, Voltarin, Betametasone, Advil	bilirubin wnl thru out study, inv. made no comments re. increased LFTs
0010	1133 Montgomery	65/F/W					-7 22 50 73	113 109 102 130	Pt. has had increased LFTs for many years, post-menopausal, R. mastectomy	Sinemet, Gyne Lotrimin Vaginal Cream	GGT increased - inv. "NCS - known for sometime", bilirubin wnl thru out study, pt. withdrawn from study due to paranoia visit 19

*Patients with ≥ 2 increased LFT abnormalities.

(Continued)

Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments-Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0010	*1226 Richter	67/M/W			-7 22 50	9 304 206	-7 29 50	27 898 1552	intermittent hypotensive episodes, constipation, kidney stones x 3 - surgery x 3 ultrasound x 2, impotence, skin cancers - removal, EKG - NSR with occ. premature supra-ventricular complexes, L. anterior fasicular block, CXR - small area discord atelectasis at L. base otherwise essentially normal chest	e-ldepryl, Donnatal, Sinemet, lortab	abn. hepatic function at visit 5 - hepatitis eval. I done for increased LFTs, pt. positive for A, AB, bilirubin remained wnl thru out study & pt. remained asymptomatic, study meds stopped due to abn hepatic function & pt. allowed into open label when LFT ret. to normal

*Patients with ≥ 2 increased LFT abnormalities.

(Continued)

Table 1 Pramipexole: Patients with Elevated LFTs (Outside Pre-defined Limits)

Adequate & Well-Controlled Studies

Protocol: M/2730

Study #	Patient # Investigator	Age/ Sex/ Race	SGOT U/L		SGPT U/L		GGT U/L		Relevant Medical History & Physical Findings	Concomitant Medication	Investigator Comments- Relevant Info
			Day of Study	Value	Day of Study	Value	Day of Study	Value			
0010	1193 Stoessl	68/F/W					-14 23 52 105 161 217 224	36 22 20 31 54 17 167	hypertension, allergy - sulfa, appendectomy, cholecystectomy, Fx R. femur - internal fixation, arthritis, occasional nocturnal visual hallucinations, no frank psychosis, levodopa related, macular degeneration, sciatrica, PX: GRII/VI murmur, osteoarthritic knees, CXR - cardiomegaly - questionable density, lingular lobe on the left - etiology unk, EKG NSR nondiagnostic inferior ST, depression - incomplete L. BBB, sinus tachycardia L. axis deviation, echo cardigram scheduled due to one episode of chest pain	Domperidone, Dulcolax, surgam, amitriptyline, calcium carbonate, Sinemet, Tylenol #2, fluviral	bilirubin wnl thru out study, increased GGT - inv. comment "repeated and judged not to be clinically significant"

(Continued)

FEB 27 1997

Review and Evaluation of Clinical Data

Safety Review

Application Information

NDA 20-667

Pharmacia & Upjohn

NDA Safety Update Submission Date: January 10, 1997

Drug Name

Generic: Pramipexole

Proposed Trade Name: Mirapex™

Drug Characteristics

Pharmacological Category: Dopamine agonist

Proposed Indications: 1) Primary symptomatic treatment of Parkinson's disease.
2) Adjunctive treatment of Parkinson's disease.

Dosage Forms: Oral tablets in 0.125 mg, 0.25 mg, 1.0 mg, 1.25 mg, and 1.5 mg

Proposed Use:

Pramipexole should be given T.I.D.. Dosages should be increased gradually from a starting dose of 0.375 mg/day and should not be increased any sooner than every 5-7 days. In most studies a 7 week dose escalation scheme was followed: 0.125 T.I.D., 0.25 T.I.D., 0.5 T.I.D., 0.75 T.I.D., 1.0 T.I.D., 1.25 T.I.D., and at the 7th week to the maximum dose of 1.5 T.I.D. Withdrawal should occur gradually over a 7-day period.

Safety Update Reviewer: John D. Balian, M.D.

Date of Review: February 27, 1997

1 Summary of Pramipexole Safety Update Review

The original ISS summarized the safety experience for 1408 patients with about 815 person-years (PYs) of pramipexole use, most of it (800 PYs) coming from the Parkinson's Disease (PD) trials. This safety update brings the total to 2146 patients with 1925 PYs of pramipexole exposure, most of it (1878 PYs) coming from the PD trials. This increased exposure does not change the findings, add new clinically significant adverse events (AEs), or new safety issues to the original review.

In the safety update, there is doubling of the number of deaths (15 new cases) in the pramipexole patients, but this is a reflection of more than doubling of the exposure, as noted above. The reports on serious AEs, dropouts, and common AEs were much of the same when compared to the original review. Since most of the new information comes from open-label uncontrolled trials, and most of the patients are not uniquely exposed, incidence rates are not presented here. There were no AEs clinically consistent or suggestive of hepatic failure or necrosis, urolithiasis, agranulocytosis, or aplastic anemia. No new cases of rhabdomyolysis were reported (there was one case in the original review).

In summary, pramipexole use is not associated with increased risk for deaths, serious AEs, or dropouts in PD patients. While there was a clear increase in CV effects (syncope and OSH) attributable to pramipexole in the phase 1 healthy volunteers, no significant differences from placebo were observed in the phase 2/3 trials.

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2 Background

Following the review of NDA 20-667 (submitted by Pharmacia & Upjohn on Dec 26, 1995), the agency informed the sponsor, with a letter dated Dec 23, 1996, that the application is approvable for the treatment of the signs and symptoms of idiopathic Parkinson's disease (PD), upon the submission and favorable review of a safety update. The present submisssion is the safety update report on pramipexole using 2/29/96 as the cutoff date.

2.1 Overview of the Safety Update

The present submisssion is a compilation of data from the original submission and data analyzed since that submission. The sponsor's presentation of the information follows the same format as the original submission, unfortunately, there is no separation of the new data from the old, thus making a clear identification of the new data very cumbersome. As in the case of the original Integrated Safety Summary (ISS), the sponsor provides pooled descriptions and analyses of the treatment emergent adverse events (AEs), but upon special request, a supplement with separate tables of early-treatment (ET) and advanced-treatment (AT) PD patients was also submitted.

3 Methods of Safety Update Review

This review will follow the format used in reviewing the original submisssion: stratification of patients into ET and AT populations with a separate review and analysis of the RCTs in the ET and AT patient populations (3 studies from the ET trials and 5 from the AT trials), and wherever pertinent, mention the findings from the other studies (open-label PD, schizophrenia, and depression).

The majority of the new safety data comes from the uncontrolled ongoing PD trials and newly completed trials in schizophrenia and depression. Since this update does not include any further completed RCTs in ET patients, the comparative information on the ET patients presented in the NDA review has not changed. There is one new completed RCT in the AT patient population and this review will update all pertinent tables in this patient population to reflect the addition of the newly completed RCT.

It is not practical to discuss incidence rates for the overall database, since most of the new information comes from open-label, uncontrolled trials, and most of the patients are not uniquely exposed (they were counted in the original NDA review, and they simply have continued their participation in the uncontrolled trials). For this reason, denominators are left out of most tables to avoid confusion.

3.1 Review of Safety Issues Identified in The Sponsor's Proposed Labeling

The sponsor's most recent updated proposed label, 1/27/97, is a very close approximation of

the division's revised version forwarded to the sponsor with the approvable letter. The sponsor has completed the missing sections requested by the division and has responded to outstanding issues. Besides few language changes (for clarity), the only glaring difference between the division's version and the sponsor's, is the sponsor's deletion of the item pertaining to rhabdomyolysis in the precautions section. The sponsor's rationale is that it brings undue attention to a case that the sponsor considers a "unique circumstance". Of minor consequence, the sponsor has not incorporated the data from the newly completed RCT in AT population in the presentation of the 1% AE table in the adverse events section.

4 Review of Findings

4.1 Description of the Pramipexole Development Program

The original ISS described pramipexole treatment emergent AEs based upon observations from 19 Clinical Pharmacology studies, 16 completed phase II-III clinical trials, and 15 ongoing trials.

Of the 19 clinical pharmacology studies involving 297 (260 PPX and 37 placebo) subjects, 17 were conducted in healthy volunteers, 1 (protocol 60) was conducted in volunteers with impaired renal function, and 1 (n=3) was conducted in APD patients.

Of the 16 completed phase II-III clinical trials (i) 9 (studies---#1, 4, 17, and 21 in ET, and studies---#10, 18, 19, 20, and 22 in AT) were PD studies involving 1253 (702 PPX and 551 placebo) patients; and (ii) 7 were completed studies in schizophrenia involving 322 (177 PPX, 50 comparator, and 95 placebo) patients. There were also 15 ongoing studies: (i) 10 ongoing PD studies (controlled and open label); (ii) 3 schizophrenia studies; and (iii) 2 depression studies.

This Safety Update Report provides additional safety data from (i) one newly completed study in PD (protocol 36); (ii) 2 studies in depression (protocols 37 and 43); (iii) 2 studies in schizophrenia (protocols 7 and 67); and (iv) safety data from the open-label ongoing studies. Data from the unfinished controlled studies are not available due to the blind. A tabulation of an updated patient accountability of the completed studies is detailed in table 4.1.1:

Table 4.1.1 Patient Accountability (All Completed Studies)				
	Number of Patients			
	Pramipexole	Placebo	Comparator	Total
Phase I (Clinical Pharmacology)	260	37	-	297
Phase II/III				
PD Total	794	633	-	1511
EPD	416	262	-	678
APD	366	371	84	821
Other*	12	-	-	12
Schizophrenia	201	95	50	346
Depression	231	69	-	300
Total	1226	797	134	2157

*Protocol 55, an Italian study was prematurely terminated (Jan. 96), because the investigator was not able to recruit enough patients.

The newly completed study in PD, protocol 36 is a randomized, double-blind, placebo-controlled study in AT involving 247 patients (80 PPX, 83 placebo, and 84 bomocriptine). This multi-center, Non-US study was similarly designed as the other AT RCTs, except for the addition of an active control arm. No major differences in the findings (exposure, demographics, deaths, serious AEs, dropouts, and other AEs) were noted between this protocol and the others, hence no separate tables of data will be presented here for this study alone, but new data tables will be presented that incorporate this study.

4.2 Description of the Population

The updated demographic information of the RCTs is not different from the demographics tables of the original review. There were no statistically significant differences between the pramipexole and placebo groups with respect to age, sex, or race. The demographic characteristics of the ET and AT population were generally representative of the expected demographics of PD patients.

4.3 Extent of Exposure

4.3.1 Extent of Exposure, Overall and Stratified by Duration of Use

The exposure in the original review was based on 1408 pramipexole patients for a total of 274.4 patient years. This safety update adds 738 pramipexole patients from newly completed and ongoing studies in all treatment groups. Table 4.6.1.1 displays the updated exposure in patient years:

Table 4.6.1.1. Number of Patients and Estimated Person-Years (PYs) in Patients with pramipexole Use up to 2 Years				
	Completed Trials		Completed + Ongoing Trials	
	N	PYs	N*	PYs
Phase I				
Healthy Volunteers+	250	--	276	--
PD Patients (0023)	3	--	3	--
Phase 2/3 (PD, Schizophrenia and Depression)				
All Patients@	1213	351.46	2146**	1924.67**
0-24 Months	1213	351.46	1924	1358.92
>6-24 Months	353	223.71	939	1196.63
>12-24 Months	2	2.84	671	986.54
All PD Patients#	782	305.72	1715	1878.94
0-24 Months	782	305.72	1493	1313.19
>6-24 Months	350	219.93	936	1192.85
>12-24 Months	0	--	669	983.70
ET Patients&	388	134.59	777	867.56
0-24 Months	388	134.59	702	699.28
>6-24 Months	137	84.66	493	662.31
>12-24 Months	0	--	401	588.26
AT Patients&&	340	161.73	884	1001.98
0-24 Months	340	161.73	737	604.50
>6-24 Months	213	135.27	443	530.54
>12-24 Months	0	--	268	395.45
Schizophrenia Patients!	200	17.77	200	17.77
0-24 Months	200	17.77	200	17.77
>6-24 Months	0	--	--	--
>12-24 Months	0	--	--	--
Depression Patients!!	231	27.96	231	27.96
0-24 Months	231	27.96	231	27.96
>6-24 Months	3	3.78	3	3.78
>12-24 Months	2	2.84	2	2.84

* Patients were counted only once

** Includes 147 AT PPX patients with continued use beyond 24 months (total of 105.48 additional PY) and 75 ET PPX patients with continued use beyond 24 months (total of 38.28 additional PY).

+ All completed Studies are 3, 25, 26, 27, 28, 29, 30, 31, 47, 51, 61, 62,63, 64, 65, 69, and 73; one ongoing study (0060)

@ All completed studies are: 1,4,7, 10, 15, 17, 18, 19, 20, 21, 22, 24, 33, 34, 36, 37, 43, 48, 49, and 67; all open-label ongoing studies are: 2, 6, 11, 13, 14, 16, and 52.
# All AT + All ET studies
& All completed ET studies are 1, 4, 17, and 21; all open-label ongoing ET studies are 2, 6, and 16.
&& All completed AT studies are 10, 18, 19, 20, 22, and 36; all open-label ongoing AT studies are 11, 13, 14, and 52.
! All completed schizophrenia studies are 7, 15, 24, 33, 34, 48, 49, and 67.
!! All completed depression studies are 37 and 43.

Overall (including the extension trials that are ongoing), a total of 2146 patients with 1924.67 PYs of pramipexole use are included in the exposure data, most of it (1878.94 PYs) coming from the PD trials.

4.4 Mortality in Phase 2/3 Studies

4.4.1 Pramipexole Mortality Compared to Placebo

Fifteen additional pramipexole patients and one placebo patient died during study participation between the NDA (cut-off January 31, 1995) and this safety update report (cut-off February 2, 1997). Therefore, the total number of pramipexole patients who died is 29 (14 deaths observed in the original review), and all 29 came from PD patients. Table 4.8.1.1 shows the estimated mortality rates for pramipexole and placebo separately in ET and AT patients, and in Schizophrenia and depression patients:

Table 4.8.1.1. Rate of Mortality Observed

	Deaths	N	PYs	Rate / 100 PYs	RR** 95% CIs
PD Completed RCTs					
ET Patients (studies 1, 4, 21)					
Pramipexole	1	388	134.60	0.74	0.79 (0.05, 12.5)
Placebo	1	235	106.5	0.90	
AT Patients (studies 10, 19, 20, 22, 36)					
Pramipexole	4	340	161.7	2.5	1.9 (0.36, 10.3)
Placebo	2	347	154.9	1.3	
Schizophrenia (studies 7, 15, 24, 33, 34, 48, 49, 67)					
Pramipexole	0	200	17.8	0	
Placebo	0	95	9.2	0	
Depression (studies 37, 44)					
Pramipexole	0	231	28.0	0.0	
Placebo	0	69	9.5	0.0	
Completed and Open-Label Ongoing Trials					
ET Patients (studies 1, 4, 21, 2, 6, 16)					
Pramipexole	8	777	867.6	0.9	not applicable#
Placebo	1	235	106.5	0.9	
AT Patients (studies 10, 19, 20, 22, 36, 11, 13, 14, 52)					
Pramipexole	18	884	1002.0	1.8	not applicable#
Placebo	2	347	154.9	1.3	

** Rate Ratio (Relative Risk) of Pramipexole is defined as: (Death/100 PYs of PPX)/ (Death/100 PYs of Placebo)
# Because all patients in the ongoing part received pramipexole.

Four patients in study 0012 died but are not included in this table because the randomization codes, # of patients, and drug exposure data were not available. Among these patients, three (#23, 599 and 424) received PPX, one (#118) received placebo.

The increase in absolute numbers of deaths (29 from 14) is simply a reflection of greatly increased exposure. The pramipexole mortality rate per 100 PYs was 3.5 fold greater in AT compared to ET pramipexole exposed patients, but equivalent in the placebo patients.

There were no deaths reported in the schizophrenia and depression (completed or ongoing) studies. There were no deaths reported in the 19 Phase 1 studies.

4.4.2 Description of Deaths Observed During Pramipexole's Use

The table below presents a summary of deaths reported in the safety update:

Table 4.4.2.1 Patients deaths which occurred between 1/31/95 and 2/29/96

Study	Patient	Days on study	Cause of death
Pramipexole			
2	2128	406	Myocardial Infarction
	2333	359	Cardiac arrest
	2334	425	Suicide (secobarbital O.D.)
11	1181	396	Pulmonary Carcinoma
	1227	237	Sudden Death
	1296	152	Cardiac failure
	1170	481	Myocardial Infarction
12	599	196	Sudden Death
13	500	62	? (lost to follw-up)
	89	87	Arrythmia/cardiogenic shock
	478	105	pneumonia
16	16128	185	accidental injury (gunshot)
36	229	238	Multi-system failure
52	423	241	Prostate carcinoma
	642	254	Myocardial Infarction
Placebo			
36	430	263	Cerebral Infarct/UTI

A complete review of the death cases did not reveal any apparent association to the use of PPX.

4.5 All-Cause and AE Dropout Risks

A tabulation of the number of patients that dropped out due to serious AEs reported in the safety update is detailed in table 4.5.2:

Table 4.5.2 Number of patients that dropped out due to serious AEs	
	Number of Patients
	Pramipexole
PD Total	32
EPD	13
APD	19
Schizophrenia	1
Depression	2
Total	35

4.5.1 ET Studies

As mentioned earlier, no new ET RCTs were completed and hence there are no changes to the original review.

4.5.2 AT Studies

Table 4.5.2.1 shows the reasons for study dropout in AT patients (completed double-blind, placebo-controlled PD trials including the newly completed study #36) by treatment groups.

Table 4.5.2.1 Premature discontinuations: AT Trials (10, 19, 20, 22, & 36)						
Reason For Discontinuation	Number (%) of Patients					
	Pramipexole (N=340)		Placebo (N=347)		Bromocriptine (N=84)	
	N	%	N	%	N	%
Adverse Events	46	13.5	77	22.2	17	20.2
Lack of efficacy	3	0.9	5	1.4	1	1.2
Protocol Violation	2	0.6	1	0.3	0	0.0
Lost to Follow-up	0	0	2	0.6	0	0.0
Other	13	3.8	9	2.6	1	1.2
Total Patients	64	18.8	94	27.1	19	22.6

This reveals no overall changes from the original review.

4.6 Clinical Characteristics of AEs that were Associated with Dropout

4.6.1 Most Common AEs associated with Dropout in ET Patients

No new ET RCTs were completed and hence there are no changes to the original review.

4.6.2 Most Common AEs associated with Dropout in AT Patients

Table 4.6.2.1 is an updated list of AEs, irrespective of severity, that were associated with dropout in more than 1% of AT patients:

Table 4.6.2.1
AT Patients
Adverse Events with PPX Which Caused Study Termination
Occurring with Frequency >= 1%

Adverse Event	Number (%) of Patients		
	Pramipexole N(%)	Placebo N(%)	Bromocriptine N(%)
Total Patients (N)	340	347	84
CONFUS	8 (2.35)	7 (2.02)	1 (1.2)
DIZZINESS	4 (1.2)	5 (1.4)	0
DYSKINESIA	6 (1.8)	4 (1.2)	0
EXTRAPYR SYND	7 (2.1)	34 (9.8)	7 (8.3)
HALLUCIN	8 (2.4)	3 (0.86)	0
HYPOTENS POST	7 (2.1)	4 (1.2)	0

Studies included M/2730/0010, M/2730/0019, M/2730/0020, M/2730/0022, and M/2730/0036

Only hallucinations were associated with dropout in more than 1% of pramipexole patients and occurred 2 times more frequently than with placebo.

4.7 Serious AEs Associated with Pramipexole

A tabulation of the number of serious AEs reported in the safety update is detailed in table 4.7.1:

Table 4.7.1 Frequency of serious AEs	
	Number of Serious AEs
	Pramipexole
PD Total	288
EPD	121
APD	167
Schizophrenia	2
Depression	5
Total	583

A tabulation of the number of patients with serious AEs reported in the safety update is detailed in table 4.7.2:

Table 4.7.2 Number of patients with serious AEs	
	Number of Patients with Serious AEs
	Pramipexole
PD Total	171
EPD	72
APD	99
Schizophrenia	2
Depression	3
Total	176

As most serious AEs reported come from open-label trials, there is no basis of comparison. A complete review of all serious AEs leading to death or discontinuation did not reveal any apparent association to the use of PPX. There were no serious AEs consistent with liver failure or necrosis, agranulocytosis, aplastic anemia, hemolytic anemia, seizures, or new cases of rhabdomyolysis. There were 2 cases of syncope in the depression trials and 1 case from the PD trials.

4.8 AE Risks Associated with Pramipexole Use Irrespective of Severity

4.8.1 Overall

4.8.1.1 ET Patients

No new ET RCTs were completed, and hence there are no changes to the original review.

4.8.1.2 AT Patients

Table 4.8.1.2.1 lists the AEs that were reported at ≥1% in the PPX arm and twice the rate of placebo in the safety update:

Table 4.8.1.2.1
AT Patients
Adverse Events Occurring Twice as Frequently as Placebo

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	340	348
Peripheral Edema	7 (2.1)	2 (0.6)
Weight Decrease	4 (1.2)	2 (0.6)
Arthritis	10(2.9)	3(0.9)
Twitching	6 (1.8)	1(0.3)
Bursitis	5 (1.5)	2 (0.6)
Hallucination	55 (16.2)	21(6.0)

Paranoid Reaction	6 (1.8)	1 (0.3)
Hypesthesia	8(2.4)	5(1.4)
Delusions	4 (1.2)	2 (0.6)
Rhinitis	9 (2.7)	3 (0.9)
Pruritis	4 (1.2)	2(0.6)
Accomodation Abnormality	12 (3.5)	6(1.7)
Vision Abnormality	10 (2.9)	3 (0.9)

Studies included M/2730/0010, M/2730/0019, M/2730/0020, M/2730/0022, and M/2730/0036

Only hallucinations (16.2%) were reported in at least 5% of pramipexole patients and were twice as frequent as with placebo.

4.9 Changes in Laboratory Parameters Associated with Pramipexole Use

There are no new significant clinical findings or safety concerns in the 8 month safety update.

4.10 Changes in Vital Signs Associated with Pramipexole Use

There are no new significant clinical findings or safety concerns in the 8 month safety update.

4.11 Changes in ECG Parameters Associated with Pramipexole Use

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5 Summary of the Safety Experience in the Pramipexole Development Program

5.1 General Comments

Overall, there are no new significant clinical findings or safety concerns in the 8 month safety update.

5.2 Cardiovascular System

Aside from the 3 new cases of syncope (2 from the depression trials and 1 from the PD trials), there are no new significant clinical findings or safety concerns in the 8 month safety update.

5.3 Central Nervous System

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.4 Dermatological

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.5 Gastrointestinal

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.6 Genitourinary/Renal

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.7 Hematologic

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.8 Metabolic Endocrine

There are no new significant clinical findings or safety concerns in the 8 month safety update. No new cases of rhabdomyolysis are reported.

5.9 Musculoskeletal

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.10 Respiratory

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.11 Special Senses

There are no new significant clinical findings or safety concerns in the 8 month safety update.

6 Conclusion

Review of the data in the safety update indicates that pramipexole is relatively safe. There were no occurrences of adverse events that were not reported previously and no general increase in incidence rates from previously reported rates.

In conclusion, when the dose of pramipexole is slowly titrated and individualized to obtain optimum response, pramipexole is a safe treatment for patients with Parkinson's disease.

7 Labeling Recommendations

Adverse Events section:

(1) The 1% table should be redone to reflect newly available data from the RCT of the AT patient population.

Precautions section:

(1) The sponsor should note the occurrence of rhabdomyolysis even if the cicumstances were unique.

John D. Balian, M.D.

2/27/97
Date

Clinical Reviewers, Safety Group
Div. of Neuropharmacologic Drug Products

Orig. NDA 20-667
HFD-120 Div. File
HFD-120 GBurkhart\RKatz\TWheelous\JFeeney\JSherry\JKnudsen\JBalian

Safety Team Leader's Review of Clinical Data

NDA:	**NDA 20-667** **Response to Approvable Letter**
Date of Submission:	**January 07, 1997**
Sponsor:	**Pharmacia & Upjohn**
Drug:	**Pramipexole 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg, 1.25 mg and 1.5 mg Tablets**
Route of Administration:	**Oral Titration**
Proposed Indication:	**Symptomatic Treatment of Parkinson's Disease**
Material Reviewed:	**January 07 Submission that Responding to the FDA approvable letter; January 10 Amendment 41; January 13 Amendment 42, and Medical Officer's Review of the Safety Update in amendments 41 and 42.**
Date of Review:	**5/13/97**

Summary

Pramipexole's sponsor responded to the approvable letter with a safety update, draft labeling and narrative responses to several queries raised by the agency in the letter and proposed labeling. There were no new safety issues raised by the safety update, and its findings were consistent with those in the NDA safety review. New analyzes conducted to evaluate the effects of dose and duration of use on AE events rates were not helpful because of limited number of events in most dose categories, and confounding of dose with duration of use.

The sponsor changed the pregnancy category from "C" to "B" arguing that the findings from animal reproductive studies were sufficient to conclude that pramipexole had no teratogenic risk in rats or rabbits. The sponsor further argued that its effects on implantation and embryo survival were similar to those with bromocriptine which is labeled pregnancy category "B". The review team, however, considers the reproductive study in rats to have failed because the embryotoxicity markedly limited the number of liters in the high dose group. Thus, until the study is repeated a pregnancy category of "C" is justified as per 201.57.

The sponsor also proposed different language in labeling to describe the retinal toxicity that was observed in albino rats. In my opinion, the effect of that language is to accentuate the uncertainty of the finding's relevance to human users of pramipexole. The FDA proposed language tells the reader not to discount the finding because the potential mechanism of the effect generalizes to humans. Such caution seems justified since there is little data addressing the long-term effects of pramipexole use in humans.

Finally, the precaution that the FDA recommended to describe the one case of rhabdomyolysis was removed from labeling by the sponsor. Since pramipexole's use was associated with slight increase in the mean CPK, the precaution seems justified.

APPEARS THIS WAY
ON ORIGINAL

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ON ORIGINAL

Background

The FDA issued an approvable letter for pramipexole on December 23, 1996. In that letter, the agency requested a safety update and suggested the conduct of in vitro studies to evaluate potential drug interactions with pramipexole. Also included with the letter was proposed labeling that made several requests of the sponsor, most notably a request to conduct dose-response and time since first exposure analyzes of the safety data for events that were numerically more frequent than with pramipexole and occurring in more than 1% of patients. On January 7, the sponsor responded by providing a safety update, new labeling, additional analyzes and a discussion of the issues raised in the approvable letter.

Dr. Balian, who was the safety reviewer for the NDA, reviewed the safety update and concluded that the findings were consistent with those in the NDA and that there were no new issues to address. After reviewing the safety update, I concur with Dr. Balian.

Dr. Steele, who was the pharmacology reviewer for the NDA, has reviewed the sponsor's proposed changes to the clinical pharmacology, animal toxicology and pregnancy sections of labeling. His comments and recommendations are considered further below. Dr. Ibrahim reviewed the in vitro studies submitted to address the FDA request for in vitro data to address potential for drug interactions. It is her opinion that these data are sufficient to conclude that pramipexole is unlikely to affect important cytochrome P450 isoenzymes.

Based upon changes to the labeling that were proposed by the sponsor, there are still three issues to consider where there may be some disagreement between the FDA and the sponsor. First, the sponsor has proposed a pregnancy category of "B" while the FDA had concluded that a pregnancy category of "C" is justified based upon the available data. Second, there is some disagreement over the nature of the language to be used to describe the uncertain relevance to humans of the retinal toxicity that was observed in albino rats. Finally, the sponsor removed the precaution that described the one patient with rhabdomyolysis that had been added by the FDA. These issues are discussed further below along with the validity of the dose response and time since first exposure analyses conducted by the sponsor at the FDA's request.

Pregnancy Category

In rabbits, there were no adverse reproductive effects observed at 10 mg/kg/day which the sponsor states is 71 times the AUC in humans. In the animal reproductive studies in rats, three effects were associated with pramipexole exposure: (1) When pramipexole was administered throughout pregnancy at 2.5 mg/kg/day, implantation was impaired. (2) In the organogenesis rat study, significant embryonic loss occurred in the high dose group (1.5 mg/kg). (3) Postnatal growth and development was impaired at doses as low as 0.5 mg/kg/day.

While the effects on implantation, and postnatal growth and development were considered by Dr. Steele to be possibly related to pramipexole's effect on prolactin, which if true may limit the relevance of these findings to humans, the embryotoxicity prevented a complete evaluation of teratogenicity by markedly reducing the number of litters available for observation in the high dose group. While the sponsor states that the AUC resulting from the exposures in the two lower dose groups covered the expected human exposure, Dr. Steele considers the high dose group to be have been paramount to evaluating the teratogenic potential of pramipexole because several rare birth defects were observed in the two lower dose groups. Since the findings in the highest dose group were critical in interpreting the study, Dr. Steele considers this organogenesis study to have failed and, in fact, recommended repeating it.

The sponsor argues that the effects observed with pramipexole were the same as those with bromocriptine which is labeled "B". However, the bromocriptine labeling suggests that the number of litters available for review were sufficient in the high dose bromocriptine group. The labeling also describes the birth outcomes from prospective follow-up of maternal exposures which may or may not have contributed to the decision to label it "B".

Thus, it seems that without even considering the relevancy of the findings that may be attributable to prolactin, a consideration that may be complex because of potential difficulties in directly attributing any effects to decreases in prolactin, pramipexole should be labeled "C" at least until the sponsor conducts the appropriate studies.

Retinal Toxicity in Albino Rats

While there is some disagreement about whether the effects (loss of photoreceptor cells, degeneration of retinal pigment epithelium) should be referred to as "retinal degeneration" or "retinotoxicity", the sponsor prefers language that does not mention any link to humans. The FDA, however, used the following wording "The potential significance of this effect in humans has not been established, but cannot be disregarded since retinal disk shedding is a universal vertebrate mechanism." Since no human data has been collected on retinal changes with long-term treatment, the FDA wording seems more prudent since the potential mechanism of the effect may generalize to humans.

Rhabdomyolysis

In the sponsor's discussion about the one case of rhabdomyolysis observed with pramipexole, more history was provided, in that the event occurred after rigorous exercise. Rigorous exercise is generally accepted as being a risk factor for rhabdomyolysis. While I would tend to agree with the sponsor in that one case of any rare event is usually not a justification for a precaution, there is more to the signal in this case.

In Dr. Balian's original review of the NDA, there was a mean increase of about 20-30 u/L in CPK across several studies, with the difference from placebo having reached statistical significance in two studies. While the evidence of a slight increase in the mean seemed compelling, there was no increase in the percentage of patients who had increases that were of clinical concern. Thus, the slight increase in the mean CPK was, by itself, not considered to be clinically significant. Nevertheless, since there was one accepted case of rhabdomyolysis, a precaution seemed appropriate. In fact, if there had been increases of CPK that were clinically significant, a warning statement could be justified. Thus, a precaution seems consistent with the safety findings.

Effect of Dose and Time Since First Exposure on AE Rates

Based upon the FDA comments contained in the proposed labeling included with the approvable letter, the sponsor has conducted more specific analyses to evaluate dose response. These analyzes were used to clarify the role of dose and time on the risk associated with pramipexole use. However, the analyzes of dose, while confounded with time since the studies allowed titration to clinical endpoints, contained are too few events in dose groups to reach a conclusion about the effect of increasing dose. Thus, I would recommend not mentioning these issues in labeling.

Conclusion and Recommendation

Review of the pramipexole safety update and the sponsor's response to the approvable letter did not identify any new safety issues for consideration. The embryotoxicity observed in the rat reproductive studies justifies a pregnancy category "C". Because the potential mechanism for the retinal toxicity observed in albino rats generalizes to humans, language should clearly articulate this potential risk. A precaution describing the one case of rhabdomyolysis is justified given the slight increase in mean CPK observed in the clinical studies.

Greg Burkhart, M.D., M.S.
Safety Team Leader, Neuropharmacological Drug Products, HFD-120

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DETIRN

OCT 2 5 1996

Statistical Review and Evaluation

NDA: 20-667

OCT 24 1996

Applicant: The Upjohn Company

Name of Drug: Pramipexole Tablets

Documents Reviewed: Vols. 324-325, 344, 346, 355

Medical Officer: John Feeney, M.D., HFD-120

Background

The sponsor has submitted a total of five (5) controlled trials in support of Pramiprexole (PX) for the treatment of Parkinson's disease. This review is restricted to the 3 large trials designated 'adequate and well-controlled' by the sponsor. The sponsor has designated the other 2 as 'supportive'. **Trials 0001 and 0004** enrolled patients with early asymptomatic, idiopathic Parkinson's disease who were not receiving replacement levodopa therapy. **Trial 0010** used PX as an adjunct to levodopa replacement therapy in patients with less than optimal response to levodopa as characterized by the presence of motor fluctuations.

Trial 0001 used stratified randomization (current selegiline use or not) among 26 centers in the US. Three hundred thirty-five (335) patients were randomized to either placebo or the PX group which experienced a 7 week dose escalation period (7 doses up to 4.5 mg/day) followed by a 24 week maintenance period.

The primary efficacy endpoint was the sum of scores of Parts II (13 activities each rated in increasing severity from 0-4) and III (14 components of physical status each rated in increasing severity from 0-4) of the UPDRS (Unified Parkinson's Disease Rating Scale). Secondary endpoints included 1) Time to Failure (worsening of disease or unsatisfactory therapeutic effect - time until patient requires levodopa), 2) Modified Hoehn and Yahr Scale, and 3) individual components (Parts II and III) of the UPDRS. The sample size of 150/arm was derived using Part III of the UPDRS results from DATATOP. The result follows from designing 90% power to find a treatment arm difference of change from baseline between 1.8 and 3.6 using a standard deviation of 5.0.

The primary data set for analysis was to be all patients who had at least one dose and who had at least one post-baseline measurement. The subset of those who actually entered the maintenance period was added before the data was unblinded and was intended to confirm the robustness of the results using primary data set. The primary analytic technique stated in the protocol was two-way ANOVA with interaction of treatment and center always in the model.

Trial 0004 randomized 264 patients among 20 centers in the US and Canada. Patients were randomized to either placebo or one of 4 doses of PX: 1.5, 3.0, 4.5 or 6.0 mg/day. The dose escalation phase lasted 6 weeks followed by a 4 week maintenance period.

The primary efficacy endpoint was the sum of scores of Parts I-III of the UPDRS. The secondary endpoints were the individual components of the UPDRS and the Hoehn and Yahr scale. The sample size of 50/arm was derived using the sum of parts II and II from a previous study. From a dose-response point of view, there was 80% power to detect a slope of 1.25 or, from a change from baseline point of view, there was 82% power to detect a difference of 5.8 between the 4.5 mg/day and placebo groups.

As in **Trial 0001**, the primary data set for analysis was to be all patients who had at least one dose and who had at least one post-baseline measurement. The subset of those who actually entered the maintenance period was added before the data was unblinded. With regard to the primary analytic technique, the protocol states only: "In this dose-response study, the primary variables will be analyzed by regression methods."

Trial 0010 (not conducted under an IND) randomized 360 patients among 26 centers in the US (22) and Canada (4). Patients were randomized to either placebo or the PX group which experienced a 7 week dose escalation period (from .375 to 4.5 mg/day) followed by a 24 week maintenance period. Patients who dropped from the trial prior to completing at least one-half of the visits during the maintenance dose interval during the double-blind part of the trial were to be replaced unless the patient was dropped from the trial because of intolerable adverse events which included worsening of the underlying Parkinson's disease.

The primary efficacy endpoints were the following: 1) Part II of the UPDRS for both 'on' and 'off' periods and 2) Part II for 'on' periods, only. Secondary endpoints included 1) Part II 'on' and 'off' separately), 2) Modified Hoehn and Yahr Scale for 'on' and 'off' periods and a myriad of other analyses. As with **Trial 0001**, the protocol-specified sample size of 150/arm was derived using Part III of the UPDRS results from DATATOP.

The primary data set for analysis was to be all patients who had at least one dose and who had at least one post-baseline measurement. The primary analytic technique was two-way ANOVA with interaction of treatment and center always in the model. AUC was also conducted as a longitudinal analysis. The timed walking test (50 feet) was analyzed using change from baseline.

Note: **All figures and graphs were produced by the sponsor.**

Results

In general, all reported results are for the LOCF analysis at the last visit during the maintenance period. This review reports only the intent-to-treat (ITT) results since similar results are obtained using only patients who entered the maintenance period.

There was no evidence of treatment by center interaction in any trial.

Trial 0001

Two (2) patients did not have any post-baseline measurements. Thus the ITT data set consists of 333 patients.

Table 1 displays the baseline characteristics of all randomized patients. There were no important treatment imbalances.

Table 2 displays the numbers of patients completing each phase of the trial. Approximately 80% of the patients completed the maintenance period.

Tables 3, 4, and 5 display the changes from baseline and statistical results for Parts II, III, and by selegiline and anti-cholinergic status, respectively. Patients treated with PX clearly improved their symptoms relative to those on placebo. On average, the LOCF change from baseline of patients who discontinued from the PX arm (N=16) was better than that of dropouts from the placebo arm (N=24): -.94 on PX, 1.58 on PBO for Part II, and -.63 on PX, 5.04 on PBO for Part III.

Tables 6 and 7 display the changes from baseline for the separate components of Parts II and III, respectively.

The distribution of **Hoehn and Yahr scale scores** also reflected a treatment effect: improvement from baseline: 27% PX, 16.5% PBO, worsening from baseline: 16.7% PX, 23.5% PBO.

The **time to treatment failure** analysis using the logrank test (p=.0015) also indicates a treatment benefit: 5 patients failed in the PX group while 22 failed in the PBO group.

There was no indication of differential treatment effect by age, race or gender.

Trial 0004

Table 8 displays the treatment group baseline characteristics and **Table 9** displays the numbers of patients completing each phase of the trial. Approximately 90% of the patients completed the maintenance phase.

Table 10 displays the statistical results for the primary endpoint using the assigned dose as the treatment group: sum of all 3 parts of the UPDRS. **Each dose was statistically different from placebo using even a conservative multiple comparison rule such as a simple Bonferroni adjustment. The sponsor states that "there was no dose-response relationship for efficacy apparent across the range of pramipexole doses studied".**

With placebo in the analysis, a linear dose-response trend was detected with a p-value of .03 using the **assigned dose group** and .005 using the dose **actually received.**

When Parts II and III were analyzed separately, the overall test was statistically significant in favor of PX for part III but not for part II. See **Tables 11 and 12.**

Table 13 displays the results for the individual components of Parts II and III which showed the greatest average change from baseline.

Table 14 displays the distribution of patients who improved or worsened from baseline on the **Hoehn and Yahr Scale.** Approximately twice the number of patients on the 3 highest doses of PX improved from baseline compared to the number who improved on placebo.

Comment

The obvious question about this trial is why there was no statistical difference between drug and placebo for Part II of the UPDRS unlike the result in **Trial 0001.** The standard deviations are the same in both trials (3.0). Comparing **Table 3** to **Table 11** indicates that the average treatment difference was approximately 2.3 units in **Trial 0001** as opposed to 1.5 in **Trial 0004.** The average change from baseline on drug was 0.5 units less in the latter trial. The slightly smaller overall sample size in **Trial 0004** contributed to some extent.

Trial 0010

Table 15 displays the baseline information for the treatment groups.

Table 16 displays the number of patients who completed each stage of the study. Approximately 80% of the patients completed the trial, a completer being one who "completed at least half of the visits during the maintenance-dose interval (i.e., through Visit 15) or any patient who discontinued trial medication because of intolerable adverse events".

Figure 1 and **Table 17** display the results when averaging the 'on' and 'off' periods for Part II of the UPDRS using LOCF.

Figure 2 and **Table 18** display the results of Part III of the UPDRS using LOCF. The sponsor did not report the results for just the 'on' period as it stated it would in the report. However, the protocol makes no mention of restricting Part III to the 'on' period.

Figures 3 and 4 display the results over time for the two respective primary endpoints. The profiles are very similar to those using LOCF, indicating that there is little effect of dropouts on the LOCF analyses.

In summary, the LOCF analyses were statistically significant on both primary endpoints.

Secondary endpoints which reached nominal significance were Part II 'off' periods ($p<.001$), Part II 'on' periods($p=.004$), average percentage 'off' time calculated from patient diaries ($p<.001$, see **Table 19** and **Figure 5**), levodopa dosage ($p<.001$), Schwab-England Disability Scale ($p<.001$) for 'off' periods and $P=.01$ for 'on' periods, and Modified Hoehn and Yahr Scale ($p<.001$). The timed walking test was not statistically significant.

Subgroup analyses

The sponsor investigated demographic subgroups and the possibility of an interaction between selegiline (l-deprenyl) and pramipexole. The demographic analyses did not produce any evidence of interactions between treatment difference and age, race or gender. In **Trials 0001, 0004 and 0010,** 67%, 61% and 54% of the patients were taking selegiline, respectively. **Table 20 (Trial 0004)** displays the mean changes from baseline for active drug groups and placebo for patients who were and were not taking selegiline on study. **Table 21 (Trial 0010)** displays results for only patients taking selegiline and for the full data set. In **Trial 0004**, the differences from placebo were larger among patients who did not take selegiline **at the two highest doses of pramiprexole**. This may be partially explained by the larger placebo effect among the selegiline-taking patients. None of the trials provide substantial evidence of an interaction between pramipexole and selegiline use.

Conclusion

Trials 0001 and **0004** provide statistically significant evidence of efficacy in patients with early PD. **Trial 0001** was dose ranging up to 4.5mg/day. In **trial 0004**, although 6.0mg/day was slightly numerically superior to 1.5mg/day on the total UPDRS, there was no statistical evidence that it is in fact more effective than 1.5mg/day.

Trial 0010 provides statistical evidence of efficacy of a dose-ranging regimen of PX of up to 4.5mg/day as an adjunct to l-dopa therapy in patients with motor fluctuations.

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TABLE 1

Demographic Characteristics of Patients at Screen

Patient Data	Number (%) of Patients		
	Pramipexole (N=164)	Placebo (N=171)	P-Value
Age (yrs)			
<65	76 (46.3)	87 (50.9)	
≥65	88 (53.7)	84 (49.1)	
Mean	63.4	62	0.183
S.E.	0.78	0.88	
Min	33	30	
Max	85	85	
Sex			
Male	105 (64.0)	98 (57.3)	0.185
Female	59 (36.0)	73 (42.7)	
Race			
White	156 (95.1)	161 (94.1)	0.740
Black	2 (1.2)	4 (2.3)	
Other	6 (3.7)	6 (3.5)	
Weight (lbs)			
Mean	168.6	168.2 (N=169)	0.856
S.E.	2.48	2.79	
Min	101	96	
Max	260	282	
Height (in)			
Mean	67.1	66.9 (N=170)	0.631
S.E.	0.3	0.33	
Min	58	54	
Max	75	76	
Smoking History			
Nonsmoker	79 (48.2)	98 (57.3)	0.010
Ex-smoker	76 (46.3)	56 (32.8)	
Smoker	9 (5.5)	17 (9.9)	
Use of Alcohol			
Never Drinks	55 (33.5)	66 (38.6)	0.689
Average Consumption	108 (65.9)	104 (60.8)	
Excessive Consumption	1 (0.61)	1 (0.58)	
Duration of Parkinson's Disease			
Mean	2	1.7	0.097
S.E.	0.16	0.12	
Min	0	0	
Max	11.6	7.2	
UPDRS Part II (ADL) Total Score			
Mean	8.2 (N=163)	8.2	0.982
S.E.	0.31	0.33	
Min	1	1	
Max	20	22	
UPDRS Part III (Motor Examination) Total Score			
Mean	18.8 (N=162)	18.7 (N=170)	0.958
S.E.	0.71	0.71	
Min	1	3	
Max	63	53	
Modified Hoehn & Yahr Scale			
Mean	1.9 (N=163)	1.9	0.643
S.E.	0.04	0.05	
Min	1	1	
Max	3	3	
Current L-deprenyl Use			
Yes	112	113	0.480
No	52	58	
Current Anti-cholinergic Use			
Yes	19	24	0.511
No	145	147	

Source: Appendix C: Table 3.
Abbreviations: ADL = Activities of Daily Living.

TABLE 2

Disposition of Patients Enrolled in the Study

Disposition	Treatment Group	
	PPX	PBO
No. of Patients Randomized	N=164	N=171
No. (%) of ITT[a] Patients	163 (99)	170 (99)
No.(%) of Patients Completing Ascending-dose Phase	152 (93)	161 (94)
No.(%) of Patients Completing Maintenance Phase	136 (83)	137 (80)
No.(%) of Patients Discontinuing Study	28 (17)	34 (20)
Reason for Discontinuation		
Adverse Events		
Worsening of Disease[b]	4 (2)	15 (9)
Worsening of Other Pre-existing Disease	0 (0)	1 (1)
Other	18 (11)	8 (5)
Unsatisfactory Therapeutic Effect[c]	1 (1)	7 (4)
Protocol Violation	1 (1)	0 (0)
Lost to Follow-up	2 (1)	0 (0)
Withdrawal of Consent	2 (1)	2 (1)
Other	0 (0)	1 (1)

Source: Appendix C: Table 2.1.

[a] Intent-to-treat, the number of patients in each treatment group is the number randomized who received at least one dose of study drug and with at least one post-baseline follow-up.

[b] Defined as worsening of Parkinson's disease.

[c] Defined as no deterioration but still unsatisfactory therapeutic effect.

TABLE 3

Adjusted[a] Mean Change from Baseline in UPDRS Part II Total Score[b], Maintenance Interval Intent-to-Treat – All Patients, LOCF

Treatment Group	Baseline[c]	Maintenance Week					
		0[d]	4	8	12	16	24
PPX (N=163)	8.2	-2.5	-2.5	-2.4	-2.3	-2.4	-1.9
PBO (N=170)	8.3	-0.9	-0.7	-0.4	-0.2	0	0.4
P-Value	–	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001

Source: Appendix C: Table 9.2.

[a] Adjusted by investigator and investigator-by-treatment interaction.
[b] Sum of 13 components of UPDRS Part II.
[c] Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.
[d] Week 0 is the endpoint of the ascending-dose interval.

TABLE 4

Adjusted[a] Mean Change from Baseline in UPDRS Part III Total Score[b], Maintenance Interval Intent-to-Treat – All Patients, LOCF

Treatment Group	Baseline[c]	Maintenance Week					
		0[d]	4	8	12	16	24
PPX (N=162)	18.8	-6	-5.4	-5.2	-5.2	-5.1	-5
PBO (N=168)	18.8	-2.6	-2.3	-1.6	-0.9	0.4	0.8
P-Value	–	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001

Source: Appendix C: Table 10.2.

[a] Adjusted by investigator and investigator-by-treatment interaction.
[b] Sum of 14 components of UPDRS Part III.
[c] Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.
[d] Week 0 is the endpoint of the ascending-dose interval.

TABLE 5

Mean Change From Baseline in UPDRS Parts II and III, Total Score by L-deprenyl and Anti-cholinergic Usage; All Patients

Concomitant Therapy	Treatment Group	Part II[a]				Part III[b]			
		N	Yes	N	No	N	Yes	N	No
l-deprenyl	PPX	112	-1.9	51	-1.5	111	-4.6	51	-4.6
	PBO	112	0.3	58	0.7	112	1.3	57	1.5
Anticholinergic	PPX	19	-1.3	144	-1.9	19	-4.5	143	-4.6
	PBO	24	0.1	146	0.4	24	1.4	145	1.4

Source: Appendix C: Tables 11.1A & 12.1A.

[a] Sum of 13 components of UPDRS Part II.
[b] Sum of 14 components of UPDRS Part III.

TABLE 6

UPDRS Part II Individual Components
Mean Change From Baseline to Endpoint
All Patients

UPDRS Component	Treatment Group	
	PPX N=163	PBO N=170
Speech	0.0	0.0
Salivation	0.0	-0.1
Swallowing	0.0	0.0
Handwriting	-0.3	0.0
Cut food/handling utensils	-0.2	0.0
Dressing	-0.2	0.1
Hygiene	-0.1	0.0
Turning in bed/adjusting clothes	-0.3	0.1
Falling	0.0	0.0
Freezing when walking	0.0	0.1
Walking	-0.1	0.0
Tremor	-0.4	0.0
Sensory complaints related to Parkinsonism	-0.1	0.1

TABLE 7

UPDRS Part III Individual Components
Mean Change From Baseline to Endpoint
All Patients

UPDRS Component	Treatment Group	
	PPX N=163	PBO N=170
Speech	-0.1	0.1
Facial expression	-0.1	0.0
Tremor at rest (face)	-0.1	0.0
Tremor at rest (Left Hand)	-0.2	0.0
Tremor at rest (Right Hand)	-0.3	0.0
Tremor at rest (Left Foot)	-0.1	0.0
Tremor at rest (Right Foot)	-0.1	0.0
Action or postural tremor of hands (Left Hand)	0.0	0.0
Action of postural tremor of hands (Right Hand)	-0.1	0.0
Rigidity (neck)	-0.1	0.0
Rigidity (left upper extremity)	-0.3	0.0
Rigidity (right upper extremity)	-0.3	0.0
Rigidity (left lower extremity)	-0.1	0.1
Rigidity (right lower extremity)	-0.1	0.0
Finger taps (left)	-0.4	0.1
Finger taps (right)	-0.4	0.1
Hand movements (left)	-0.4	0.1
Hand movements (right)	-0.3	0.1
Rapid alternating movements (Left Hand)	-0.2	0.1
Rapid alternating movements (Right Hand)	-0.3	0.1
Leg agility (left)	-0.1	0.1
Leg agility (right)	-0.2	0.1
Arising from chair	0.0	0.2
Posture	0.0	0.1
Gait	-0.1	0.0
Postural stability	-0.1	-0.1

TABLE 8

SELECTED DEMOGRAPHIC AND BASELINE FACTORS

Parameter	Pramipexole - assigned dose				Placebo n=51	p value
	1.5 mg/day n=54	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55		
age (mean years)	60.2	62.2	62.7	62.8	60.4	0.67
sex (% male)	64.8	62.0	63.0	69.1	62.8	0.90
race (% caucasian)	96.3	98.0	96.3	98.2	96.1	0.58
duration of disease (mean years)	1.8	2.0	1.9	2.3	1.6	0.16
current selegiline use (% yes)	55.6	66.0	66.7	58.2	58.8	0.65
UPDRS total score (mean points)	29.0	28.3	27.3	32.9	28.7	0.08
Hoehn and Yahr score (mean points)	1.8	1.9	1.8	1.9	1.8	0.52

TABLE 9

PATIENT DISPOSTION AND TOLERABILITY - NUMBER PATIENTS (%)

Endpoint	Pramipexole - assigned dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
Number randomized	54	50	54	55	51
number (%) completing ascending dose	47 (87.0)	48 (96.0)	52 (96.3)	47 (85.5)	51 (100.0)
number (%) completing maintenance	44 (81.5)	48 (96.0)	50 (92.6)	46 (83.6)	50 (98.0)
number (%) completing at assigned dose - tolerability	44 (81.5)	46 (92.0)	43 (79.6)	37 (67.3)	49 (96.1)
number (%) completing with one or no dose reductions	44 (81.5)	48 (96.0)	50 (92.6)	44 (80.0)	50 (98.0)
number (%) dose limited during ascending dose interval due to clinical intolerance	2 (3.7)	3 (6.0)	7 (13.0)	10 (18.2)	1 (2.0)

TABLE 10

UPDRS TOTAL SCORE CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	28.5	28.3	27.3	32.9	28.7
mean change*	-6.1	-5.8	-6.6	-7.1	-1.2
pairwise p value vs placebo	0.0027	0.0057	0.0008	0.0003	–
overall p value	0.0022	–	–	–	–

*Adjusted for center effect and treatment by center interaction

TABLE 11

UPDRS PART II - CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	8.0	8.0	7.3	8.8	8.2
mean change*	-1.8	-1.9	-1.8	-1.8	-0.3
pairwise p value vs placebo**	N.D.	N.D.	N.D.	N.D.	N.D.
overall p value	0.0613	–	–	–	–

*Adjusted for center and treatment by center interaction
**N.D. - not done since overall p value not significant

TABLE 12

UPDRS PART III - CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	19.4	19.3	19.2	22.9	19.6
mean change*	-4.2	-3.8	-4.7	-5.1	-0.6
pairwise p value vs placebo	0.0052	0.0151	0.0016	0.0005	–
overall p value	0.0048	–	–	–	–

*Adjusted for center and treatment by center interaction

TABLE 13

UPDRS PART II - INDIVIDUAL ITEMS WITH GREATEST MEAN CHANGE FROM BASELINE

Item	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
handwriting	-0.4	-0.4	-0.4	-0.4	0.0
dressing	-0.1	-0.3	-0.3	-0.3	-0.1
tremor	-0.1	-0.3	-0.2	-0.3	-0.1

UPDRS PART III - INDIVIDUAL ITEMS WITH GREATEST MEAN CHANGE FROM BASELINE

Item	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
tremor - left hand	-0.2	-0.3	-0.2	-0.4	0.0
tremor - right hand	-0.1	-0.2	-0.3	-0.4	0.0
tremor - left foot	0.0	-0.1	-0.3	0.0	0.0
rigidity - neck	-0.1	0.0	-0.2	-0.3	0.1
rigidity - left upper extremity	-0.2	-0.2	-0.4	-0.2	-0.1
rigidity - right upper extremity	-0.2	-0.3	-0.3	-0.3	-0.1
rigidity - right lower extremity	0.0	-0.3	-0.2	-0.1	0.0
finger taps - left	-0.4	-0.2	-0.3	-0.3	-0.1
finger taps - right	-0.6	-0.2	-0.2	-0.3	0.0
hand movements - left	-0.2	-0.2	-0.3	-0.2	0.1
hand movements - right	-0.3	-0.1	-0.3	-0.3	0.0
rapid alternating movements - left	-0.2	-0.3	-0.2	-0.1	0.2
rapid alternating movements - right	-0.4	-0.2	-0.2	-0.2	0.1
bradykinesia	-0.3	-0.2	-0.2	-0.3	0.0

TABLE 14

MODIFIED HOEHN AND YAHR SCALE - PERCENT CHANGE

Category	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
improved from baseline (%)	19.2	36.7	25.0	30.2	13.7
worsened from baseline (%)	17.3	6.1	5.8	9.4	25.5

TABLE 15

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Characteristics	Placebo N=179	Pramipexole N=181	Total N=360
Age (yrs)			
N	179 (100%)	181 (100%)	360 (100%)
< 65	90 (50.3%)	95 (47.9%)	175 (48.6%)
>=65	89 (49.7%)	96 (53.0%)	185 (51.4%)
N	179	181	360
Mean	62.3	63.4	62.9
S.E.	0.72	0.72	0.51
Range			
Sex			
Male	115 (64.8%)	119 (65.7%)	235 (65.3%)
Female	63 (35.2%)	62 (34.3%)	125 (34.7%)
Race			
White	172 (96.1%)	172 (95.0%)	344 (95.6%)
Black	4 (2.2%)	3 (1.7%)	7 (1.9%)
Other	3 (1.7%)	6 (3.3%)	9 (2.5%)
Height (cm)			
N	179	179	358
Mean	170.9	170.8	170.8
S.E.	0.75	0.77	0.54
Range			
Weight (kg)			
N	178	180	358
Mean	72.9	73.7	73.3
S.E.	[illegible]	1.04	0.83
Range			
Duration of Parkinson's Disease (yrs)			
N	179	181	360
Mean	5.0	5.4	5.2
S.E.	0.38	0.45	0.29
Range			
Smoking History			
Non-smoker	95 (53.1%)	103 (56.9%)	198 (55.0%)
Ex-smoker	69 (38.5%)	70 (38.7%)	139 (38.6%)
Smoker	15 (8.4%)	8 (4.4%)	23 (6.4%)
Use of Alcohol			
Never Drinks	83 (46.4%)	76 (42.0%)	159 (44.2%)
Average Consumption	96 (53.6%)	105 (58.0%)	201 (55.8%)
Current L-deprenyl Use			
No	85 (47.5%)	80 (44.2%)	165 (45.8%)
Yes	94 (52.5%)	101 (55.8%)	195 (54.2%)
Current Anticholinergic Use			
No	158 (88.3%)	155 (85.6%)	313 (86.9%)
Yes	21 (11.7%)	26 (14.4%)	47 (13.1%)
UPDRS Part II 'on' Total Scores			
N	178	181	359
Mean	7.7	7.3	7.5
S.E.	0.40	0.40	0.28
Range	0		
UPDRS Part II 'off' Total Scores			
N	177	181	358
Mean	17.4	17.4	17.4
S.E.	0.48	0.52	0.36
Range			
UPDRS Part III Total Scores			
N	179	181	360
Mean	23.3	22.8	23.0
S.E.	0.94	0.97	0.67
Range			
Modified Hoehn and Yahr Scale 'on'			
0	1 (0.6%)	1 (0.6%)	2 (0.6%)
1	3 (1.7%)	3 (1.7%)	6 (1.7%)
1.5	6 (3.4%)	3 (1.7%)	9 (2.5%)
2	95 (53.4%)	97 (53.6%)	192 (53.5%)
2.5	37 (20.8%)	35 (19.3%)	72 (20.1%)
3	34 (19.1%)	38 (21.0%)	72 (20.1%)
4	2 (1.1%)	5 (2.8%)	7 (1.9%)
N	178	181	359
Mean	2.3	2.3	2.3
S.E.	0.04	0.04	0.03
Range			
Modified Hoehn and Yahr Scale 'off'			
1	3 (1.7%)		3 (0.8%)
1.5		1 (0.6%)	1 (0.3%)
2	36 (20.2%)	27 (14.9%)	63 (17.5%)
2.5	37 (20.8%)	53 (29.3%)	90 (25.1%)
3	68 (38.2%)	62 (34.3%)	130 (36.2%)
4	22 (12.4%)	30 (16.6%)	52 (14.5%)
5	11 (6.2%)	9 (5.0%)	20 (5.6%)
N	178	181	359
Mean	2.9	3.0	2.9
S.E.	0.06	0.06	0.04
Range			
Chest Xray Findings			
Normal	125 (70.2%)	114 (64.0%)	239 (67.1%)
Abnormal	53 (29.8%)	64 (36.0%)	117 (32.9%)

TABLE 16

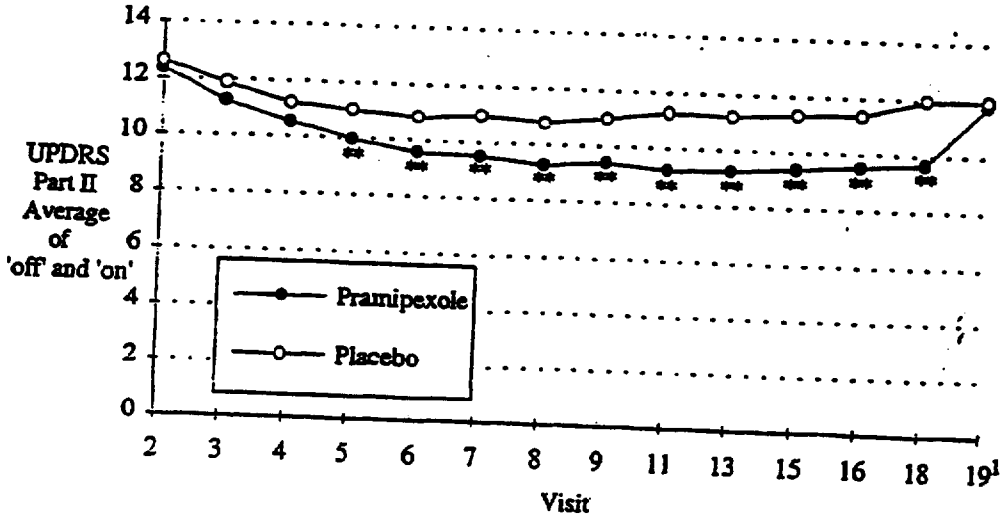
Disposition for Patients Randomized Into the Trial

	Number of Patients (%)		
	PRAMIPEXOLE	PLACEBO	TOTAL
Number of Patients Randomized	181 (100)	179[1] (100)	360 (100)
Number of Patients Treated	181 (100)	178[1] (99.4)	359 (99.7)
Number of Patients Who Completed the Trial	151 (83.4)	140 (78.2)	291 (80.8)
Number of Patients Who Prematurely Discontinued	30 (16.6)	39 (21.8)	69 (19.2)
Discontinued Due To:			
Adverse Events			
Worsening of Disease Under Trial	3 (1.7)	9 (5.0)	12 (3.3)
Worsening of Pre-Existing Diseases	0 (0.0)	3 (1.7)	3 (0.8)
Other Adverse Events	21 (11.6)	18 (10.1)	39 (10.8)
Lack of Efficacy	0 (0.0)	0 (0.0)	0 (0.0)
Administrative Reasons			
Protocol Violation	1 (0.6)	0 (0.0)	1 (0.3)
Lost to Follow-up	0 (0.0)	2 (1.1)	2 (0.6)
Withdrawal of Consent	4 (2.2)	3 (1.7)	7 (1.9)
Other	1 (0.6)	4 (2.2)	5 (1.4)

Source Data: Appendices 15.12 LISTING 1.1, 15.12 LISTING 7.1, 15.12 LISTING 7.2

[1] One patient (1054, Center 7) was randomized into the placebo treatment group but discontinued prior to receiving drug.

FIGURE 1



Average UPDRS Part II 'off' and 'on' Means by Visit.
Last Observation Carried Forward Analysis

TABLE 17

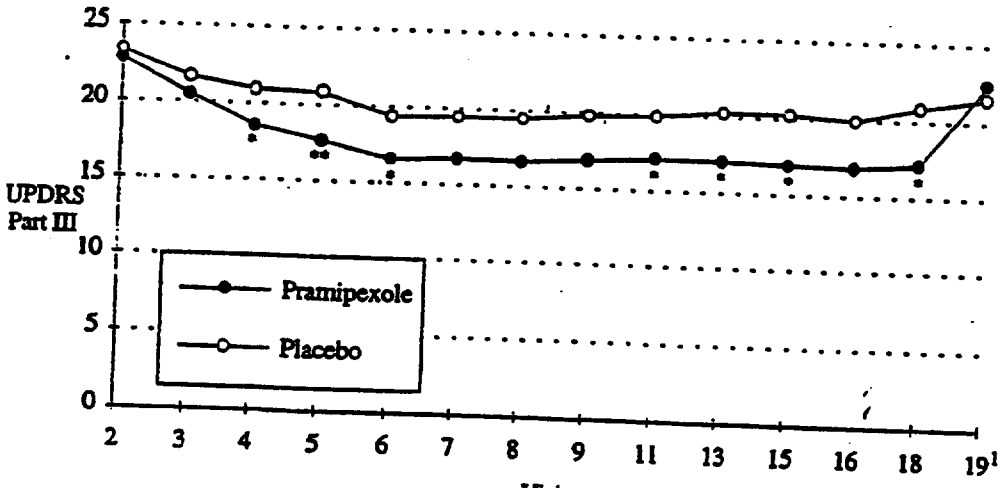
Adjusted[1] UPDRS Part II Average of 'off' and 'on' Period Means, Sample Sizes, and p-values for Change from Baseline and Area Under the Curve.

	LOCF Change from Baseline to Final Maintenance Visit	OC Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (11-18)	OC Area Under the Curve over Maintenance Visits (11-18)
Pramipexole	-2.72 n = 179	-2.83 n = 171	-56.86 n = 179	-54.29 n = 134
Placebo	-0.47 n = 171	-0.46 n = 156	-17.63 n = 171	-17.36 n = 124
p-value	≤ 0.0001	≤ 0.0001	≤ 0.0001	≤ 0.0001

Source Data: Appendix 15.9.2 STATDOC 4.1.3.1, 4.1.3.2, 4.1.5.1 & 4.1.5.2

1 Adjusted by center and center-by-treatment interaction (as per protocol).

FIGURE 2



UPDRS Part III Means by Visit.

Last Observation Carried Forward Analysis

TABLE 18

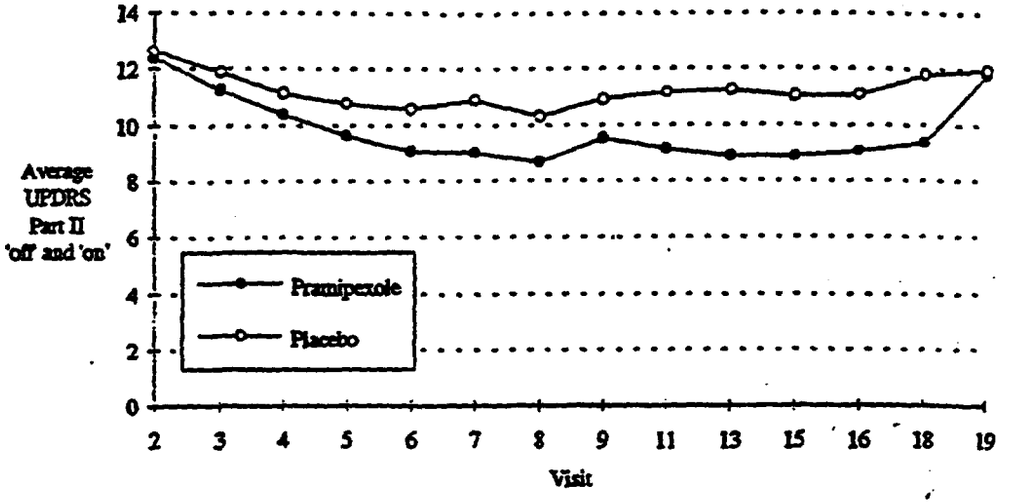
Adjusted[1] UPDRS Part III Means, Sample Sizes, and p-values for Change from Baseline and Area Under the Curve.

	LOCF Change from Baseline to Final Maintenance Visit	OC Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (11-18)	OC Area Under the Curve over Maintenance Visits (11-18)
Pramipexole	-5.64 n = 179	-5.73 n = 170	-113.84 n = 179	-125.60 n = 148
Placebo	-2.79 n = 171	-3.65 n = 157	-63.53 n = 171	-74.78 n = 133
p-value	0.01	0.08	0.01	0.02

Source Data: Appendix 15.9.2 STATDOC 4.2.3.1, 4.2.3.2, 4.2.5.1 & 4.2.5.2

1 Adjusted by center and center-by-treatment interaction (as per protocol).

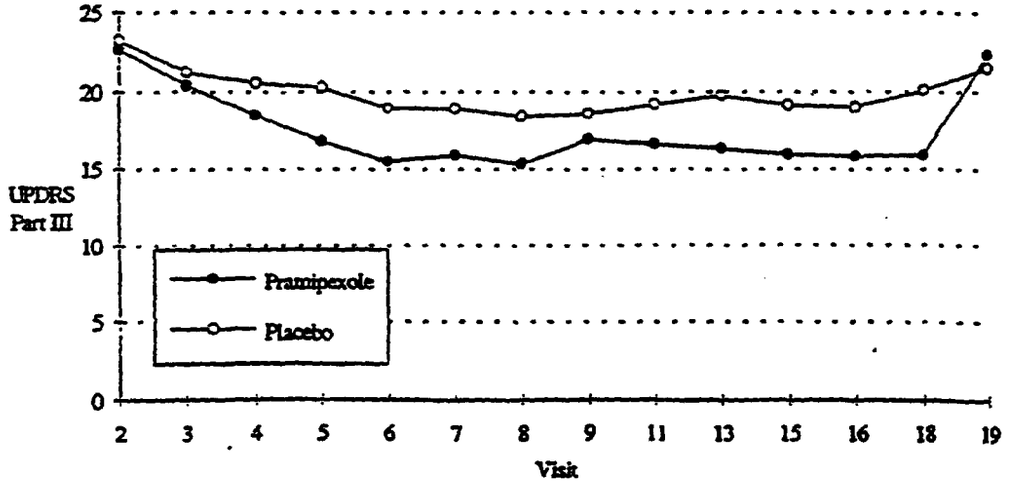
FIGURE 3



Average UPDRS Part II 'off' and 'on' Means by Visit.

Observed Cases Analysis

FIGURE 4



UPDRS Part III Means by Visit.

Observed Cases Analysis

TABLE 19

Unadjusted Means, Standard Deviations, and Sample Sizes for Average Percentage of 'off' Period Time by Visit.

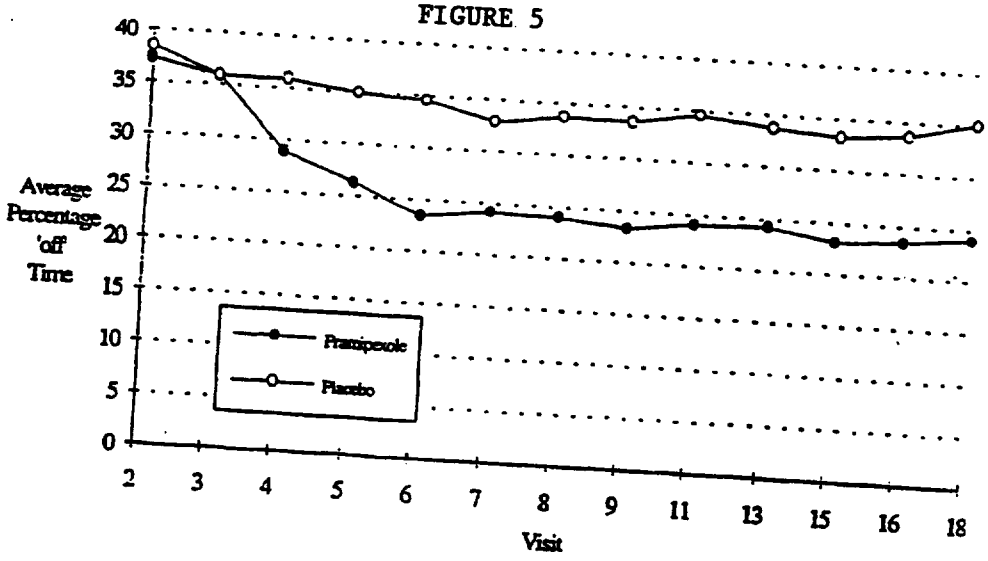
Last Observation Carried Forward Analysis

Group	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Pramipexole:							
Mean =	37.20	35.88	28.85	26.24	23.46	24.22	24.02
S.D. =	19.91	21.06	20.42	20.43	20.43	22.32	21.59
n =	173	173	173	173	173	173	173
Placebo:							
Mean =	38.28	35.91	35.88	34.92	34.54	32.79	33.61
S.D. =	20.35	18.88	19.80	20.71	21.20	21.07	21.64
n =	172	172	172	172	172	172	172

Group	Visit 9	Visit 11	Visit 13	Visit 15	Visit 16	Visit 18
Pramipexole:						
Mean =	23.31	24.06	24.24	23.08	23.39	24.01
S.D. =	21.46	22.75	22.28	21.25	20.79	22.45
n =	173	173	173	173	173	173
Placebo:						
Mean =	33.48	34.55	33.70	33.18	33.59	35.13
S.D. =	21.99	22.32	22.76	23.69	24.63	24.24
n =	172	172	172	172	172	172

Source Data: Appendix 15.9.2 STATDOC 4.5.1

FIGURE 5



Average Percentage 'off' Time by Visit.

Last Observation Carried Forward Analysis

TABLE 20

Protocol M/2730/0004
UPDRS I-III TOTAL SCORE+
BY L-DEPRENYL AND ANTICHOLINERGIC USE AT BASELINE
MEAN CHANGE FROM BASELINE TO ENDPOINT@@ - ALL PATIENTS

			PFX 1.5 mg	PFX 3.0 mg	PFX 4.5 mg	PFX 6.0 mg	Placebo
L-Deprenyl	Yes	N	30	33	26	22	30
		Mean Baseline	27.9	26.7	28.2	29.9	28.3
		Mean Endpoint	20.3	19.2	19.1	24.8	23.4
		Mean Change	-7.6	-7.5	-6.1	-5.7	-1.9
		S.E.	1.32	0.98	0.99	1.17	1.49
	No	N	23	17	18	23	21
		Mean Baseline	29.3	31.3	31.5	37.0	33.6
		Mean Endpoint	24.5	28.4	24.0	28.0	34.2
		Mean Change	-4.8	-2.9	-7.5	-9.0	0.6
		S.E.	2.28	1.66	2.71	1.98	2.26
Anticholinergic	Yes	N	35	37	41	37	34
		Mean Baseline	28.2	27.1	26.8	31.8	28.3
		Mean Endpoint	20.9	20.5	20.3	25.3	24.0
		Mean Change	-7.4	-6.6	-6.5	-6.2	-1.3
		S.E.	1.26	0.99	0.91	1.14	1.37
	No	N	18	13	13	10	17
		Mean Baseline	29.0	31.5	29.1	35.7	35.5
		Mean Endpoint	24.5	27.6	22.3	26.9	35.5
		Mean Change	-4.5	-3.9	-6.8	-8.8	0.0
		S.E.	2.71	2.04	3.71	2.38	2.71

+ Sum of the 31 components of UPDRS Parts I, II and III (Range = 0 - 176).
@ Values taken at the baseline visit, Visit 2 (Week 0).
@@ Last visit, prior to dose-reduction.
Treatment groups are classified by assigned (target) dose.

TABLE 21

UPDRS Part II Average of 'off' and 'on' Periods Change from Baseline to Final for L-Deprenyl Users Only and All Patients.

Last Observation Carried Forward Analysis

	Intent-to-Treat Data Set	L-Deprenyl Users
Pramipexole	-2.72 n = 179	-2.97 n = 97
Placebo	-0.47 n = 171	-0.82 n = 93
p-value	≤0.0001	0.0005

UPDRS Part III Change from Baseline to Final for L-Deprenyl Users Only and All Patients.

Last Observation Carried Forward Analysis

	Intent-to-Treat Data Set	L-Deprenyl Users
Pramipexole	-5.64 n = 179	-6.82 n = 97
Placebo	-2.79 n = 171	-3.06 n = 93
p-value	0.01	0.01

1641

AMENDMENT

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 12, 1996

FROM: Paul Leber, M.D., Director,
Division of Neuropharmacological Drug Products, HFD-120

RETURN
AUG 1996

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

TO: Daniel Boring, Chair
Labeling and Nomenclature Committee
HFD-600, Metropark North II

Proposed Trademark: MIRAPEX (Pramipexole) Tablets NDA 20-667

Established name, including dosage form: Pramipexole Tablets

Other trademarks by the same firm for companion products: None

Indications for Use (may be a summary if proposed statement is lengthy):

treatment of the signs and symptoms of idiopathic Parkinson's disease

Initial comments from the submitter: (concerns, observations, etc.)

See attached copies of the "Description, Indications and Usage, Overdosage, and Dosage and Administration" Sections of the package insert.

Any questions call Jack Purvis, 4-5525.

HIGGINS

cc: ORIG NDA 20-667, HFD-120, HFD-120/SBlum/Zarifa, HFD-120/JPurvis/rd4/22/96

7/12/96

Consult #641

MIRAPEX pramipexole tablets

The LNC noted the following look alike/sound alike conflicts with the trademark: MIRASEPT (OTC contact lens solution) and minaprine (antipsychotic unavailable in the U.S.) however, the Committee believes there is a low potential for confusion with these names given the different storage environments for each product. The Committee found no misleading or fanciful aspects in the proposed proprietary name.

The Committee has no reason to find the proposed name unacceptable.

D L Boring 8/22/96, Chair
CDER Labeling and Nomenclature Committee

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

TRADE NAME NOT GIVEN

(Pramipexole) USAN, INN

COMPRESSED TABLET 0.125, 0.25, 1.0, 1.25, 1.5 mg

NDA 20-667

THE UPJOHN COMPANY

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

(HFD-120)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-667

TRADE NAME NOT GIVEN

(Pramipexole) Tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Pramipexole, The UpJohn Company prepared an environmental assessment (attached) in accordance with 21 CFR 25.31a which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Pramipexole is a chemically synthesized drug which is administered as a tablet in the treatment of Parkinson's disease. The drug substance will be manufactured by . The drug product will be manufactured by The UpJohn Company, Arecibo, Puerto Rico. The finished drug product will be used in hospitals, clinics and/or by patients in their homes.

Pramipexole may enter the environment from manufacturing sites, disposal of pharmaceutical waste, and from excretion from patients. Due to the relatively small projected use in this country, adverse environmental effects from distribution are not anticipated.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages

will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

RETURN

MAY 08 1996

5/6/96
Date

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

5/6/96
Date

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheet for drug substance included

Copies:

HFD-120

Jack Purvis
Original NDA 20-667
Division File for NDA 20-667

HFD-205

FOI Copy

HFD-357

EA File
Docket File
C. Berninger 5/6/96

NON-CONFIDENTIAL

Pramipexole Tablets NDA
Item 3. Chemistry, Manufacturing and Controls
Part V. Environmental Assessment Report - Revised

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ENVIRONMENTAL ASSESSMENT REPORT (EA)

1. DATE

December 8, 1995
February 22, 1996 (revision)

2. NAME OF APPLICANT

The Upjohn Company

3. ADDRESS

The mailing address and telephone number of The Upjohn Company are:

7000 Portage Road
Kalamazoo, Michigan 49001
Corporate telephone number: (616) 323-4000

4. DESCRIPTION OF THE PROPOSED ACTION

4.a. Requested Approval

This environmental assessment is submitted in compliance with 21CFR Part 25.31a to accompany the New Drug Application (NDA) #20-667 for pramipexole tablets.

4.b. Need for Action

This environmental assessment is required to accompany the NDA #20-667 for pramipexole tablets. Pramipexole tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The first-year patient population is estimated to be 9,600.

4.c. Production Locations

- Drug Substance

The drug substance will be purchased by The Upjohn Company (Upjohn) from:

Boehringer Ingelheim KG
D-55216 Ingelheim am Rhein
Germany

- Drug Product

The drug product will be formulated and packaged at The Upjohn Manufacturing Company (UMC) in Arecibo, Puerto Rico, located south of Puerto Rico Highway No. 2 Km 60.0 (see non-confidential Appendix 1). This facility is in the Barceloneta Industrial Complex which was promoted by the Puerto Rico Industrial Development Corporation (PRIDCO) to attract pharmaceutical and other industrial plants. At this time, there are at least ten industries located in this industrial area. Some of those nearby companies include Pfizer, Abbott, and Merck. The nearest school is approximately three kilometers east of the project site, on PR Highway No. 2. Most of the land surrounding the site continues to be used for agricultural purposes with pineapples as the chief crop. The plant site occupies a portion of 94.3 hectares lying south of State Road PR-2 and 3 kilometers west of State Road PR-140 at Cruce Dávilla. About 13.8 hectares of the Upjohn land consist of karst formation [an area of irregular limestone in which erosion has produced fissures, sinkholes, underground streams, and caverns]. The remaining 80.5 hectares of the land that were formerly used for cultivation of sugar cane and for pasture are relatively flat in a tropical climate. The Upjohn Manufacturing Company consists of nine main buildings and some outside facilities and storage tanks.

4.d. Locations of Use

The ultimate use and disposal of the finished product will be mainly at residences, hospitals, and clinics, and nursing homes. Finished products will be stored in distribution centers throughout the U.S. prior to transportation for sale.

4.e. Disposal Sites

Disposal of drug substance or drug product may result from processing or distribution activities in the form of off-specification lots, returned goods, or from end user disposal of individual units of empty or partly empty finished product containers.

The present infrastructure at the proposed manufacturing sites provides for the following recovery and/or ultimate disposal mechanisms:

- Off-Specification Lots

Off-specification lots or rejected goods will be disposed of by incineration at Chambers Medical Technologies (CMT) in Hampton, South Carolina. [CMT has the following permits granted by the South Carolina Department of Health: air permit #1280-0021-CG; NPDES permit No. SC0042242.]

- Returned Goods

Returned goods of the drug product received at Upjohn will be incinerated in an on-site incinerator (interim status treatment storage and disposal facility).

- *Incinerator.* The incinerator is being operated as a Resource Conservation and Recovery Act (RCRA) interim status treatment storage and disposal facility under #MID000820381 in compliance with 40 CFR 264, Subpart O requirements. Additionally, 40 CFR 265.1(b) and Section 3005(e) of RCRA provide for the continued operation of an existing facility that meets certain conditions, until final administrative disposition of the owner's and operator's permit application is made.

The incinerator is a two-stage system: the primary chamber rotary kiln operates at a minimum of 700°F; the secondary chamber, where final destruction of the product and off-gasses occurs, operates at a minimum of 1,904°F. The incinerator is equipped with a pollution control equipment train designed to remove gaseous and particulate pollutants. The pollution control equipment consists of: a quench section, an acid-gas pre-scrubber, a Venturi scrubber, an entrainment separator, an induced draft fan, and an exhaust stack.

A hazardous-waste RCRA Part B/Act 451, Part 111 permit application has been submitted to the Waste Management Division of the Michigan Department of Natural Resources (now the Michigan Department of Environmental Quality , MDEQ) in Lansing, Michigan. The Upjohn facility is operating under interim status provisions until action is taken on the permit application. MDEQ action on the permit application is expected in 1996. The State air permit issued on July 15, 1980 (#242-80), revised to incorporate the Act 451, Part 111 requirements, was approved on May 26, 1993.

All necessary permits are in place for the manufacture of this product to begin, as an existing interim status facility in accordance with Section 3005(e) of RCRA and Michigan Act 451, Part 111 licensing requirements.

Ash generated as a result of the incineration process will be sent to a permitted hazardous waste landfill. At the present time, Upjohn uses the following facilities:

- Chemical Waste Management, Trade Waste Incinerator Division, 7 Mobile Avenue, Sauget, IL, operating under EPA ID No. ILD 098 642 424 and Illinois Environmental Protection Agency No. IEPA 1631210009;
- Systech Environmental Corporation in Alpena, MI, operating under EPA ID No. MID981200835 and State Air Permit No. 587-93; or in Paulding, OH, operating under EPA ID No. OHD005048947 and State Air Permit Nos. 0363000002P016 and 0363000002P017;
- Continental Cement in Hannibal, MO, operating under EPA ID No. MOD054018288 and Air Permit No. 1086-004A;
- Upjohn may use other facilities for such disposal which are suitable for that purpose and properly permitted.

We have identified hazardous waste as well as air permits as given to us by these facilities, but there may be other permits and licenses applicable which are currently held by the facilities. While Upjohn has contracts with each of these facilities that require compliance with all applicable laws and regulations, Upjohn does not own, operate, or control these facilities. The waste stream profiles established with the hazardous waste landfill sites contain an affirmation by the facility of its compliance status. All facilities are audited and approved for use by Upjohn environmental auditors prior to the first shipment of waste from Upjohn to the site.

- Discarded Product in Hospital or Clinic Setting

Any discarded product or product containers generated in a hospital or clinic setting would typically be disposed in accordance with applicable Federal, State and local regulations.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

Pharmaceutical Formulation

The material safety data sheet (MSDS) for the drug substance, pramipexole, is included as non-confidential Appendix 2.

The list of ingredients used in formulating the drug product, pramipexole tablets, is included as non-confidential Appendix 3.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The drug substance and drug product are not expected to be introduced into the environment through transportation and storage. Product will be shipped in Department of Transportation (DOT) specification packaging. Pramipexole is not regulated as a hazardous material under current DOT regulations. Product ready for shipment will be stored in either the manufacturing facility or distribution centers. Both maintain security through limited access.

6.a. Substances Expected to be Emitted

Portions of the ingredients, as listed in non-confidential Appendix 3, may be released to the environment as a result of the proposed action.

Please refer to format item 6.b. for further specific disposal operations covering air, water, and solid waste streams.

Permits and other actions covering specific environmental regulations in force at UMC's chemical-processing complex, including permit numbers and expiration dates where applicable, are summarized in the Permits Chart included as non-confidential Appendix 5 to include:

- Permit Description
- Regulatory Agency
- Permit No.
- Issue Date
- Expiration Date

See also The Upjohn Company's Permits Chart included as non-confidential Appendix 6 for an itemization of regulations and permits specific to the on-site approved incinerator.

6.b. Controls Exercised

- Chemical Process

See the letter dated 26 October 1995 from the Ministry for the Environment and Forestry (non-confidential Appendix 4) certifying Boehringer Ingelheim's (BI) manufacture in accordance with all German environmental laws and regulations.

- Pharmaceutical Formulation

- Air Emissions

Particulate emissions from the drug product are controlled through the use of the following equipment, with efficiencies at 99% by weight.

- dust collectors
- pre-filter system followed by HEPA filters for each dryer plus dust collector at the dryer room

This equipment is covered by the Puerto Rico Environmental Quality Board (EQB) under Temporary Air Operation Permit No. PFE-09-1194-1317-I-O [see Appendix 4 for a listing of permits/renewal status]

- Aqueous Waste Streams

Aqueous waste streams are generated from washes of process equipment at the pharmaceutical area. The equipment is washed with water and detergents [LC-30 or Alconox, Darmex Krystal, alcohol 3A, or isopropyl alcohol (IPA), Sprex AC]. These streams are discharged to the Puerto Rico Aqueduct & Sewer Authority (PRASA). [see Appendix 4 for a listing of permits/renewal status]

- Waste Solvents

The pramipexole tablets process does not generate waste solvents.

- Solid Waste

Residues from dust collectors and rags and towels used on cleaning of packaging lines and drying of small equipment parts are stored onsite at the container storage area (CSA) (permitted area for storage of hazardous, special, and nonhazardous wastes) prior to shipment to Chambers Medical Technologies (CMT) in Hampton, South Carolina. [CMT has the following permits granted by the South Carolina Department of Health: air permit #1280-0021-CG; NPDES permit No. SC0042242.]

6.c. Citation of and Statement of Compliance with Applicable Emission Requirements

The following regulations or standards are cited as applicable to the proposed action:

1. P.R. Public Law 9, The Environmental Public Policy Act of 1970, as amended (local regulation applicable to the Commonwealth of Puerto Rico):
   - Air Pollution Control Regulations
   - Water Quality Standards
   - Regulations for the Control of Hazardous and Non-Hazardous Wastes
   - Underground Injection Control Regulations
2. Puerto Rico Public Law #163 of May 3, 1949, as amended, The Puerto Rico Aqueduct and Sewer Authority, as amended.
3. P.R. Occupational Safety and Health Act of 1907, as amended (local regulation applicable to the Commonwealth of Puerto Rico).

- *Emission Requirements.* UMC states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the manufacture of the drug product, pramipexole tablets, at its facilities in Arecibo, Puerto Rico, as well as emission requirements set forth in applicable Federal, State, and local statutes and regulations applicable to the manufacture of the drug product, pramipexole tablets, at its facilities in Arecibo, Puerto Rico.

- *OSHA Requirements.* Upjohn certifies that it has comprehensive programs and practices in place addressing all applicable OSHA requirements.

6.d. Discussion of the Effect of the Approval on Current Emissions

Approval of the proposed action will not result in the modification of the UMC Puerto Rico site existing facilities.

Projecting to the fifth year of production, all discharges from the production of pramipexole tablets are permitted and will not affect compliance with current emission requirements. Waste water emission for this drug product will be <1% of the permit limit.

6.e. Maximum Expected Environmental Concentration (MEEC)

Estimations of the theoretical maximum environmental concentration (MEEC) can be made using the following equation:

MEEC (ppm) = lbs/yr production X 8.9 E^{-9}

= (A)(B)(C)(D)(E)(F)

where:

A	=	pounds per year production
B	=	year/365 days
C	=	day person/150 gallons
D	=	1/264 million person US population
E	=	gallons/8.34
F	=	1 million

Utilizing the fifth-year production forecast of 172.4 kg, the maximum environmental concentration that could be achieved is 3.3 x $10E^{-6}$ ppm. This concentration assumes complete and instantaneous release of the entire year's production, with no degradation.

These MEECs reflect the worst-case assumptions of instantaneous release and dispersion of the entire year's production with no allowance for biodegradation, hydrolysis, or other removal mechanisms.

CDER has routinely found that drugs at concentrations less than 1 ppb have no significant effect on relevant standard test organisms and therefore are unlikely to have a significant effect on the environment. CDER has also determined that information for environmental assessment format items 7, 8, 9, 10, 11, and 15 will normally not be needed whose expected introduction concentration is less than 1 ppb.

Since the calculated MEEC for pramipexole is less than 1 ppb, the format items mentioned above have not been included.

In summary, based on worst-case analysis, pramipexole may reasonably be anticipated to be nontoxic according to the definition found at 21 CFR 25.15(b)(6).

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

9. USE OF RESOURCES AND ENERGY

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

10. MITIGATION MEASURES

Based on information in CDER's revised guidance document (see Reference 14.J.), information for this format item is not included for this document.

11. ALTERNATIVES TO THE PROPOSED ACTION

Based on information in CDER's revised guidance document (see Reference [illegible] have a significant effect on the environment. CDER has also determined that information for environmental assessment format items 7, 8, 9, 10, 11, and 15 will normally not be needed whose expected introduction concentration is less than 1 ppb.

Since the calculated MEEC for pramipexole is less than 1 ppb, the format items mentioned above have not been included.

12. LIST OF PREPARERS

Following is a listing of those persons, and corresponding qualifications, who participated in the preparation of this assessment. No government agency was consulted for this specific evaluation other than for routine implementation of ongoing environmental programs conducted at existing facilities.

Jeffrey S. Mehring	Environmental Quality and Safety Division Manager, Environmental Health Sciences Ph.D., Agriculture Professional experience: 24 years
Susan I. Shedore	Environmental Quality and Safety Division Environmental Technician A.A., Liberal Arts Corporate experience: 24 years
Evelyn Perez	Environmental Affairs Associate Environmental & Safety Unit B.S., Environmental Sciences Professional experience: 12 years
John S. Purvis	Supervisory Project Manager Food and Drug Administration CDER Rockville, Maryland
ABC Laboratories, Inc.	7200 E. ABC Lane P.O. Box 7237 Columbia, MO

13. CERTIFICATION

The undersigned officials certify that the information presented is true, accurate, and complete to the best of their knowledge.

The undersigned officials certify that the EA summary document (pages 1-12) and Appendices 1-7 (pages A 13 - A 25) contain non-confidential information and acknowledge that this information will be made available to the public in accordance with 40 CFR § 1506.6. **Appendix 8 (page A 26) contains confidential information that is not to be made available to the public.**

Randal S. Senger, Manager
Corporate Environmental Affairs
(telephone 616/323-5341)

Feb 23, 1996
Date

Jeffrey S. Mehring, Manager
Environmental Health Sciences
(telephone 616/323-4746)

22 FEB 96
Date

14. REFERENCES

A. Aerobic Biodegradation of Pramipexole in Water. Final Report #41293. Columbia, Missouri: ABC Laboratories, Inc, March 31, 1995.

B. Aerobic Biodegradation of Pramipexole in Water. Draft Raw Data Package #41592R. Columbia, Missouri: ABC Laboratories, Inc., September 15, 1995.

C. Aerobic Biodegradation of Pramipexole in Water. Final Raw Data Package #41293R. Columbia, Missouri: ABC Laboratories, Inc, March 31 1995.

D. Aerobic Biodegradation of Pramipexole in Water. Quality Assurance Statement. Kalamazoo, Michigan: The Upjohn Co, April 17, 1995.

E. Determination of Air-Water Henry's Law Constant with Pramipexole. Final Report #42872. Columbia, Missouri: ABC Laboratories, Inc, December 7, 1995.

F. Determination of Air-Water Henry's Law Constant with Pramipexole. Final Raw Data Package #42872R. Columbia, Missouri: ABC Laboratories, Inc., December 7, 1995.

G. Determination of Air-Water Henry's Law Constant with Pramipexole. Quality Assurance Statement. Kalamazoo, Michigan: The Upjohn Co, December 11, 1995.

H. Determination of the Aqueous Photodegradation of Pramipexole. Final Report #41592. Columbia, Missouri: ABC Laboratories, Inc, September 15, 1995.

I. Determination of the Aqueous Photodegradation of Pramipexole. Quality Assurance Statement. Kalamazoo, Michigan: The Upjohn Co, September 28, 1995.

J. Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements. Center for Drug Evaluation and Research, CMC 6, November 1995.

K. Microbial Inhibition with Pramipexole. Final Report #41294. Columbia, Missouri: ABC Laboratories, Inc, March 23, 1995.

L. Microbial Growth Inhibition with Pramipexole. Quality Assurance Statement. Kalamazoo, Michigan: The Upjohn Co, April 4, 1995.

15. APPENDICES

Non-Confidential

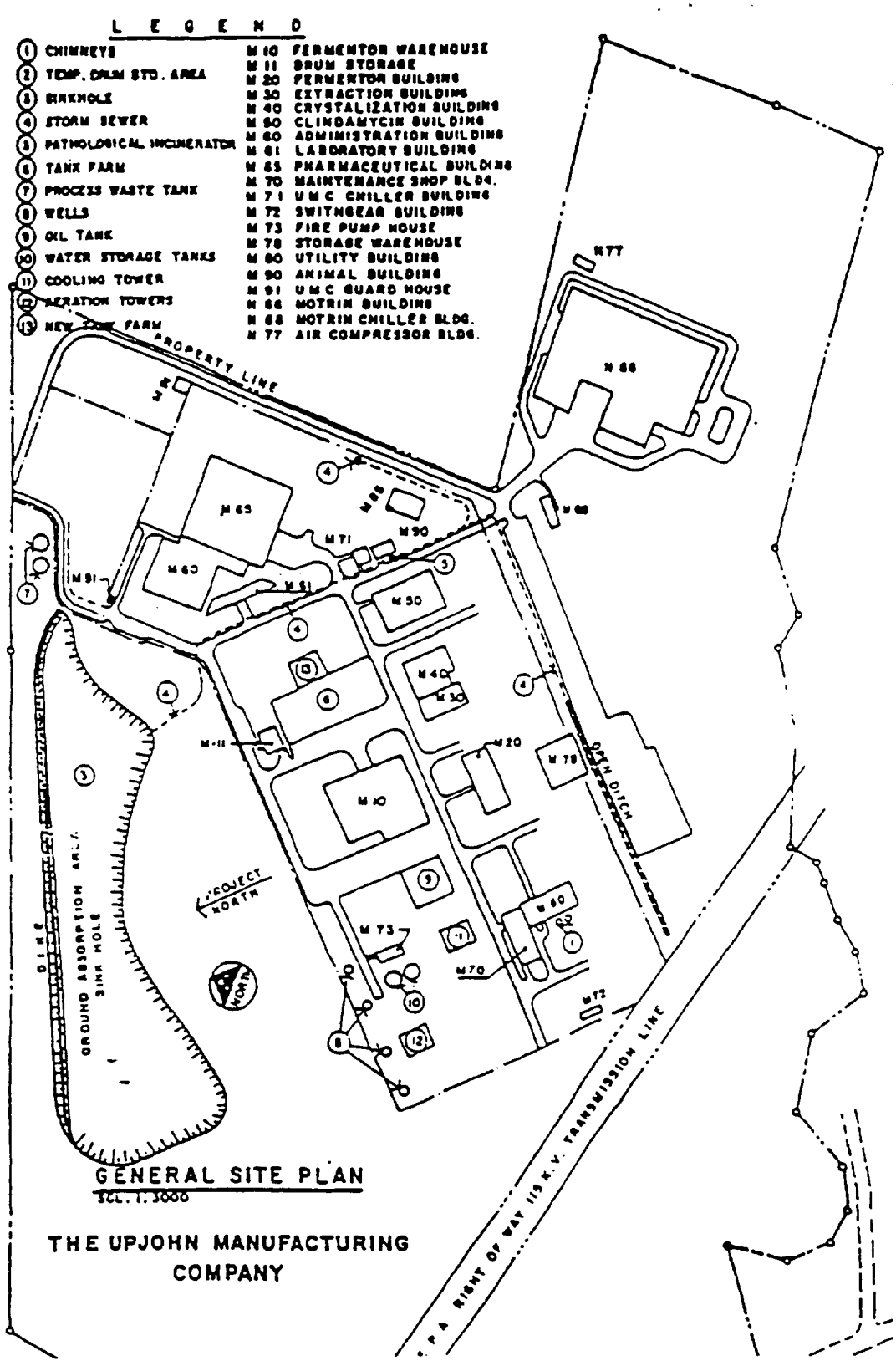
1 Map of UMC's Puerto Rico Pharmaceutical Manufacturing site complex
2 MSDS for the active ingredient, pramipexole
3 Pramipexole Tablets: List of Ingredients Used in Formulation
4 Certification letter covering BI manufacture: Ministry of the Environment and Forestry, Mainz, Germany
5 The Upjohn Manufacturing Company Permits Chart
6 The Upjohn Company Permits Chart
7 Chemical Summary

Confidential

8 Five-Year Marketing Figures

NON-CONFIDENTIAL
APPENDIX 1

Map of UMC's Puerto Rico Pharmaceutical Manufacturing Site Complex


L E G E N D
1 CHIMNEYS
2 TEMP. DRUM STD. AREA
3 SINKHOLE
4 STORM SEWER
5 PATHOLOGICAL INCINERATOR
6 TANK FARM
7 PROCESS WASTE TANK
8 WELLS
9 OIL TANK
10 WATER STORAGE TANKS
11 COOLING TOWER
12 AERATION TOWERS
13 NEW TANK FARM
M 10 FERMENTOR WAREHOUSE
M 11 DRUM STORAGE
M 20 FERMENTOR BUILDING
M 30 EXTRACTION BUILDING
M 40 CRYSTALIZATION BUILDING
M 50 CLINDAMYCIN BUILDING
M 60 ADMINISTRATION BUILDING
M 61 LABORATORY BUILDING
M 65 PHARMACEUTICAL BUILDING
M 70 MAINTENANCE SHOP BLDG.
M 71 U M C CHILLER BUILDING
M 72 SWITHGEAR BUILDING
M 73 FIRE PUMP HOUSE
M 78 STORAGE WAREHOUSE
M 80 UTILITY BUILDING
M 90 ANIMAL BUILDING
M 91 U M C GUARD HOUSE
N 66 MOTRIN BUILDING
N 68 MOTRIN CHILLER BLDG.
N 77 AIR COMPRESSOR BLDG.
PROPERTY LINE
N 77
N 66
M 65
M 60
M 71
M 90
M 91
M 30
M 40
M 11
M 20
M 78
M 10
M 73
M 70
M 72
M 60
DRAIN DITCH
DIKE
GROUND ABSORPTION AREA
SINK HOLE
PROJECT NORTH
NORTH
P P A RIGHT OF WAY 115 K.V. TRANSMISSION LINE
GENERAL SITE PLAN
SCL. 1: 3000
THE UPJOHN MANUFACTURING COMPANY

NON-CONFIDENTIAL
APPENDIX 2

Material Safety Data Sheet
Pramipexole

NON-CONFIDENTIAL
APPENDIX 2

MATERIAL SAFETY DATA SHEET

Revision Date: November 21, 1995
Agent ID#: 54

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

COMMON NAME: PRAMIPEXOLE
SYNONYMS: 104632-26-0 - CAS NUMBER
(S)-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazolediamine dihydrochloride monohydrate
U-98,528E - UPJOHN U#
MOLECULAR FORMULA: C10-H17-N3-S.2HCl.H2O
USE: Investigational drug for the treatment of Parkinson's disease.
MANUFACTURER/SUPPLIER: PHARMACIA & UPJOHN INC
7171 PORTAGE RD
KALAMAZOO, MI 49001-0199
TELEPHONE NUMBERS: (616) 323-5122 - (24 HOURS)
(616) 323-7555 - (8:00 a.m. - 4:30 p.m.)
(616) 385-7358 - (SAMPLE REQUEST/TECHNICAL ASSISTANCE)

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENT 1
COMMON NAME: Pramipexole
CHEMICAL NAME: (S)-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazolediamine dihydrochloride monohydrate
% BY WEIGHT: 100 %
CAS NUMBER: 104632-26-0
EXPOSURE LIMIT(S):
UPJOHN EXPOSURE LIMIT-TWA: 7 UG/M3

3. HAZARDS IDENTIFICATION

PRIMARY ROUTE(S) OF EXPOSURE: Skin contact, eye contact, ingestion and inhalation. As a hydrochloride, the substance is soluble in water, methanol and ethanol. The absorption from the gastrointestinal tract is

very good. Absorption after inhalation of dusts and aerosols, after contact with the eyes and, under certain circumstances, absorption of solutions through the intact skin are to be expected. It is expected that as the free base, the compound will penetrate intact skin very easily; this can lead rapidly to high blood levels, especially after skin contact with solutions in hydrophobic solvents.
EFFECTS OF OVEREXPOSURE: Overexposure to this material may lower blood pressure (especially when standing upright; nausea, vomiting, weakness, headache, dizziness and reduced heart rates. Hallucinations and confusion is possible with exposure to high concentrations.
MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Hypotension.

4. FIRST AID MEASURES

EYES: Flush with water for 15 minutes. Hold eyelids open to assure complete contact with water.
SKIN: Wash with soap and water. Remove contaminated clothing.
INHALATION: Remove from exposure.
INGESTION: Call a physician.
ANTIDOTE: The antidote for pramipexole is metoclopramide {Reglan(R)}. It is diluted and administered as a continuous intravenous infusion.
NOTES TO PHYSICIAN: The compound exerts highly potent agonistic effects in special pharmacological models of pre- and postsynaptic dopamine D2 receptors. Depending on the animal species investigated and the dose administered, sedation or agitation, decrease in blood pressure, drop in heart rate, sterotypic behavior, vomiting and reduction in sleeping time were observed as general pharmacodynamic effects. In case of intoxication, the patient should not be placed in an upright position. If there is a severe drop in blood pressure, the shock recovery position (elevation of the legs) can be recommended. If the patient vomits, it must be ensured that the airways are kept free and vomit is not aspirated.

5. FIRE FIGHTING MEASURES

FLASH POINT: Not applicable (solid).
EXTINGUISHING MEDIA: Water, carbon dioxide, or dry chemical.
FIRE-FIGHTING PROCEDURES: Wear self-contained breathing apparatus and full body protective equipment.
UNUSUAL FIRE OR EXPLOSION HAZARDS: As with all finely divided organic powders, it is advisable to eliminate explosion hazards by methods such

as grounding mechanical equipment in contact with the material to prevent the buildup of static electricity, inerting the atmosphere or controlling dust levels.
HAZARDOUS COMBUSTION PRODUCTS: Carbon monoxide. Carbon dioxide. Sulfur oxides. Nitrogen oxides. Acrid, flammable fumes may develop.

6. ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED: Remove ignition sources; control the generation of dust/vapors; provide ventilation and respiratory, skin and eye protection to prevent overexposure. Keep out of drains; prevent entry to surface water, groundwater and soil. Vacuum (with HEPA-filtered and explosion-proof equipment) or scoop spilled material and place in container.

7. EXPOSURE CONTROLS/PERSONAL PROTECTION

RESPIRATORY PROTECTION: Approved respirator or dust mask.
VENTILATION: Local exhaust at point of manufacture or use.
PROTECTIVE GLOVES: Rubber.
EYE PROTECTION: Safety glasses with side shields.

8. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE/PHYSICAL STATE: White, crystalline powder.
MELTING RANGE: 298 - 301 C (568 - 574 F) (with decomposition)
MOLECULAR WEIGHT: 302.27
SOLUBILITY IN WATER: > 10 % (at 20 C)
VAPOR PRESSURE: Negligible.
VOLATILITY: Negligible.

9. TOXICOLOGICAL INFORMATION

ACUTE STUDIES:
SKIN IRRITATION (RABBIT): Non-irritating.
INTRAVENOUS TOXICITY: Single intravenous doses of 10 to 100 micrograms were well tolerated in normal, healthy individuals. Adverse effects were mild and included headache and fatigue. Hypotension and other adverse effects may occur at higher doses.
INTRAVENOUS LD50 (RAT): 210 MG/KG (approximate)
INTRAVENOUS LD50 (MOUSE): 155 MG/KG (males)

IV LD50 for female mice is 188 mg/kg.
ORAL TOXICITY (HUMAN): In safety and tolerance studies in normal, healthy individuals, single oral doses up to 100 micrograms were well tolerated. Hypotension was observed at doses of 100 micrograms or above. The single oral maximum tolerated dose of 400 micrograms was established.
ORAL LD50 (RAT): 548 MG/KG (females)
Oral LD50 for male rats is >800 mg/kg.
ORAL LD50 (MOUSE): 1,700 MG/KG (approximate)
OTHER STUDIES:
GENOTOXICITY: Negative in the Ames assay, Micronucleus test, Cell Transformation assay in SHE cells, and the Chromosome Aberration assay in CHO cells.
REPRODUCTION/FERTILITY: No treatment-related effects were observed in rats at oral dosages of 0.1 mg/kg. Decreased fertility and low birth weight were observed at higher oral dosages of 2.5 mg/kg.
TERATOGENICITY: Studies in rats and rabbits revealed no teratogenic effects.

10. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL METHOD: Dispose of by incineration in accordance with applicable international, national, state, and/or local waste disposal regulations.

11. SHIPPING REGULATIONS

Not regulated for transportation by the United States Department of Transportation (DOT), International Maritime Organization (IMO), or International Air Transport Association (IATA). May be subject to state and/or local transportation requirements.

12. OTHER INFORMATION

REVIEWED BY: Environmental Health Sciences.
DISCLAIMER: The MSDS information is believed to be correct but should only be used as a guide. Pharmacia & Upjohn, Inc. disclaims any express or implied warranty as to the accuracy of the MSDS information and shall not be held liable for any direct, incidental or consequential damages resulting from reliance on the information.

13. LABELING

UPJOHN PRECAUTIONARY LABEL CODE(S): P
HAZARD: POTENT MATERIAL.
SIGNAL WORD: DANGER!
STATEMENT OF HAZARD/RISK PHRASE: May cause immediate and serious adverse effects.
PRECAUTIONARY MEASURES: Do not get in eyes, on skin, on clothing. Avoid breathing dust, vapor, mist or gas. Keep container closed. Use with adequate ventilation. Wash thoroughly after handling.

NON-CONFIDENTIAL
APPENDIX 3

Pramipexole Tablets: Ingredients Used in the Formulation

NON-CONFIDENTIAL
APPENDIX 3

Pramipexole Tablets: Ingredients Used in the Formulation

Name	CAS No.	M.W.	Formula	Appearance
Colloidal silicon dioxide	7631-86-9	60.09	SiO_2	Fine white powder
Corn starch	9005-84-9	162.06	$C_{16}H_{10}O_6$	White powder
Magnesium stearate	557-04-0	591.2	$C_{36}H_{70}MgO_4$	Fine white powder
Mannitol	69-65-8	182.17	$C_6H_{14}O_6$	White powder
Povidone	9003-39-8	N/A	$(C_6H_9NO)_x$	Off-white powder
Pramipexole	104632-26-0	302.27	$C_{10}H_{21}Cl_2N_3OS$	White crystalline powder
Purified water	7732-18-5	18.0	H_2O	Clear liquid

NON-CONFIDENTIAL
APPENDIX 4

Certification Letter

RheinlandPfalz

Ministerium für Umwelt und Forsten Postfach 3160 55021 Mainz

Ministerium für Umwelt und Forsten

Kaiser-Friedrich-Str 7, 55116 Mainz
Postfach 3160, 55021 Mainz

Telefon-Durchwahl (06131) 16-
Aktenzeichen: 10615 Mf- 82 331-29.1
Bearbeitet von:

Mainz, den 26. Oktober 1995

Bescheinigung

Zur Vorlage bei der zuständigen Behörde

Das Ministerium für Umwelt und Forsten Rheinland-Pfalz bescheinigt hiermit, daß

PRAMIPEXOL Wirkstoff

in Ingelheim/Rhein, Deutschland, durch die Firma

BOEHRINGER INGELHEIM KG
Binger Str. 173
D-55218 Ingelheim/Rhein

in Übereinstimmung mit allen deutschen Umweltschutzgesetzen und -verordnungen hergestellt wird.

To whom it may concern

The Ministerium für Umwelt und Forsten Rheinland-Pfalz hereby certifies that

PRAMIPEXOLE DRUG SUBSTANCE

is manufacrured in Ingelheim/Rhein, Germany, by

BOEHRINGER INGELHEIM KG
Binger Str. 173
D-55218 Ingelheim/Rhein

in accordance with all German environmental laws and regulations.

Im Auftrag

Dr. Wilhelm Streit
Leitender Ministerialrat

Telefon (Zentrale) 16-0 Telefax (06131) 164646 · Umwelt-Info Telefon (06131) 222425

NON-CONFIDENTIAL
APPENDIX 5

The Upjohn Manufacturing Company Permits Chart

NON-CONFIDENTIAL
APPENDIX 5

THE UPJOHN MANUFACTURING COMPANY PERMITS CHART

PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
Air Operating Permit	Puerto Rico Environmental Quality Board (EQB)	PFE-07-0391-0331-I-II-O	02/24/92	02/24/94[1]
Temporary Air Operating Permit	EQB	PFE-09-0694-0731-I-O	6/20/94	12/31/95
Extension to Temporary Air Operating Permit	EQB	PFE-09-1195-1427-I-O	submitted to EQB 11/2/95	[2]
Underground Injection Control (Class VI)	Puerto Rico EQB	UIC 84-0253	10/20/92	10/19/97
Wastewater Discharge Permit	Puerto Rico Aqueduct & Sewer Authority (PRASA)	GDA-93-202-051	11/18/95	11/18/97
Well Water Extraction Franchise	Puerto Rico Department of Natural & Environmental Resources	RF-95-92	06/18/92	07/18/95[2]
Biomedical Waste Generator	Puerto Rico EQB	DBM-07-91-9-0028-R-95	9/19/95	11/20/97
RCRA Part B	U.S. EPA	PRD-090398074	12/26/91	12/26/96

[1]Permit renewal application submitted on time; EQB sent letter extending permit until Title V permit is issued in 1995-1996.
[2]Permit renewal applications submitted on time; they remain in effect until acted upon.

NON-CONFIDENTIAL
APPENDIX 6

The Upjohn Company Permits Chart

NON-CONFIDENTIAL
APPENDIX 6

THE UPJOHN COMPANY PERMITS CHART

PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
Air Consent Judgment	Michigan Department of Natural Resources, Air Quality Division		03/15/91	08/01/96
Air Use Permit	MDNR, Air Quality Division	923-92	03/29/94	
National Pollutant Discharge Elimination System (NPDES)	Michigan Department of Natural Resources Michigan Water Resources Commission	MI0002941	09/20/90 reissued 12/1/95, effective 3/1/96	10/1/2000
RCRA/Michigan Hazardous Waste Management Act 451/Part 111 (On-site Incinerator)	Michigan Department of Natural Resources Waste Management Division	Incinerator operated as a RCRA Interim Status Treatment Storage and Disposal Facility under #MID 000820381 pending action on Act 451/ Part 111 permit application.		
Michigan Air Pollution Act 348 (On-site Incinerator)	Michigan Department of Natural Resources Air Quality Division	242-80	07/15/80 (revised to incorporate the Act 64 requirements) approved 05/26/93	non-expiring until modified

PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
Wastewater Discharge Permit	City of Kalamazoo Industrial Pretreatment Program	The City of Kalamazoo Sewer Use Ordinance and Sewer Use Regulations/Industrial Control Document	03/25/94	03/31/99
Chemical Process Water Management (CPWM) Injection System (Class 1 wells) Underground Injection Control Permit	U.S. EPA, Region 5 Safe Drinking Water Act	MI-077-1W-0001 MI-077-1W-0002	07/09/93	10/27/96

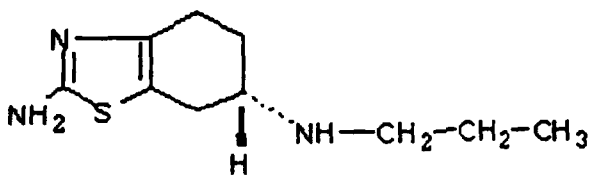
NON-CONFIDENTIAL
APPENDIX 7

Chemical Summary

APPENDIX 7

CHEMICAL SUMMARY

Structure



• 2 HCl
• H_2O

Chemical name	(S)-2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazol dihydrochloride monohydrate
CAS Registry number	104632-26-0
Upjohn U-number	98528E
USAN approved generic name	Pramipexole
Empirical formula	$C_{10}H_{21}Cl_2N_3OS$
Molecular weight	302.27
Melting point	296-301°C with decomposition
Appearance	white crystalline powder
Solubility, water (mg/mL)	> 20%

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20,667

	letterdate	stampdate	rec'd by chemist	COMPLETED
INITIAL SUBMISSION:	26-DEC-95	29-DEC-95	01-JAN-96	15-JUL-96
AMENDMENT:	06-SEP-96	09-SEP-96	11-SEP-96	16-SEP-96

OCT 16 [illegible]

CHEMIST REVIEW: # 2 **SPONSOR: PHARMACIA & UPJOHN**

REVIEW CHEMIST: M.Zarifa, Ph.D **ADDRESS:** **7000 Portage Road**
Kalamazoo, Michigan 49001-0199

PRODUCT NAME:

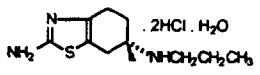
Proprietary:	**MIRAPEX**
USAN:	NA
INN:	**PRAMIPEXOLE**
Code Name/Number:	SND 919 CL 2 Y; U-98528E

DOSAGE FORM/ROUTE OF ADMINISTRATION: 0.125-mg, 0.25-mg,1-mg, 1.25-mg, and 1.5-mg compressed tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Parkinson's Disease

STRUCTURAL FORMULA & CHEMICAL NAME:

$H_{21}Cl_2N_3OS$ **Mol. Wt.** 302.27



(S)-2-Amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole dihydrochloride monohydrate

REMARKS: In this amendment the sponsor responds to the CMC deficiencies telefaxed to them on August 12, 1996. All missing/unclear information is now provided/ clarified or will follow as requested (see Telecon. Report 9/13/96). Updated 18-month stability data are provided.

CONCLUSIONS & RECOMMENDATIONS: RECOMMEND THAT **NDA 20-667 FOR PRAMIPEXOLE TABLETS IS APPROVED CONTINGENT UPON RECEIPT OF THE AGREED UPON REQUESTED INFORMATION.** INSPECTION OF THE FACILITIES WAS DONE AND AN ACCEPTABLE RECOMMENDATION FROM COMPLIANCE WAS RECEIVED (SEE CMC REVIEW 1). **THE REQUESTED EXPIRY DATE OF 24 MONTHS IS NOW ACCEPTABLE.**

Mona Zarifa

Mona Zarifa, Ph.D., Chemist

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/JPurvis
HFD-120/SBlum/MZarifa
HFD-810/CHoiberg (cover page, def.table only)
INIT:

SMB 10/11/96

filename: N020667.001

OCT 16 1996

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 20,667

	letterdate	stampdate	rec'd by chemist	COMPLETED
INITIAL SUBMISSION:	26-DEC-95	29-DEC-95	01-JAN-96	15-JUL-96
AMENDMENT:	07-OCT-96	08-OCT-96	11-OCT-96	11-OCT-96

CHEMIST REVIEW: # 3

SPONSOR: PHARMACIA & UPJOHN

REVIEW CHEMIST: M.Zarifa, Ph.D

ADDRESS: 7000 Portage Road
Kalamazoo, Michigan 49001-0199

PRODUCT NAME:

Proprietary: MIRAPEX

USAN: NA

INN: PRAMIPEXOLE

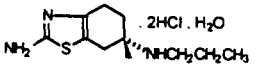
Code Name/Number: SND 919 CL 2 Y; U-98528E

DOSAGE FORM/ROUTE OF ADMINISTRATION: 0.125-mg, 0.25-mg,1-mg, 1.25-mg, and 1.5-mg compressed tablets/Oral

PHARMACOL.CATEGORY/PRINCIPAL INDICATION: Parkinson's Disease

STRUCTURAL FORMULA & CHEMICAL NAME:

$C_{10}H_{21}Cl_2N_3OS$ **Mol. Wt.** 302.27



(S)-2-Amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole dihydrochloride monohydrate

REMARKS: In this amendment the firm provides the information agreed upon in the Telecon dated 9/13/96. **SEE CMC REVIEW #2.**

CONCLUSIONS & RECOMMENDATIONS: RECOMMEND THAT **NDA 20-667 FOR PRAMIPEXOLE TABLETS IS APPROVED** as was recommended in CMC Review #2.

Mona Zarifa

Mona Zarifa, Ph.D., Chemist

cc: ORIG: NDA
HFD-120/Div. File
HFD-120/JPurvis
HFD-120/SBlum/MZarifa
HFD-810/CHoiberg (cover page, def.table only)
INIT:

10/11/96

filename: N020667.002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20667 Submission Dates: Dec. 26, 1995
SPONSOR: Upjohn Feb. 9, 1996
Kalamazoo MI March 20, 1996
DRUG: Pramipexole (0.125, 0.25, 1.0, 1.25, and 1.5 mg tablets)
INDICATION: Parkinson's Disease
TYPE OF SUBMISSION: NME
REVIEWER: Robert Harris, Ph.D.

SYNOPSIS:

Pramipexole is a dopamine receptor agonist used in the treatment of Parkinson's Disease. The sponsor plans on marketing 0.125, 0.25, 1.0, 1.25, and 1.5 mg tablets. The recommended starting dose is 0.125 mg administered tid. Patients are gradually titrated up to the lowest effective dose. The maximum dose described in labeling is 4.5 mg/day. Pramipexole can be administered in monotherapy or in combination therapy with carbidopa/levodopa.

Pramipexole is rapidly absorbed, reaching peak concentrations in approximately 2 hours. Over 90% of an oral dose reaches systemic circulation, indicating that pramipexole is almost completely absorbed and does not undergo first pass metabolism. Food does not affect the extent of pramipexole absorption, although Tmax is increased by about one hour when the drug is taken with a meal.

Pramipexole is extensively distributed, having a volume of distribution of approximately 500 L (cv = 20%). It is only about 15% bound to plasma proteins, binding primarily to albumin. Pramipexole distributes into red blood cells, having an erythrocyte to plasma ratio of approximately 2.

Pramipexole displays linear kinetics over the labeled dosing range. The terminal half life is about 8 h (cv = 20%) in young healthy volunteers and about 12 h (cv = 20%) in elderly volunteers. Steady state concentrations are achieved within 2 days of dosing.

Approximately 90% of a pramipexole dose is recovered in the urine, almost all as unchanged drug. Non renal routes may contribute to a small extent to pramipexole elimination, although no metabolites have been identified in the plasma or urine. The clearance of pramipexole is approximately 400 mL/min (cv = 25%), which is about three times higher than GFR. Thus, pramipexole is probably secreted via the renal organic cation transport system. Pramipexole clearance correlates moderately well with creatinine clearance.

Pramipexole clearance is about 30% lower in women than in men. This gender difference is primarily due to differences in body weight, and is greatly reduced after weight normalization.

Pramipexole clearance is also about 30% lower in the elderly compared to the young, indicating that pramipexole clearance, like creatinine clearance, decreases with age. This age related decline in pramipexole elimination is potentially noteworthy because the majority of Parkinson's patients are elderly. Pramipexole clearance also appears to be additionally reduced, by about 30%, in Parkinson's patients compared to healthy elderly volunteers. The reason for this is unknown, but may be related to the generally poorer overall health of Parkinson's patients. The effect of race on pramipexole elimination is unknown. Because the dosage of pramipexole is titrated up from a low starting dose, no specific alterations in pramipexole dosing based on gender, age, or the presence of Parkinson's disease are necessary.

Pramipexole clearance is reduced in renally impaired patients. The clearance of pramipexole was about 75% lower in patients with severe renal impairment (Clcr ≈ 20 mL/min) and about 60% lower in patients with moderate impairment (CLcr ≈ 30-49 mL/min) compared to healthy volunteers. There is a good correlation between creatinine clearance and pramipexole clearance in patients with decreased renal function. Thus, creatinine clearance can be used as a predictor of the degree of impairment of pramipexole clearance. Because of the decreased pramipexole clearance in patients with renal disease, lower daily doses should be administered. In addition, because of the increase in pramipexole half-life in these patients, it is possible to administer the drug less frequently. Pramipexole is eliminated extremely slowly in hemodialysis patients, making it virtually impossible to predict plasma concentration versus time profiles in these individuals. Very little pramipexole is eliminated by the dialysis process.

Hepatic impairment would not be expected to have a significant effect on the elimination of pramipexole, although this has not been studied.

Pramipexole clearance is reduced by concomitant administration of drugs that inhibit organic base secretion in the kidneys. Cimetidine, a known inhibitor of basic drug secretion caused a 35% reduction in pramipexole clearance. Probenecid, an agent that primarily inhibits organic acid secretion, but also may slightly inhibit base secretion, caused a 10% decrease in pramipexole clearance. Levodopa, carbidopa, and selegiline did not affect the pharmacokinetics of pramipexole. Pramipexole did not affect the systemic elimination of levodopa or carbidopa, although it did alter the rate of levodopa absorption as indicated by Tmax decreasing from about 2.5 hr to 0.5 hr. Drugs that inhibit or induce CYP enzymes would not be expected to alter pramipexole pharmacokinetics. It is possible that pramipexole inhibits CYP enzymes, although this possibility was not investigated by the sponsor.

The sponsor has adequately linked the to be marketed tablets to the tablets used in the clinical trials. The to be marketed tablets are manufactured in Puerto Rico. The dissolution methodology and specification submitted by the sponsor are acceptable.

COMMENTS:

1. Pramipexole elimination is so slow in patients with very severe renal impairment (creatinine CL < 10 mL/min) and in those undergoing hemodialysis that it is virtually impossible to predict the plasma levels upon multiple dosing to these patients. Thus, when writing labeling, the Medical Officer may want to put strong warnings about the use of pramipexole in renally impaired subjects. Please see review of Study 3060, starting on p. A30, for a detailed analysis of renal impairment data.

2. A maximal dose of 1.5 mg/TID was given to patients in the clinical efficacy studies. The table provided in the Renal Impairment subsection of the Dosage and Administration section of labeling (p.11 of this review) assumes that the Agency will decide to limit dosing to this amount within labeling. The third column of this table can be removed if it is decided that a maximum dose will not be given in labeling. Alternatively, the table could be replaced with a sentence instructing BID administration to patients with moderate renal impairment and QD administration to patients with severe renal impairment.

3. In the future, in addition to presenting separate gender analyses for phase I/II studies, the sponsor should also present mean data.

4. Pramipexole may inhibit certain cytochrome P-450 enzymes despite the fact it is not metabolized by these enzymes in vivo. The sponsor is requested to utilize to determine whether pramipexole inhibits any of the major P-450 enzymes.

5. The sponsor should analyze their population PK database to determine whether race affects pramipexole pharmacokinetics. In addition, if possible, they should examine whether the population PK database can provide any additional information regarding drug interactions.

6. The sponsor is requested to adopt the following dissolution methodology and specification for all tablet strengths:

Apparatus:	USP Dissolution Apparatus 2 (paddle)
Media:	citrate/phosphate buffer, pH 6.8
Volume:	500 mL
Speed:	50 rpm
Sampling time:	30 minutes
Specification:	not less than (Q)

7. The sponsor is requested to incorporate the labeling provided at the end of the Summary section of this review on page 9.

RECOMMENDATION: The submission (NDA 20,667) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and has been found to be acceptable. Please convey Comments 1-2 to the Medical Officer, and Comments 3-7 to the firm.

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SUMMARY

ABSORPTION

Rate: After administration of pramipexole, the time to reach maximal plasma concentration is approximately 2 hours (0065, 0069).

Extent: Over 90% of a pramipexole dose is absorbed from the GI tract (0030). Over 90% of the absorbed dose reaches systemic circulation (0030). Thus, pramipexole is almost completely bioavailable.

Food effect: Food does not affect the extent of pramipexole absorption, although Tmax is increased by about one hour when the drug is taken with food (0065).

DISTRIBUTION

Volume of distribution: The volume of distribution is about 500 L (cv = 20%), indicating that pramipexole distributes into tissues (0065, 0069, 0047).

Protein and red blood cell binding: Pramipexole is only about 15% bound to plasma proteins, binding primarily to albumin (0030). Pramipexole distributes into red blood cells, having an erythrocyte to plasma ratio of approximately 2 (0030).

METABOLISM AND ELIMINATION

Route: About 90% of a pramipexole dose is excreted in the urine as unchanged drug (0030). About 5% of a dose may be excreted in the urine as metabolites (0030), although no specific metabolites have been identified in the urine or plasma. In some pharmacokinetic studies submitted in the NDA (e.g. 0069, 0047), there appears to be a significant amount of nonrenal clearance (contributing up to 1/3 of the total clearance in study 0069). However, this may be largely due to fact that renal clearance was computed as CLpo multiplied by the fraction of the dose that was not recovered as unchanged drug in the urine. Thus, any drug that was not recovered unchanged in the urine, including drug that was not absorbed from the GI tract, was considered to be eliminated by nonrenal routes. Because it is often technically very difficult to recover 100% of a dose, a majority of what is called nonrenal clearance may simply be due to experimental limitations in accurately quantifying renally excreted drug. This concept is supported by the observation that the calculated nonrenal clearance of pramipexole decreases with renal impairment (0060, see discussion of renal impairment below).

Rate: The clearance and terminal half-life of pramipexole in healthy volunteers are about 400 (cv = 25%) mL/min and 8 h respectively (cv = 20%; 0061, 0065, 0069). These parameters are altered in certain special populations (see below). Pramipexole displays linear kinetics over the labeled dosing range (0047, 0017, 0062). The renal clearance of pramipexole is about three

...ives higher than creatinine clearance (130 mL/min), suggesting that pramipexole is extensively secreted via the renal organic cation transport system (0061).

SPECIAL POPULATIONS

General note: Pramipexole displays a moderate amount of intersubject variability (cv= 30% from population analysis). Certain factors such as age and gender account for a portion of this variability (see below), although most of this variability is unpredictable (see graphs from population analysis). Because the dose of pramipexole is titrated up from a low dose for each patient, the effects of covariates such as weight, age and gender should not affect the dosing of the drug. An exception is with patients who have moderate to severe renal impairment because pramipexole clearance is greatly reduced in these individuals. In these patients, a lower starting dose and less frequent dosing may be necessary (see below).

Gender: Pramipexole clearance is about 25% higher in men than in women (0064, 0063, 0047, 0069, population analysis). This gender difference is primarily due to differences in body weight, and is greatly reduced when data is weight normalized.

Age: Pramipexole clearance decreases with age (0069, population analysis). The half-life and clearance are about 40% longer and 30% lower respectively in the elderly (0069). Consistent with this result, creatinine clearance is also know to decrease with age.

Parkinson's Disease patients: Parkinson's disease patients are usually elderly, so they would be expected to eliminate pramipexole more slowly than did the young subjects studied in the phase I/II studies. In addition, a comparison of population pharmacokinetic data (patients) to data obtained in healthy elderly volunteers suggests that the clearance of pramipexole is further reduced, by about 30%, in Parkinson's patients compared to healthy elderly individuals (300 mL/min vs 425 mL/min). The reason for this additional decrease in clearance is unknown, but may be related to the poorer general health of Parkinson's patients. Because the clinical studies were performed in Parkinson's patients, and because doses are titrated for each patient, no dosage adjustments on account of Parkinson's disease are necessary.

Renal impairment: Pramipexole clearance is reduced in renally impaired patients. The clearance of pramipexole was about 75% lower in patients with severe renal impairment (Clcr ≈ 20 mL/min) and about 60% lower in patients with moderate impairment (CLcr ≈ 40 mL/min) compared to healthy volunteers. In patients with varying degrees of renal impairment, pramipexole clearance correlates very well with creatinine clearance (0060). Thus, creatinine clearance can be used as a predictor of the degree of impairment of pramipexole clearance. For example, if creatinine clearance is ½ normal then pramipexole clearance would be expected to be ½ normal. Because of the decrease in clearance in renally impaired patients, a lower or less frequent initial dose is necessary, and the maximal allowable doses must also be adjusted (see review of Study 0060 on page A30 and the OCPB labeling / Dosing and Administration section). Pramipexole is removed extremely slowly in patients who are undergoing dialysis, and it is very

difficult to predict plasma drug concentrations in these patients. Very little pramipexole is removed by the dialysis process.

Hepatic impairment: The effect of hepatic impairment on pramipexole pharmacokinetics has not been investigated. Because the drug is predominantly renally excreted, hepatic impairment would not be expected to have a notable effect on pramipexole elimination.

Race: The effect of race on pramipexole kinetics is unknown. The population pk database may contain information about this topic although the sponsor has not yet organized this information. Again, because the dose is titrated, racial differences in pramipexole kinetics, if present, are not likely to be clinically important.

DRUG INTERACTIONS

Effects of drugs on pramipexole renal elimination: Drugs that affect renal filtration or secretion would be expected to affect pramipexole elimination.

Cimetidine (300 mg, Q 6 h), a well characterized inhibitor of the renal organic cation transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (0061).

Probenecid, a drug that primarily inhibits organic anion transport, caused a 10% increase in pramipexole AUC, and half-life was not affected (0061). The small increase in AUC could be due to the fact that probenecid may weakly inhibit cation secretion.

Interactions with other drugs used in Parkinson's disease: *SINEMET* 25/250 (carbidopa/levodopa) administered as a single dose, did not affect pramipexole kinetics. Pramipexole (1.5 mg tid) did not affect the systemic elimination of carbidopa or levodopa, although it did appear to increase the rate of levodopa absorption (Tmax decreased by about 2 hr and Cmax increased by about 600 ng/mL)(0063). The sponsor speculates that this increase in the rate of absorption is due to a decrease in GI transit time caused by pramipexole binding to dopamine receptors in the GI tract.

Selegiline (5 mg bid) did not have a significant effect on pramipexole elimination when data from male (n=6) and female (n=5) subjects was combined. If the data was analyzed by gender, selegiline appeared to increase pramipexole clearance in women, and decrease pramipexole clearance in men. Due to the small number of subjects studied, it is inappropriate to make conclusions about gender differences based on this study. The effect of pramipexole on selegiline pharmacokinetics was not examined.

Effects of pramipexole on the elimination of other drugs: Pramipexole could potentially cause increases in the concentrations of drugs that are eliminated via renal secretion such as ranitidine, procainamide and quinidine. In addition, although pramipexole in not significantly metabolized by CYP enzymes in vivo, it could nonetheless inhibit these enzymes. The sponsor has not performed in vitro studies to examine the potential for pramipexole to inhibit CYP mediated drug

metabolism.

BIOEQUIVALENCE / FORMULATIONS

One large pivotal bioequivalence study has been performed (0062). This study utilized 0.125, 0.5 and 1 mg clinical tablets and 0.125 and 1.5 mg to be marketed tablets. The study demonstrated that the 0.125 mg to be marketed tablet (Puerto Rico,) is bioequivalent to the 0.125 mg clinical tablet, and that the 1.5 mg to be marketed tablet (Puerto Rico,) is bioequivalent to the 1.0 mg clinical tablet plus the 0.5 mg clinical tablet. Because the to be marketed dosage strengths are compositionally identical for all excipients, dissolution data has been used to approve the other tablet strengths.

ANALYTICAL

The sponsor utilized several analytical techniques including to measure pramipexole in biological fluids. was used in the pivotal biostudy. All of the assays are valid.

DISSOLUTION

Pramipexole is a highly soluble, highly permeable drug. It is very rapidly dissolved in aqueous solutions spanning the physiological pH range. The sponsor has utilized pH 6.8 citrate/phosphate buffer for the collection of all stability data. Pramipexole dissolution in this media is similar to its dissolution in pH 1.2 gastric fluid and in pH 7.5 intestinal fluid. Although dissolution is fast (over dissolved in 10 minutes), the sponsor has demonstrated that after one year of storage the dissolution is moderately slowed. Based on this information, the following dissolution specification, which is the same as requested by the sponsor, applies to all tablet strengths:

Apparatus:	USP Dissolution Apparatus 2 (paddle)
Media:	citrate/phosphate buffer, pH 6.8
Volume:	500 mL
Speed:	50 rpm
Sampling time:	30 minutes
Specification:	not less than (Q)

LABELING

CLINICAL PHARMACOLOGY

Pharmacokinetics

Pramipexole is rapidly absorbed reaching peak concentrations in approximately 2 hours. The absolute bioavailability of pramipexole is greater than 90% indicating that it is well absorbed and undergoes little presystemic metabolism. Food does not affect the extent of pramipexole absorption, although Tmax is increased by about one hour when the drug is taken with a meal.

Pramipexole is extensively distributed, having a volume of distribution of about 500 L (cv = 20%). It is about 15% bound to plasma proteins. Pramipexole distributes into red blood cells as indicated by an erythrocyte to plasma ratio of approximately 2.

Pramipexole displays linear kinetics over the clinical dosing range. Its terminal half-life is about 8 h in young healthy volunteers and about 12 h in elderly volunteers (see Pharmacokinetics in Special Populations). Steady-state concentrations are achieved within 2 days of dosing.

Metabolism and elimination

Urinary excretion is the major route of pramipexole elimination with 90% of a pramipexole dose recovered in the urine, almost all as unchanged drug. Non renal routes may contribute to a small extent to pramipexole elimination, although no metabolites have been identified in plasma or urine. The clearance of pramipexole is approximately 400 mL/min (cv = 25%), which is about three times higher than the glomerular filtration rate. Thus, pramipexole is secreted by the renal tubules, probably by the organic cation transport system.

Special Populations

Because the pramipexole dose is gradually titrated upward, no dosage adjustments based on gender, weight or age are necessary. However, renal insufficiency, which can cause a large decrease in the ability to eliminate pramipexole, may necessitate dosage adjustment (see Renal Insufficiency).

Gender: Pramipexole clearance is about 30% lower in women than in men, although most of this difference can be accounted for by differences in body weight. There is no difference in half-life between males and females.

Age: Pramipexole clearance decreases with age as the half-life and clearance are about 40% longer and 30% lower respectively in elderly (ages 65 years or older) compared to young healthy volunteers (ages less than 40 years). This difference is likely due to a reduction in renal function with age.

Parkinson's Disease Patients: A cross-study comparison of data suggests that the clearance of pramipexole may be reduced by about 30% in Parkinson's patients compared to healthy elderly volunteers. The reason for this decrease is unknown, but may be related to the poorer general health of Parkinson's patients. Because the dosing regimen is based on clinical efficacy studies performed in Parkinson's patients, no dosage adjustments are necessary.

Pediatric: The pharmacokinetics of pramipexole in the pediatric population has not been evaluated.

Race: The influence of race on pramipexole pharmacokinetics has not been evaluated.

Hepatic Insufficiency: The influence of hepatic insufficiency on pramipexole pharmacokinetics has not been evaluated. However, because approximately 90% of the recovered dose is excreted in the urine as unchanged drug, hepatic impairment would not be expected to have large effect on pramipexole elimination.

Renal Insufficiency: The clearance of pramipexole was about 75% lower in patients with severe renal impairment (Clcr ≈ 20 mL/min) and about 60% lower in patients with moderate impairment (CLcr ≈ 40 mL/min) compared to healthy volunteers. A less frequent starting dose is recommended in these patients (see Dosage and Administration). In patients with varying degrees of renal impairment, pramipexole clearance correlates well with creatinine clearance. Therefore, creatinine clearance can be used as a predictor of the extent of decrease in pramipexole clearance. Pramipexole clearance is extremely low in dialysis patients, as a negligible amount of pramipexole is removed in the dialysis process. Caution should be exercised when administering pramipexole to patients with renal disease.

Drug Interactions

Carbidopa/Levodopa: Carbidopa/levodopa did not influence the pharmacokinetics of pramipexole in healthy volunteers (n=10). Conversely, pramipexole did not alter the extent of absorption (AUC) or the elimination of carbidopa/levodopa, although it caused an increase in levodopa Cmax by about 40% and a decrease in Tmax from 2.5 to 0.5 hr.

Selegiline: In healthy volunteers (n=11), selegiline did not influence the pharmacokinetics of pramipexole.

Cimetidine: Cimetidine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (n=12).

Probenecid: Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic transporter did not notably influence pramipexole pharmacokinetics (n=12).

Other drugs eliminated via renal secretion: Drugs that interact with the renal organic cation

transport system including ranitidine, procainamide, and quinidine could potentially inhibit pramipexole elimination. Likewise, pramipexole could potentially inhibit the elimination of these drugs.

CYP Interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes in vivo. The ability of pramipexole to inhibit CYP enzymes has not been examined.

Patients with renal impairment:

Pramipexole Dose in the Renally Impaired		
Renal status	Starting Dose (mg)	Maximum Dose (mg) ?
Normal-mild impairment (Creatinine CL > 60 mL/min)	0.125 TID	1.5 TID
Moderate impairment (Creatinine CL = 35-59 mL/min)	0.125 BID	1.5 BID
Severe impairment (Creatinine CL = 15-34 mL/min)	0.125 QD	1.5 QD
Very severe impairment (Creatinine CL < 15 mL/min and hemodialysis patients)	WARNING	

Biopharm Day: June 18, 1996

Robert Z. Harris, Ph.D.
Division of Pharmaceutical Evaluation I

Robert Harris 7/26/96

FT initialed by Raman Baweja, Ph.D.

R. Baweja 7/26/96

cc: NDA 20667, HFD-120, HFD-860 (Harris, Baweja, Malinowski), HFD-340 (Viswanathan), Chron, Reviewer, Drug (Clarence Bott HFD-870, PKLN RM. 13B-31), HFD-19 (FOI).

ACTION

OCT 25 1996

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-667 Submission Date: August 1, 1996

Name, Strength(s), and Formulation: **Pramipexole 0.125 mg, 0.25 mg, 1.0 mg, 1.25 mg, and 1.5 mg Immediate-Release Tablets For Oral Administration.**

Sponsor: The Upjohn Company
Kalamazoo, MI

Indication: Parkinson's Disease

Reviewer: Safaa Ibrahim, Ph.D.

Type of Submission: Review of Population PK Analysis

REVIEW OF POPULATION PK ANALYSIS

This submission contains an updated study report for the population pharmacokinetic (PK) analysis of sparse plasma data that were obtained from patients who participated in Phase III clinical trials of pramipexole (Protocols M/2730/0001, M/2730/0004, and M/2730/0010).

Method:

(**Attachment 1** presents the detailed population PK method used in the analysis of pramipexole data).

Briefly, data obtained from 484 patients with pramipexole concentrations ranging from 0.75-23 ng/mL at doses ranging from 0.375-6 mg/day (given TID) were used in the analysis. The patient population in the database ranged in age from 31-87 years, in weight from 44-135 kg. Sixty-five percent of the population was male and 35 % female. Ninety-seven percent was white, 1.3 % black, and 1.7 % classified as 'other'. Creatinine clearance values ranged from 25-168 mL/min. Figure 1 shows the frequency distribution of pramipexole concentrations and sampling times. Figure 2 shows the frequency distribution of age, weight, and creatinine clearance values.

Table 1 shows the number of patients and pramipexole samples for each study for each medication coadministered with pramipexole. The medications included in the analysis were selegiline, trihexyphenidyl, cationic and anionic transport system medications, estrogen, benztropine, levodopa, and amantadine.

Using NONMEM computer program, a 1-compartment open model with first-order absorption and elimination was found to best describe the steady-state plasma concentration/time data of pramipexole. Interindividual variability (% CV in Cl and Ka) variability was modeled using the proportional error model. % CV in Vd could not be estimated due to numerical difficulties within NONMEM. Residual variability was modeled using the proportional error model.

Basic Model:

$$Cl = \Theta_{Cl} \cdot (1 + \eta_j^{Cl})$$
$$Vd = \Theta_{Vd}$$
$$Ka = \Theta_{Ka} \cdot (1 + \eta_j^{ka})$$

Parameter estimates, standard error of the estimates (%SEM), and interindividual and residual variabilities for the basic structural model (no covariates added) are shown in Table 2.

As pramipexole is eliminated almost entirely unchanged by the kidneys, creatinine clearance was added to the basic model as a linear predictor of pramipexole clearance. In order to obtain a more precise and more meaningful estimate for the intercept parameter, Θ_{Cl}, creatinine clearance values were centered by subtracting the minimum CrCl value (25.6 mL/min) for this population from each observation.

Table 3 shows the parameter estimates, % SEM, interindividual variability, and residual variability after accounting for creatinine clearance. Addition of CrCl decreased interindividual variability by 9 % from the basic model.

Basic Model with creatinine clearance:

$$Cl = \Theta_{Cl} + \Theta_{Cl}^{CrCl} (CrCl_j - 25.6) \cdot (1 + \eta_j^{Cl})$$
$$Vd = \Theta_{Vd}$$
$$Ka = \Theta_{Ka} \cdot (1 + \eta_j^{ka})$$

Various covariates (demographics and comedications) were then tested in the above model (i.e. basic model with CrCL) to determine their effect on the oral clearance of pramipexole. Age and weight were modeled as linear continous variables. Gender, race, obesity, comedications were modeled as dichotomous variables. The results of this modeling are presented in Tables 4-7. Covariates having significant effect on pramipexole Cl were incorporated in the final model (Table 8).

Results: (See also Attachment 1)

Table 4 shows the effect of demographics (weight, age, gender, race, and obesity) on the oral clearance of pramipexole. Gender, race, and obesity were found to be significant covariates affecting pramipexole Cl. Backward elimination of these covariates from the model (Table 5) showed that only gender and race affects pramipexole Cl.

The effect of concomitant medications on the oral clearance of pramipexole is shown in Tables 6. Initially, amantadine, drugs that are secreted by the cationic transport system (cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine), and drugs that are secreted by the anionic transport system (cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide), were found to be significant covariates affecting pramipexole Cl. Backward elimination of these comedications from the model (Table 7) showed that amantadine and drugs that are secreted by cationic transport system were significant covariates affecting pramipexole Cl.

The **final model** describing the population Pk model of pramipexole is as follows:

$$Cl = \Theta_{Cl} + \Theta_{Cl}^{CrCl} (CrCl_j - 25.6) * (1 + SEX * \Theta_{CL}^{SEX}) * (1 + RACE1 * \Theta_{Cl}^{RACE1}) * (1 + RACE2 * \Theta_{Cl}^{RACE2}) * (1 + X_j * \Theta_{Cl}^{X}) * (1 + \eta_j^{Cl})$$

$$Vd = \Theta_{Vd}$$

$$Ka = \Theta_{Ka} . (1 + \eta_j^{ka})$$

where X_j = concomitant medication in the jth patient.

Final parameter estimates (%SEM), interindividual variability, and residual variability are shown in Table 8 (Attachment 1). Figure 3 shows the scatterplots of predicted versus observed pramipexole concentrations, and weighted residuals versus predicted pramipexole concentration for the final PK model including patients demographics and concomitant medications.

For a white male patient with normal renal function (CrCl=120 mL/min) and not taking any comedication, the oral clearance of pramipexole would be:

$$Cl = 480 \text{ mL/min}$$

which is close to the value obtained in healthy volunteers, 400 mL/min.

In conclusion, population PK modeling of steady state plasma concentration data revealed that the oral clearance of pramipexole increased by 17 % in black patients and by 28 % in patients classified as 'Other' compared to white male patients. Drugs which are secreted by the cationic transport system decreased the oral clearance of pramipexole by 18 %. The effect of these covariates may not be clinically important as the dose of the drug is individually titrated to response.

COMMENTS

Reference is made to the labeling provided for pramipexole in the OCPB review of July 26, 1996:

1. Under **Special Populations/Race** (on Page 10), the statement: "The influence of race on pramipexole pharmacokinetics has not been evaluated" should be written as:

   "Population PK analysis revealed that oral clearance of pramipexole was 17 % higher in black male patients and was 28 % higher in male patients classified as 'Other' than in white male patients"

2. Under **Drug Interactions** on page 10, the following statement should be added:

   "Amantadine: Population PK analysis showed that amantadine does not alter the oral clearance of pramipexole (n=54 patients)."

3. Under **Drug Interactions** on page 10, the statement, "Other drugs eliminated via renal secretion: Drugs that interact with the renal....." should be modified to the following:

   "Other Drugs Eliminated Via Renal Secretion: Population PK analysis revealed that coadministration of drugs that are secreted by the cationic transport system (cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine) decreased the oral clearance of pramipexole by 18 % while those secreted by the anionic transport system (cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide) had no effect on the oral clearance of pramipexole.

COMMENT (To the Clinical Division):

New additional information from population PK analysis relates to race and drug interactions issues as mentioned in Comments 1-3 above. The technical aspects of the above Comments should be included in the labeling for pramipexole.

Safaa Ibrahim

Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

RD/FT initialed by R. Baweja, Ph.D. R. Baweja 10/25/96

cc: NDA # 20-667 (Suppl.), HFD-120, HFD-860 (Ibrahim, Baweja, Malinowski), Chron, Drug, and Reviewer Files (Clarence Bott, HFD-870, Parklawn, Rm 13B-31).

APR 30 1997

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,667
Pramipexole 0.125, 0.25, 1.0, 1.25 and 1.5 mg Tablets
Submission Dates: January 6, 1997; January 7, 1997;
January 24, 1997; January 27, 1997
Indication: Parkinson's Disease
Reviewer: Raman Baweja, Ph.D.

Pharmacia and Upjohn
Kalamazoo, MI 49001

OCTIRN
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REVIEW OF RESPONSES TO APPROVABLE LETTER

An Approvable letter was sent to the sponsor on December 23, 1996 for their drug, pramipexole, which is indicated for the treatment of Parkinson's disease. From an OCPB stanpoint the two main items in the letter were labelling and the sponsor's acceptance of the dissolution method and specification. The sponsor has now responded to the approvable letter and the review below will address their responses.

I. Labelling:

(A) Essentially the sponsor has accepted entire portions of OCPB's version of labelling that was sent to them in the approvable letter of December 23, 1996. Current labelling is attached to this review as Appendix I. There are two issues that need to be discussed, viz., Drug Interactions, and Dosing and Administration to the very severely renally impaired group. These follow:

(B) In the Drug Interactions section of labelling the sponsor was requested to expand the subsection on CYP Interactions. More specifically, it had been mentioned in the Agency's labelling that ...."The ability of Pramipexole to inhibit CYP enzymes has not been examined". It should be mentioned that pramipexole is about 90 % recovered in the urine as unchanged drug, and therefore, the issue was not whether it would be a substrate for CYP enzymes; instead the issue was if pramipexole would inhibit CYP enzymes.

The sponsor mentions that Pramipexole does not inhibit enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Further, the drug will not inhibit CYP2D6. All this is correct and can be placed in the labelling. Substantiation for this is provided in Appendix II which shows the percent inhibition of CYP P450 activity by various concentrations of pramipexole. These CYP P450 isoform activities were refractory to inhibition by pramipexole in its concentrations of 1μM and 10 μM (relevant concentrations), and 100 μM (very high and irrelevant concentration).
Appendix II also shows the Dixon plot of pramipexole's inhibition of debrisoquin 4-hydroxylation (CYP 2D6). Inhibition of CYP2D6 was observed with an apparent Ki of 30 μM indicating that pramipexole will not inhibit this enzyme even after administration of the highest recommended clinical dose of 1.5 mg t.i.d.

Overall then, it can be concluded that pramipexole will not inhibit the CYP P450 enzymes and this information can be placed in the labelling.

(C) Dosage and Administration section/Patients with Renal Impairment: A table was made in the labelling for dosing recommendations to this population. The sponsor has accepted these dosing recommendations as they pertain to the normal-mild group (starting dose: 0.125 mg tid), the moderately impaired group (starting dose: 0.125 mg bid), and the severe group (starting dose: 0.125 mg qd). However, it is with regard to the 'very severe impairment group (Creatinine Clearance < 15 ml/min and hemodialysis patients)' where a change has been made by the sponsor. We had written that for this group this be a "Warning"; instead the sponsor has written -- 'the use of Mirapex is not recommended.' The statement from the sponsor appears to be the stronger of the two, and the Medical Officer is requested to look into this.

II. Dissolution:

The Approvable letter requested that the sponsor adopt the following dissolution methodology and specification for all tablet strengths of pramipexole:

Apparatus:	USP Dissolution Apparatus 2 (paddle)
Media:	citrate/phosphate buffer, pH 6.8
Volume:	500 mL
Speed:	50 rpm
Sampling time:	30 minutes
Specification:	Not less than (Q)

In their response they mention that they accept the above methodology and specification for all strengths; this is acceptable to OCPB.

Comment to the Clinical Division: OCPB accepts the labelling as provided by the sponsor in their latest response. The Medical Officer is requested to note Item I (C) above -- Dosing in the 'very severely renally impaired group'.

Raman Baweja

Raman Baweja, Ph.D. 4/28/97.
Team Leader
DPE I

RD/FT Initialed by M.Mehta, Ph.D. MMM 4/30/97

cc: NDA 20,667, HFD-120, HFD-860 (Baweja, Mehta, Malinowski), Drug files (Barbara Murphy, Central Documents Room)

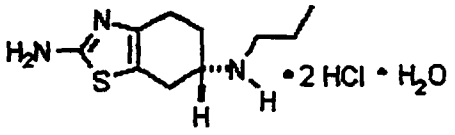
MIRAPEX™
brand of pramipexole tablets

APPENDIX I

DESCRIPTION

MIRAPEX Tablets contain pramipexole, a dopamine agonist indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease. The chemical name of pramipexole is (S)-2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole dihydrochloride monohydrate. Its empirical formula is $C_{10}H_{17}N_3S \cdot 2\ HCl \cdot H_2O$, and its molecular weight is 302.27.

The structural formula is:



Pramipexole is a white to off-white powder substance. Melting occurs in the range of 296°C to 301°C, with decomposition. Pramipexole is more than 20% soluble in water, about 8% in methanol, about 0.5% in ethanol, and practically insoluble in dichloromethane.

MIRAPEX Tablets, for oral administration, contain 0.125 mg, 0.25 mg, 1.0 mg, 1.25 mg, or 1.5 mg of pramipexole. Inactive ingredients consist of mannitol, corn starch, colloidal silicon dioxide, povidone, and magnesium stearate.

CLINICAL PHARMACOLOGY

Pramipexole is a nonergot dopamine agonist with high relative specificity in in vitro binding studies for the D_2 subfamily of dopamine receptors; it possesses full intrinsic activity for D_2 subfamily receptors and has a preferential affinity for D_3 receptors measured in vitro. 1a

The precise mechanism of action of pramipexole as a treatment for Parkinson's disease is unknown, although it is believed to be related to its ability to stimulate dopamine receptors in the striatum. This conclusion is supported by electrophysiologic studies in animals that have demonstrated that pramipexole influences striatal neuronal firing rates via activation of dopamine receptors in the striatum and the substantia nigra, the site of neurons that send projections to the striatum. Animal studies have also shown that pramipexole depresses dopamine synthesis, release, and turnover, and reduces neuronal degeneration of dopamine neurons in some experiments. The significance of this observation for humans is unknown. 1b

Pharmacokinetics

Pramipexole is rapidly absorbed, reaching peak concentrations in approximately 2 hours. The absolute bioavailability of pramipexole is greater than 90%, indicating that it is well absorbed and undergoes little presystemic metabolism. Food does not affect the extent of

pramipexole absorption, although the time of maximum plasma concentration (T_{max}) is increased by about 1 hour when the drug is taken with a meal.

Pramipexole is extensively distributed, having a volume of distribution of about 500 L (coefficient of variation [cv]=20%). It is about 15% bound to plasma proteins. Pramipexole distributes into red blood cells as indicated by an erythrocyte-to-plasma ratio of approximately 2.

Pramipexole displays linear pharmacokinetics over the clinical dosage range. Its terminal half-life is about 8 hours in young healthy volunteers and about 12 hours in elderly volunteers (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations). Steady-state concentrations are achieved within 2 days of dosing.

Metabolism and elimination: Urinary excretion is the major route of pramipexole elimination, with 90% of a pramipexole dose recovered in urine, almost all as unchanged drug. Nonrenal routes may contribute to a small extent to pramipexole elimination, although no metabolites have been identified in plasma or urine. The renal clearance of pramipexole is approximately 400 mL/min (cv=25%), approximately three times higher than the glomerular filtration rate. Thus, pramipexole is secreted by the renal tubules, probably by the organic cation transport system. 2a

Pharmacokinetics in Special Populations

Therapy with pramipexole is initiated at a subtherapeutic dosage and gradually titrated upward according to clinical tolerability to obtain the optimum therapeutic effect. Adjustment of the initial dose based on gender, weight, or age is not necessary. However, renal insufficiency, which can cause a large decrease in the ability to eliminate pramipexole, may necessitate dosage adjustment (see CLINICAL PHARMACOLOGY, Renal Insufficiency). 2b

Gender: Pramipexole clearance is about 30% lower in women than in men, but most of this difference can be accounted for by differences in body weight. There is no difference in half-life between males and females.

Age: Pramipexole clearance decreases with age as the half-life and clearance are about 40% longer and 30% lower, respectively, in elderly (aged 65 years or older) compared with young healthy volunteers (aged less than 40 years). This difference is most likely due to the well-known reduction in renal function with age, since pramipexole clearance is correlated with renal function, as measured by creatinine clearance (see CLINICAL PHARMACOLOGY, Renal Insufficiency). 2c

Parkinson's disease patients: A cross-study comparison of data suggests that the clearance of pramipexole may be reduced by about 30% in Parkinson's disease patients compared with healthy elderly volunteers. The reason for this difference appears to be reduced renal function in Parkinson's disease patients, which may be related to their poorer general health. ~~(The pharmacokinetics of pramipexole were comparable between early and advanced Parkinson's disease patients.)~~ 2d

Pediatric: The pharmacokinetics of pramipexole in the pediatric population have not been evaluated.

2e

Hepatic insufficiency: The influence of hepatic insufficiency on pramipexole pharmacokinetics has not been evaluated. Because approximately 90% of the recovered dose is excreted in the urine as unchanged drug, hepatic impairment would not be expected to have a significant effect on pramipexole elimination.

Renal insufficiency: The clearance of pramipexole was about 75% lower in patients with severe renal impairment (creatinine clearance approximately 20 mL/min) and about 60% lower in patients with moderate impairment (creatinine clearance approximately 40 mL/min) compared with healthy volunteers. A lower starting and maintenance dose is recommended in these patients (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). In patients with varying degrees of renal impairment, pramipexole clearance correlates well with creatinine clearance. Therefore, creatinine clearance can be used as a predictor of the extent of decrease in pramipexole clearance. Pramipexole clearance is extremely low in dialysis patients, as a negligible amount of pramipexole is removed by dialysis. Caution should be exercised when administering pramipexole to patients with renal disease.

CLINICAL STUDIES

The effectiveness of MIRAPEX Tablets in the treatment of Parkinson's disease (PD) was evaluated in a multinational drug development program consisting of seven randomized, controlled trials. Three were conducted in patients with early PD who were not receiving concomitant levodopa (MIRAPEX, N=388; placebo, N=235) and four were conducted in patients with advanced PD who were receiving concomitant levodopa (MIRAPEX, N=260; placebo, N=264). Among these seven studies, three studies provide the most persuasive evidence of pramipexole's effectiveness in the management of patients with PD who were and were not receiving concomitant levodopa. Two of these three trials enrolled patients with early PD (not receiving levodopa), and one enrolled patients with advanced PD who were receiving maximally tolerated doses of levodopa.

In all studies, the Unified Parkinson's Disease Rating Scale (UPDRS), or one or more of its subparts, served as the primary outcome assessment measure. The UPDRS is a four part multi-item rating scale intended to evaluate mentation (part I), activities of daily living (part II), motor performance (part III), and complications of therapy (part IV).

Part II of the UPDRS contains 13 questions relating to activities of daily living (ADL), which are scored from 0 (normal) to 4 (maximal severity) for a maximum (worst) score of 52. Part III of the UPDRS contains 27 questions (for 14 items) and is scored as described for part II. It is designed to assess the severity of the cardinal motor findings in patients with PD (eg, tremor, rigidity, bradykinesia, postural instability, etc), scored for different body regions, and has a maximum (worst) score of 108.

Studies in Patients With Early PD

Patients (N=599) in the two studies of early PD had a mean-disease duration of 2 years, limited or no prior exposure to levodopa (generally none in the preceding 6 months), and were not experiencing the "on-off" phenomenon and dyskinesia characteristic of later stages of the disease.

One of the two early PD studies (N=335) was a double-blind, placebo-controlled, parallel trial consisting of a 7-week dose-escalation period and a 6-month maintenance period.

Patients could be on selegiline, anticholinergics, or both, but could not be on levodopa products or amantadine. Patients were randomized to MIRAPEX or placebo. Patients treated with MIRAPEX had a starting daily dose of 0.375 mg and were titrated to a maximally tolerated dose, but no higher than 4.5 mg/day in three divided doses. At the end of the 6-month maintenance period, the mean improvement on part II (ADL) of the UPDRS was 1.9 in the group receiving MIRAPEX and -0.4 in the placebo group, a difference that was statistically significant. The mean improvement on part III of the UPDRS was 5.0 in the group receiving MIRAPEX and -0.8 in the placebo group, a difference that was also statistically significant. A statistically significant difference between groups in favor of MIRAPEX was seen beginning at Week 2 of the UPDRS part II (maximum dose 0.75 mg/day) and at Week 3 of the UPDRS part III (maximum dose 1.5 mg/day). 3d

The second early PD study (N=264) was a double-blind, placebo-controlled, parallel trial consisting of a 6-week dose-escalation period and a 4-week maintenance period. Patients could be on selegiline, anticholinergics, amantadine, or any combination of these, but could not be on levodopa products. Patients were randomized to 1 of 4 fixed doses of MIRAPEX (1.5 mg, 3.0 mg, 4.5 mg, or 6.0 mg per day) or placebo. At the end of the 4-week maintenance period, the mean improvement on part II of the UPDRS was 1.8 in the patients treated with MIRAPEX, regardless of assigned dose group, and 0.3 in placebo-treated patients. The mean improvement on part III of the UPDRS was 4.2 in patients treated with MIRAPEX and 0.6 in placebo-treated patients. No dose-response relationship was demonstrated. The between-treatment differences on both parts of the UPDRS were statistically significant in favor of MIRAPEX for all doses.

No differences in effectiveness based on age or gender were detected. There were too few non-Caucasian patients to evaluate the effect of race. Patients receiving selegiline or anticholinergics had responses similar to patients not receiving these drugs. 3e

Studies in Patients With Advanced PD

In the advanced PD study, the primary assessments were the UPDRS and daily diaries that quantified amounts of "on" and "off" time.

Patients in the advanced PD study (N=360) had a mean disease duration of 9 years, had been exposed to levodopa for long periods of time (mean 8 years), used concomitant levodopa during the trial, and had "on-off" periods.

The advanced PD study was a double-blind, placebo-controlled, parallel trial consisting of a 7-week dose-escalation period and a 6-month maintenance period. Patients were all treated with concomitant levodopa products and could additionally be on concomitant selegiline, anticholinergics, amantadine, or any combination. Patients treated with MIRAPEX had a starting dose of 0.375 mg/day and were titrated to a maximally tolerated dose, but no higher than 4.5 mg/day in three divided doses. At selected times during the 6-month maintenance period, patients were asked to record the amount of "off," "on," or "on with dyskinesia" time per day for several sequential days. At the end of the 6-month maintenance period, the mean improvement from baseline on part II of the UPDRS was 2.7 in the group treated with MIRAPEX and 0.5 in the placebo group, a difference that was statistically significant. The mean improvement on part III of the UPDRS was 5.6 in the group treated with MIRAPEX and 2.8 in the placebo group, a difference that was statistically significant. A statistically significant difference between groups in favor of 3f

MIRAPEX was seen at Week 3 of the UPDRS part II (maximum dose 0.75 mg/day) and at Week 2 of the UPDRS part III (maximum dose 1.5 mg/day). Dosage reduction of levodopa was allowed during this study if dyskinesia (or hallucinations) developed; levodopa dosage reduction occurred in 76% of patients treated with MIRAPEX versus 54% of placebo patients. On average, the levodopa dose was reduced 27%.

The mean number of "off" hours per day during baseline was 6 hours for both treatment groups. Throughout the trial, patients treated with MIRAPEX had a mean of 4 "off" hours per day, while placebo-treated patients continued to experience 6 "off" hours per day.

No differences in effectiveness based on age or gender were detected. There were too few non-Caucasian patients to evaluate the effect of race. 3g

INDICATIONS AND USAGE

MIRAPEX Tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The effectiveness of MIRAPEX was demonstrated in randomized, controlled trials in patients with early PD who were not receiving concomitant levodopa therapy as well as in patients with advanced disease on concomitant levodopa (see CLINICAL STUDIES).

CONTRAINDICATIONS

MIRAPEX Tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Symptomatic Hypotension: Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, with resulting orthostatic hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to an orthostatic challenge. For these reasons, Parkinson's disease patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk (see PRECAUTIONS, Information for Patients). 4a

In clinical trials of pramipexole, however, and despite clear orthostatic effects in normal volunteers, the reported incidence of clinically significant orthostatic hypotension was not greater among those assigned to MIRAPEX than among those assigned to placebo. This result is clearly unexpected in light of the previous experience with the risks of dopamine agonist therapy.

While this finding could reflect a unique property of pramipexole, it might also be explained by the conditions of the study and the nature of the population enrolled in the clinical trials. Patients were very carefully titrated, and patients with active cardiovascular disease or significant orthostatic hypotension at baseline were excluded.

Hallucinations: In the three double-blind, placebo-controlled trials in early PD, hallucinations were observed in 9% (35 of 388) of patients receiving MIRAPEX Tablets, 4b

compared with 2.6% (6 of 235) of patients receiving placebo. In the four double-blind, placebo-controlled trials in advanced PD, where patients received MIRAPEX and concomitant levodopa, hallucinations were observed in 16.5% (43 of 260) of patients receiving MIRAPEX, compared with 3.8% (10 of 264) of patients receiving placebo. Hallucinations were of sufficient severity to cause discontinuation of treatment in 3.1% of the early PD patients and 2.7% of the advanced PD patients compared with about 0.4% of placebo patients in both populations.

Age appears to increase the risk of hallucinations attributable to pramipexole. In the early PD patients, the risk of hallucinations was 1.9 times greater than placebo in patients younger than 65 years and 6.8 times greater than placebo in patients older than 65 years. In the advanced PD patients, the risk of hallucinations was 3.5 times greater than placebo in patients younger than 65 years and 5.2 times greater than placebo in patients older than 65 years. 4c

PRECAUTIONS

General

5a

Renal: Since pramipexole is eliminated through the kidneys, caution should be exercised when prescribing MIRAPEX Tablets to patients with renal insufficiency (see DOSAGE AND ADMINISTRATION).

Dyskinesia: MIRAPEX may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate preexisting dyskinesia. Decreasing the dose of levodopa may ameliorate this side effect.

Retinal degeneration in albino rats: Retinal degeneration was observed in albino rats in the 2-year carcinogenicity study, but the significance of this effect in humans is not known (see ANIMAL TOXICOLOGY). 5b

Events Reported With Dopaminergic Therapy

Although the events enumerated below have not been reported in association with the use of pramipexole in clinical trials, they are associated with the use of other dopaminergic drugs. The expected incidence of these events, however, is so low that even if pramipexole caused these events at rates similar to those attributable to other dopaminergic therapies, it would be unlikely that even a single case would have occurred in a cohort of the size exposed to pramipexole in studies to date. 5c

Withdrawal-emergent hyperpyrexia and confusion: Although not reported with pramipexole in clinical trials, a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy. 5c

Fibrotic complications: Although not reported with pramipexole in clinical trials, cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot-derived dopaminergic agents. These pulmonary events were associated with long-term treatment (longer than 6 months) 5c

and reverted to normal in those cases in which treatment was terminated.

Information for Patients: Patients should be instructed to take MIRAPEX only as prescribed.

Patients should be informed that hallucinations can occur and that the elderly are at a higher risk than younger patients with PD.

Patients may develop postural (orthostatic) hypotension, with or without symptoms such as dizziness, nausea, fainting or blackouts, and sometimes, sweating. Hypotension may occur more frequently during initial therapy. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods, and especially at the initiation of treatment with MIRAPEX.

Since any psychoactive drug may impair judgement, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with MIRAPEX does not adversely affect their ability to engage in such activities. Because of the possible additive sedative effects, caution should also be used when patients are taking other CNS depressants in combination with MIRAPEX. 5d

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see PRECAUTIONS, Pregnancy). 5e

Because of the possibility that pramipexole may be excreted in breast milk, patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.

If patients develop nausea, they should be advised that taking MIRAPEX with food may reduce the occurrence of nausea.

Laboratory Tests: During the development of MIRAPEX, no systematic abnormalities on routine laboratory testing were noted. Therefore, no specific guidance is offered regarding routine monitoring; the practitioner retains responsibility for determining how best to monitor the patient in his or her care.

Drug Interactions

Carbidopa/ levodopa: Carbidopa/levodopa did not influence the pharmacokinetics of pramipexole in healthy volunteers (N=10). Pramipexole did not alter the extent of absorption (AUC) or the elimination of carbidopa/levodopa, although it caused an increase in levodopa C_{max} by about 40% and a decrease in T_{max} from 2.5 to 0.5 hours.

Selegiline: In healthy volunteers (N=11), selegiline did not influence the pharmacokinetics of pramipexole.

Amantadine: Population pharmacokinetic analysis suggests that amantadine is unlikely to alter the oral clearance of pramipexole (N=54).

Cimetidine: Cimetidine, a known inhibitor of renal tubular secretion of organic bases via

the cationic transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (N=12).

Probenecid: Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic transporter, did not noticeably influence pramipexole pharmacokinetics (N=12).

Other drugs eliminated via renal secretion: Population pharmacokinetic analysis suggests that coadministration of drugs that are secreted by the cationic transport system (eg, cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine) decreases the oral clearance of pramipexole by about 20%, while those secreted by the anionic transport system (eg, cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide) are likely to have little effect on the oral clearance of pramipexole.

CYP interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes in vivo or in vitro. Pramipexole does not inhibit CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Inhibition of CYP2D6 was observed with an apparent Ki of 30 µM, indicating that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the highest recommended clinical dose (1.5 mg tid). OK; (accept). 5f

Dopamine antagonists: Since pramipexole is a dopamine agonist, it is possible that dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of MIRAPEX. 5g

Drug/Laboratory Test Interactions: There are no known interactions between MIRAPEX and laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered in the diet to Chbb:NMRI mice at doses of 0.3, 2, and 10 mg/kg/day (0.5, 3.4, and 17.2 times the highest recommended clinical dose [1.5 mg tid] on a mg/m^2 basis). In mice dosed at these levels, the plasma levels were at least 0.1, 0.49, and 4.4 times the observed C_{max} in humans dosed 1.5 mg tid. Pramipexole was administered in the diet to Wistar rats at 0.3, 2, and 8 mg/kg/day (0.8, 5, and 20 times the highest clinical dose on a mg/m^2 basis). In rats dosed at these levels, the plasma AUC was 0.3, 2.5, and 12.5 times the AUC in humans dosed at 1.5 mg tid. 5h

Testicular Leydig cell adenomas were found in male rats as follows: 13 of 50 control group A males, 9 of 60 control group B males, 17 of 50 males given 0.3 mg/kg/day, 22 of 50 males given 2 mg/kg/day, and 22 of 50 males given 8 mg/kg/day. In contrast to the findings in rats, examination of the testes from mice after 2 years of treatment did not exhibit evidence of a drug-related increase in Leydig cell adenomas. Leydig cell hyperplasia and increased numbers of adenomas are attributed to pramipexole-induced decreases in serum prolactin levels, causing a down-regulation of Leydig cell luteinizing hormone (LH) receptors and a compensatory elevation of LH secretion by the pituitary gland. The endocrine mechanisms believed to be involved in rats are not relevant to humans.

Pramipexole was not mutagenic or clastogenic in a battery of assays including the in vitro Ames assay, V79 gene mutation assay for HGPRT mutants, and chromosomal aberration assay in Chinese hamster ovary cells, and the in vivo mouse micronucleus assay.

In rat fertility studies, pramipexole at a dose of 2.5 mg/kg/day (6.2 times the highest clinical dose on a mg/m^2 basis), prolonged estrus cycles and inhibited implantation. In rats dosed at 2.5 mg/kg/day, the plasma levels were 19.3 times the observed C_{max} in humans dosed 1.5 mg tid. These effects were associated with reductions in serum levels of prolactin, a hormone necessary for implantation and maintenance of early pregnancy in rats.

Pregnancy: Pregnancy Category B. When pramipexole was given to female rats throughout pregnancy, implantation was inhibited at a dose of 2.5 mg/kg/day (6.2 times the highest clinical dose on a mg/m^2 basis). In rats dosed at 2.5 mg/kg/day, the plasma levels were 19.3 times the observed C_{max} in humans dosed 1.5 mg tid. Administration of 0.1, 0.5, or 1.5 mg/kg/day of pramipexole to pregnant rats during the period of organogenesis (gestation days 7 through 16) resulted in a high incidence of total resorption of embryos at 1.5 mg/kg/day (3.7 times the highest clinical dose on a mg/m^2 basis), but no teratogenic effects were observed. In rats dosed at these levels, the plasma AUC was 0.3, 1.5, and 4.3 times the AUC in humans dosed at 1.5 mg tid. These findings are thought to be due to the prolactin-lowering effect of pramipexole, since prolactin is necessary for implantation and maintenance of early pregnancy in rats (but not rabbits or humans). There was no evidence of adverse effects on embryo-fetal development following administration of up to 10 mg/kg/day (47.2 times the highest clinical dose on a mg/m^2 basis) to pregnant rabbits during organogenesis. In rabbits dosed at 10 mg/kg/day, the plasma AUC was 71 times that in humans dosed at 1.5 mg tid. Postnatal growth was inhibited in the offspring of rats treated with 0.5 mg/kg/day (approximately equivalent to the highest clinical dose on a mg/m^2 basis) or greater during the latter part of pregnancy and throughout lactation. In pregnant rats dosed at 0.5 mg/kg/day, the plasma AUC was 1.5 times the AUC in humans dosed at 1.5 mg tid. 5i

There are no studies of pramipexole in human pregnancy. Because animal reproduction studies are not always predictive of human response, pramipexole should be used during pregnancy only if clearly needed.

Nursing Mothers: A single-dose, radio-labeled study showed that drug-related materials were excreted into the breast milk of lactating rats. Concentrations of radioactivity in milk were three to six times higher than concentrations in plasma at equivalent time points.

Other studies have shown that pramipexole treatment resulted in an inhibition of prolactin secretion in humans and rats.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from pramipexole, a decision should be made as to whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of MIRAPEX in pediatric patients has not been established.

Geriatric Use: Pramipexole total oral clearance was approximately 30% lower in subjects older than 65 years compared with younger subjects, because of a decline in pramipexole renal clearance due to an age-related reduction in renal function. This resulted in an increase in elimination half-life from approximately 8.5 hours to 12 hours. In clinical studies, 38.7% of patients were older than 65 years. There were no apparent differences in efficacy or safety between older and younger patients, except that the relative risk of hallucination associated with the use of MIRAPEX was increased in the elderly. 5j

ADVERSE EVENTS

During the premarketing development of pramipexole, patients with either early or advanced PD were enrolled in clinical trials. Apart from the severity and duration of their disease, the two populations differed in their use of concomitant levodopa therapy. Patients with early disease did not receive concomitant levodopa therapy during treatment with pramipexole; those with advanced PD all received concomitant levodopa treatment. Because these two populations may have differential risks for various adverse events, this section will, in general, present adverse-event data for these two populations separately.

Early Parkinson's Disease

In the three double-blind, placebo-controlled trials of patients with early Parkinson's disease, the most commonly observed adverse events (>5%) that were numerically more frequent in the group treated with MIRAPEX Tablets were nausea, dizziness, somnolence, insomnia, constipation, asthenia, hallucinations, accidental injury, and dyspepsia. 6a

Approximately 12% of 388 patients with early PD and treated with MIRAPEX who participated in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 11% of 235 patients who received placebo. The adverse events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [3.1% on MIRAPEX vs 0.4% on placebo]; dizziness [2.1% on MIRAPEX vs 1% on placebo]; somnolence [1.6% on MIRAPEX vs 0% on placebo]; extrapyramidal syndrome [1.6% on MIRAPEX vs 6.4% on placebo]; headache and confusion [1.3% and 1.0%, respectively, on MIRAPEX vs 0% on placebo]); and gastrointestinal system (nausea [2.1 % on MIRAPEX vs 0.4% on placebo]). The events that appeared to be dose related were hallucinations, dizziness, and somnolence. 6b

Adverse-event incidence in controlled clinical studies in early PD: Table 1 lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies in early Parkinson's disease that were reported by ≥1% of patients treated with MIRAPEX and were numerically more frequent than in the placebo group. In these studies, patients did not receive concomitant levodopa. Adverse events were usually mild or moderate in intensity. 6c

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution

of drug and nondrug factors to the adverse-event incidence rate in the population studied.

Table 1
Treatment-Emergent Adverse-Event* Incidence in Double-Blind, Placebo-Controlled Trials in Early Parkinson's Disease (Events ≥1% of Patients Treated With MIRAPEX and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	MIRAPEX N=388	Placebo N=235
Body as a Whole		
Asthenia	13.9	11.5
Accidental injury	8.8	8.5
General edema	4.9	3.0
Malaise	1.8	0.9
Reaction unevaluable	1.5	0.9
Fever	1.0	0.4
Cardiovascular System		
Syncope	1.3	0.9
Digestive System		
Nausea	27.6	17.9
Constipation	13.7	6.0
Dyspepsia	7.2	6.8
Anorexia	4.4	2.1
Dysphagia	1.8	0.4
Flatulence	1.8	1.7
Tooth disease	1.8	1.7
Metabolic & Nutritional System		
Peripheral edema	4.9	4.3
Decreased weight	1.8	0.4
Musculoskeletal System		
Leg cramps	4.4	3.8
Twitching	1.5	1.3
Nervous System		
Dizziness	25.0	24.3
Somnolence	21.9	8.9
Insomnia	17.0	11.5
Hallucinations	9.0	2.6
Dream abnormalities	4.4	4.3
Confusion	4.1	1.3
Amnesia	3.6	1.7
Hypesthesia	2.8	0.9
Dystonia	1.8	1.3
Akathisia	1.5	0.0
Thinking abnormalities	1.5	0.4
Decreased libido	1.3	0.0
Myoclonus	1.3	0.4

Skin & Appendages		
Pruritus	1.3	0.9
Special Senses		
Accommodation abnormalities	2.8	2.6
Vision abnormalities	2.6	0.0
Tinnitus	1.3	0.9
Diplopia	1.0	0.9
Taste perversions	1.0	0.9
Urogenital System		
Impotence	1.8	1.3

* Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

Other events reported by 1% or more of patients with early PD and treated with MIRAPEX but reported equally or more frequently in the placebo group were infection, headache, pain, tremor, back pain, postural hypotension, hypertonia, depression, abdominal pain, anxiety, diarrhea, rash, ataxia, dry mouth, extrapyramidal syndrome, pharyngitis, sinusitis, sweating, rhinitis, urinary tract infection, vasodilation, flu syndrome, increased saliva, dyspnea, increased cough, gait abnormalities, urinary frequency, vomiting, allergic reaction, hypertension, hypokinesia, increased creatine PK, nervousness, chest pain, neck pain, paresthesia, tachycardia, vertigo, voice alteration, conjunctivitis, and paralysis. 6e

Among the treatment-emergent adverse events in patients with early PD who were treated with MIRAPEX, the following appeared to exhibit a positive relationship to dose: constipation, somnolence, and insomnia. In addition, the occurrence of common adverse events such as confusion, dizziness, nausea, and headache in patients treated with MIRAPEX showed a tendency to diminish with time. 6f 6g

Advanced Parkinson's Disease

In the four double-blind, placebo-controlled trials of patients with advanced Parkinson's disease, the most commonly observed adverse events (>5%) that were numerically more frequent in the group treated with MIRAPEX and concomitant levodopa were postural (orthostatic) hypotension, dyskinesia, extrapyramidal syndrome, insomnia, dizziness, hallucinations, accidental injury, dream abnormalities, confusion, constipation, asthenia, somnolence, dystonia, gait abnormality, hypertonia, dry mouth, amnesia, urinary frequency, and leg cramps. 6h

Approximately 12% of 260 patients with advanced PD who received MIRAPEX and concomitant levodopa in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 16% of 264 patients who received placebo and concomitant levodopa. The events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [2.7% on MIRAPEX vs 0.4% on placebo]; dyskinesia [1.9% on MIRAPEX vs 0.8% on placebo]; extrapyramidal syndrome [1.5% on MIRAPEX vs 4.9% on placebo]; dizziness [1.2% on MIRAPEX vs 1.5% on placebo]; and confusion [1.2% on MIRAPEX vs 2.3% on placebo]); and cardiovascular system (postural [orthostatic] hypotension [2.3% on MIRAPEX vs 1.1% on placebo]). The 6i

adverse events that appeared to be dose related were extrapyramidal syndrome and confusion.

Adverse-event incidence in controlled clinical studies in advanced PD: Table 2 lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies in advanced Parkinson's disease that were reported by ≥1% of patients treated with MIRAPEX and were numerically more frequent than in the placebo group. In these studies, MIRAPEX or placebo was administered to patients who were also receiving concomitant levodopa. Adverse events were usually mild or moderate in intensity. 6j

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-events incidence rate in the population studied.

Table 2
Treatment-Emergent Adverse-Event* Incidence in Double-Blind, Placebo-Controlled Trials in Advanced Parkinson's Disease (Events ≥ 1% of Patients Treated With MIRAPEX and Numerically More Frequent Than in the Placebo Group) 6k

Body System/ Adverse Event	MIRAPEX† N=260	Placebo† N=264
Body as a Whole		
Accidental injury	16.5	14.8
Asthenia	10.0	8.0
General edema	3.8	2.7
Chest pain	3.1	1.5
Malaise	2.7	1.9
Cardiovascular System		
Postural hypotension	52.7	48.1
Digestive system		
Constipation	10.0	8.7
Dry Mouth	6.5	2.7
Flatulence	1.2	0.8
Metabolic & Nutritional System		
Peripheral edema	2.3	0.8
Increased creatine PK	1.2	0.4
Musculoskeletal System		
Leg cramps	5.4	4.5
Arthritis	2.7	1.1
Twitching	2.3	0.0
Bursitis	1.5	0.4
Myasthenia	1.2	0.0

Nervous System		
Dyskinesia	47.3	31.4
Extrapyramidal syndrome	27.7	25.8
Insomnia	26.9	21.6
Dizziness	25.8	25.0
Hallucinations	16.5	3.8
Dream abnormalities	10.8	9.5
Confusion	10.0	7.2
Somnolence	8.8	6.1
Dystonia	8.1	7.2
Gait abnormalities	6.9	4.9
Hypertonia	6.5	6.1
Amnesia	5.8	4.2
Akathisia	2.7	2.3
Thinking abnormalities	2.7	1.5
Hypesthesia	1.9	1.5
Paranoid reaction	1.9	0.4
Delusions	1.2	0.4
Sleep disorders	1.2	0.0
Respiratory System		
Dyspnea	3.8	3.0
Rhinitis	2.7	1.1
Sinusitis	2.3	1.5
Pneumonia	1.9	0.0
Skin & Appendages		
Sweating	3.5	3.4
Skin disorders	1.9	1.1
Pruritus	1.2	0.8
Special Senses		
Accommodation abnormalities	3.8	2.3
Vision abnormalities	3.1	0.8
Conjunctivitis	1.2	1.1
Diplopia	1.2	0.0
Lacrimation disorders	1.2	0.8
Urogential System		
Urinary frequency	5.8	2.7
Urinary tract infection	3.8	3.4
Urinary incontinence	1.9	1.1

*Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.
†Patients received concomitant levodopa.

Other events reported by 1% or more of patients with advanced PD and treated with MIRAPEX but reported equally or more frequently in the placebo group were nausea, pain, infection, headache, depression, tremor, hypokinesia, anorexia, back pain, dyspepsia, 61

ataxia, flu syndrome, diarrhea, myalgia, abdominal pain, anxiety, rash, paresthesia, hypertension, increased saliva, tooth disorder, apathy, hypotension, vasodilation, vomiting, increased cough, nervousness, neck pain, syncope, arthralgia, dysphagia, palpitations, pharyngitis, and vertigo.

Among the treatment-emergent adverse events in patients with advanced PD who were treated with MIRAPEX, the following appeared to exhibit a positive relationship to dose: constipation and extrapyramidal syndrome. In addition, the occurrence of common adverse events such as confusion, dizziness, headache, and nausea in patients treated with MIRAPEX showed a tendency to diminish with time. 6m 6n

Adverse Events; Relationship to Age, Gender, and Race: Among the treatment-emergent adverse events in patients treated with MIRAPEX, hallucination appeared to exhibit a positive relationship to age. No gender-related differences were observed. Only a small percentage (4%) of patients enrolled were non-Caucasian, therefore, an evaluation of adverse events related to race is not possible. 6o

Other Adverse Events Observed During All Phase 2/3 Clinical Trials: MIRAPEX has been administered to 1,408 individuals during all clinical trials (Parkinson's disease and other patient populations), 648 of whom were in seven double-blind, placebo-controlled Parkinson's disease trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 1,408 individuals exposed to MIRAPEX who experienced events of the type cited on at least two occasions (one if the event is serious) while receiving MIRAPEX. All reported events, except those already listed above, are included, without regard to determination of a causal relationship to MIRAPEX. 6p

Events are further classified within body-system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients and infrequent adverse events are those occurring in 1/100 to 1/1,000 patients. 6q

Body as a whole - *Infrequent*: enlarged abdomen, death, fever, suicide attempt.

Cardiovascular system - *Infrequent*: peripheral vascular disease, myocardial infarction, angina pectoris, atrial fibrillation, heart failure, arrhythmia, atrial arrhythmia, pulmonary embolism.

Digestive system - *Infrequent*: thirst.

Musculoskeletal system - *Infrequent*: joint disorder, myasthenia.

Nervous system - *Infrequent*: agitation, CNS stimulation, hyperkinesia, psychosis, convulsions.

Respiratory system - *Infrequent*: pneumonia.

Special senses - *Infrequent*: cataract, eye disorder, glaucoma.

Urogenital system - *Infrequent*: dysuria, abnormal ejaculation, prostate cancer, hematuria, prostate disorder.

DRUG ABUSE AND DEPENDENCE

Pramipexole is not a controlled substance.

Pramipexole has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. However, in a rat model on cocaine self-administration, pramipexole had little or no effect.

OVERDOSAGE

There is no clinical experience with massive overdosage. One patient, with a 10-year history of schizophrenia, took 11 mg/day of pramipexole for 2 days; this is two to three times the protocol recommended daily dose. No adverse events were reported related to the increased dose. Blood pressure remained stable although pulse rate increased to between 100 and 120 beats/minute. The patient withdrew from the study at the end of week 2 due to lack of efficacy.

There is no known antidote for overdosage of a dopamine agonist. If signs of central nervous system stimulation are present, a phenothiazine or other butyrophenone neuroleptic agent may be indicated; the efficacy of such drugs in reversing the effects of overdosage has not been assessed. Management of overdose may require general supportive measures along with gastric lavage, intravenous fluids, and electrocardiogram monitoring.

DOSAGE AND ADMINISTRATION

In all clinical studies, dosage was initiated at a subtherapeutic level to avoid intolerable adverse effects and orthostatic hypotension. MIRAPEX should be titrated gradually in all patients. The dosage should be increased to achieve a maximum therapeutic effect, balanced against the principal side effects of dyskinesia, hallucinations, somnolence, and dry mouth.

Dosing in Patients with Normal Renal Function

Initial Treatment: Dosages should be increased gradually from a starting dose of 0.375 mg/day given in three divided doses and should not be increased more frequently than every 5 to 7 days. A suggested ascending dosage schedule that was used in clinical studies is shown below: 7a

Ascending Dosage Schedule of MIRAPEX		
Week	Dosage (mg)	Total Daily Dose (mg)
1	0.125 tid	0.375
2	0.25 tid	0.75

3	0.5 tid	1.50
4	0.75 tid	2.25
5	1.0 tid	3.00
6	1.25 tid	3.75
7	1.5 tid	4.50

Maintenance Treatment: MIRAPEX Tablets were effective and well tolerated over a dosage range of 1.5 to 4.5 mg/day, administered in equally divided doses three times per day, with or without concomitant levodopa (approximately 800 mg/day).

In a fixed-dose study in early Parkinson's disease patients, doses of 3 mg, 4.5 mg, and 6 mg per day of MIRAPEX were not shown to provide any significant benefit beyond that achieved at a daily dose of 1.5 mg/day.

When MIRAPEX is used in combination with levodopa, a reduction of the levodopa dosage should be considered. In a controlled study in advanced Parkinson's disease, the dosage of levodopa was reduced by an average of 27% from baseline.

Patients With Renal Impairment:

Pramipexole Dose in the Renally Impaired		
Renal Status	Starting Dose (mg)	Maximum Dose (mg)
Normal to mild impairment (Creatinine Cl > 60 mL/min)	0.125 tid	1.5 tid
Moderate impairment (Creatinine Cl = 35 to 59 mL/min)	0.125 bid	1.5 bid
Severe impairment (Creatinine Cl = 15 to 34 mL/min)	0.125 qd	1.5 qd
Very severe impairment (Creatinine Cl < 15 mL/min and hemodialysis patients)	The use of MIRAPEX is not recommended.	

Agency Add'l written 7b WARNIN

Discontinuation of Treatment: It is recommended that MIRAPEX be discontinued over a period of 1 week; in some studies, however, abrupt discontinuation was uneventful.

HOW SUPPLIED

MIRAPEX Tablets are available as follows:

8

0.125 mg: white, round tablet with "U" on one side and "2" on the reverse side.

Bottles of 63NDC 0009-0002-02

0.25 mg: white, oval, scored tablet with "U" twice on one side and "4" twice on the reverse side.

Bottles of 90NDC 0009-0004-02

1.0 mg: white, round, scored tablet with "U" twice on one side and "6" twice on the reverse side.

Bottles of 90NDC 0009-0006-02

1.5 mg: white, round, scored tablet with "U" twice on one side and "37" twice on the reverse side.

Bottles of 90NDC 0009-0037-02

Store at controlled room temperature of 20°C to 25°C (68°F to 77°F) [see USP]. Protect from light.

Caution: Federal law prohibits dispensing without a prescription.

ANIMAL TOXICOLOGY

Retinal Degeneration in Albino Rats

9a

Retinal degeneration was observed in albino rats in the 2-year carcinogenicity study with pramipexole. Degeneration was first observed during week 76 and was dose dependent in animals receiving 2 or 8 mg/kg/day (5 and 20 times the highest clinical dose on a mg/m^2 basis). Degeneration was not observed in that study at 0.3 mg/kg/day (0.8 times the highest clinical dose on a mg/m^2 basis). In rats dosed at 0.3, 2, or 8 mg/kg/day, the plasma AUC was 0.3, 2.5, and 12.5 times the AUC in humans dosed at 1.5 mg tid.

Investigative studies demonstrated that pramipexole reduced the rate of disk shedding from the photoreceptor rod cells of the retina in albino rats, which was associated with enhanced sensitivity to the damaging effects of light. In a comparative study, retinal degeneration occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day of pramipexole (62 times the highest clinical dose on a mg/m^2 basis) and constant light (100 lux), but not in pigmented rats exposed to the same dose and higher light intensities (500 lux). Thus, the retina of albino rats is considered to be uniquely sensitive to the damaging effects of pramipexole and light. Retinal degeneration did not occur in a 2-year carcinogenicity study in albino mice treated with 0.3, 2, or 10 mg/kg/day (0.5, 3.4, and 17.2 times the highest clinical dose on a mg/m^2 basis). Evaluation of the retinas of monkeys given 0.1, 0.5, or 2.0 mg/kg/day of pramipexole (0.5, 2.6, and 10.4 times the highest clinical dose on a mg/m^2 basis) for 12 months and minipigs given 0.3, 1, or 5

mg/kg/day of pramipexole for 13 weeks also detected no changes in the retina.

The potential significance of this effect in humans has not been established. Disk shedding is a universal mechanism of the vertebrate retina, and a decreased rate could be associated with degeneration of the retina.

Fibro-osseous Proliferative Lesions in Mice 9b

An increased incidence of fibro-osseous proliferative lesions occurred in the femurs of female mice treated for 2 years with 0.3, 2.0, or 10 mg/kg (0.5, 3.3, and 17.2 times the highest clinical dose on a mg/m^2 basis). Lesions occurred at a lower rate in control animals. Similar lesions were not observed in male mice or rats and monkeys of either sex that were treated chronically with pramipexole. The fibro-osseous lesions in female mice are thought to be due to an estrogen:progesterone imbalance attributed to the prolactin-lowering effect of pramipexole. The endocrine mechanisms believed to be involved in mice are not relevant to humans.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA
Original Summary

NDA No.: 20667 **Submission Date:** 12/28/95

Drug: Pramipexole Oral Compressed Tablets

Sponsor: The Upjohn Co.
7000 Portage Rd.
Kalamazoo, MI 49001-0199

Reviewer: T.D. Steele

Indication: Parkinson's disease

Pharmacologic Class: Dopamine agonist

Chemical Information:

CAS Name: (S)-N6-Propyl-4,5,6,7-tetrahydro-2,6-benzothiazolediamine, dihydrochloride, monohydrate

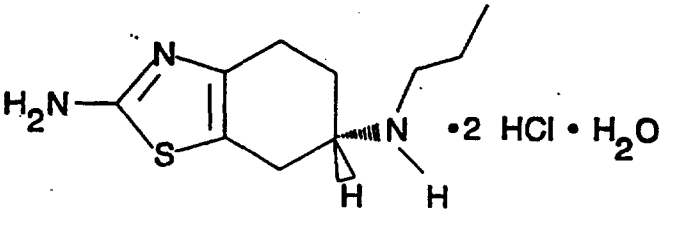
IUPAC Name: (S)-2-Amino-4,5,6,7-tetrahydro-6-propylaminobenzothiazole dihydrochloride monohydrate

Other Names: SND 919 CL 2 Y; U-98528E

Empirical Formula: $C_{10}H_{21}Cl_2N_3OS$

Molecular Weight: 302.27

Structure:



Note: Portions of this review were excerpted directly from the sponsor's submission.

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A. PHARMACOLOGY

Volumes: 1.27-1.31 Upjohn Technical Reports
1.62 Published articles

The following is a summary of preclinical pharmacology studies on the mechanism of action and efficacy of pramipexole. Most of these studies were reviewed under IND
The "Neuroprotection" studies (sec. A.3) that were submitted to support a labeling claim were not previously reviewed.

A.1. Mechanism of Action

A.1.a *In vitro* studies

In receptor binding assays, PPX displays high affinity for both D_3 and D_2 cloned receptors (4 to 8-fold higher at D_3; Tables A.1.a.1, 2). By comparison, the dopamine (DA) agonists bromocriptine and apomorphine are less potent and selective for D_3 and D_2 receptors, whereas pergolide has a higher affinity than PPX for both receptor subtypes (Table A.1.a.2). Consistent with the known receptor-effector coupling schemes for DA receptors, PPX binding to D_2 and D_4 receptors is inhibited by a non-hydrolyzable GTP analog indicating G-protein involvement in the mechanism; D_3 binding is not markedly affected. Autoradiographic studies indicate that the distribution of [^{3}H]-PPX binding sites is consistent with receptor subtype mRNA distribution, high in mesolimbic areas (islets of Calleja, nucleus accumbens, olfactory tubercle) that are abundant in D_3 and D_2 receptors, and also in the D_2-rich caudate nucleus (Table A.1.a.3). Binding sites were less abundant in the ventral tegmental area (VTA) and the substantia nigra (SN). In a Novascreen receptor binding assay, the only other significant binding by PPX was at α_2 receptors (Table A.1.a.4).

In functional studies, PPX (0.1-100 μM) decreased cAMP in primary cultures of cerebellar granule cells by a putative D_3 receptor mechanism. PPX inhibited electrically-stimulated DA release in rat striatal slices, presumably via activation of nerve terminal D_2 autoreceptors (i.e., block with haloperidol). PPX did not block synaptosomal uptake of radiolabelled monoamines at concentrations up to 10 μM.

A.1.a.1

Table [illegible] Affinities of Pramipexole to Cloned Dopamine Receptors Expressed in Cultured Human Embryonic Kidney and Chinese Hamster Ovary Cells

Receptor	Radioligand	K_i* of pramipexole (nM)
Human D_{2L} receptor	[^{3}H]pramipexole	3.9†
Human D_{3a} receptor	[^{3}H]pramipexole	3.3†
Human D_3 receptor	[^{3}H]pramipexole	0.5†
Human D_4 receptor	[^{3}H]pramipexole	5.1‡

*K_i: Values are means of two to four experiments.
† Data from [22]
‡ Data from [23]

Tab. A.1.a.2

Internal Use Only
DESTROY UPON DISPOSAL

Table 1. Binding Affinities of Dopamine Agonists for Dopamine Receptor Subtypes.

Compound	Binding at Dopamine Receptors (Ki ± SEM in nM)			
	D1-Dopamine	D2-Dopamine	D3-Dopamine	D4-Dopamine
Bromocriptine U-43714E	3418 ± 129	27 ± 9	18 ± 2	373 ± 15
Apomorphine U-19542E	491 ± 29	26	17 ± 1	8.2 ± 1
Pergolide U-68326E	1300 ± 132	1 ± 0.2	0.4 ± 0.03	9.3 ± 1
Lisuride U-64047E	62 ± 4	0.3 ± 0.1	2.2 ± 0.2	3.2 ± 0.5
Pramipexole U-98528E	> 2,381	5.3 ± 0.3	1.3 ± 0.2	18 ± 4

Table 2. Binding Affinities of Dopamine Agonists for Serotonin Receptor Subtypes.

Compound	Binding at Serotonin Receptors (Ki ± SEM)			
	5-HT1A	5-HT1Dα	5-HT1Dβ	5-HT2
Bromocriptine	24 ± 9	22 ± 5	708 ± 84	119 ± 37
Apomorphine	103 ± 11	1,399 ± 109	> 4,000	343 ± 51
Pergolide	1.8 ± 0.4	21 ± 6	111 ± 8	26 ± 7
Lisuride	0.2 ± 0.03	7.6 ± 0.8	20 ± 3	5.1 ± 1.1
Pramipexole	> 1,698	2,429 ± 301	> 4,000	> 1,131

TABLE # A.1.a.3

Densities of D_2 and D_3 Receptors Bound By [^{3}H]-PPX in Areas of Rat Brain

The data were derived from quantification of autoradiograms produced from coronal sections.

Structure	Specific Bound (mean±SEM)* right left	B_{max} D_2 Receptor*	B_{max} D_3 Receptors*
N. accumbens	42±3 42±9	97±7 97±21	45±3 45±10
Anterior cingulate cortex	13±4 12±5	30±9 28±13	
Sensory cortex	16±3 12±6	37±7 37±18	
Olfactory Tubercle	46±11 47±15	105±25 108±34	49±12 50±16
Islets of Calleja Major	58±14 60±14	133±32 138±32	62±16 64±16
Islets of Calleja Medial	52±8 52±15	120±18 120±35	62±9 62±18
N. caudate	43±8 48±11	99±18 110±25	

* fmol/mg P based on K_d = 6.5 nM (D_2) or 0.37 nM (D_3).

A.1.a.1

Table [redacted] Affinities of Pramipexole to Different Receptor Preparations From Brain Homogenates as Estimated by Receptor Binding Assays ([30] unless otherwise indicated).

Receptor	Radioligand	K_i of pramipexole (nM)
Dopamine D2 receptor	[^{3}H]spiroperidol	1350
Dopamine D2 receptor*	[^{3}H]spiroperidol (high affinity state)	105
Dopamine (D2) receptor†	[^{3}H]pramipexole	2.9
Dopamine D1 receptor‡	[^{3}H]SCH 23390§	>100,000‖
α_1-Adrenoceptor	[^{3}H]prazosin	28,700
α_2-Adrenoceptor	[^{3}H]clonidine	250
Muscarinic receptor	[^{3}H]QNB¶	30,700
Serotonin 5-HT_1 receptor	[^{3}H]serotonin	4,200
Serotonin 5-HT_2 receptor	[^{3}H]spiroperidol	>40,000‖
Histamine H_1 receptor	[^{3}H]pyrilamine	>10,000‖
Histamine H_2 receptor	[^{3}H]tiotidine	5,300
β_1-Adrenoceptor‡	[^{3}H]DH-Alprenolol	>10,000‖
β_2-Adrenoceptor‡	[^{3}H]DH-Alprenolol	>10,000‖
Serotonin-5-HT1A‡	[^{3}H]8-OH-DPAT	3,069
Adenosine-A2‡#	[^{3}H]CGS 21680	>100,000‖
Benzodiazepine‡	[^{3}H]Flunitrazepam	>10,000‖
NMDA/MK-801‡#	[^{3}H]MK-801	>10,000‖
NMDA/Glycine‡	[^{3}H]DCKA	>100,000‖
AMPA#	[^{3}H]Glutamate	>10,000‖

A.1.b. *In vivo* studies

In behavioral studies, low doses of PPX decreased locomotor activity in mice (ED_{50} = 0.084 mg/kg, p.o.). This is presumably due to activation of D_2 autoreceptors which shut down release of endogenous DA. Higher doses of PPX (0.3-1 mg/kg, s.c.) stimulated locomotor activity in rats, but did not induce apomorphine-like stereotypic climbing in mice (0.003 - 10 mg/kg, p.o.). Other behavioral effects of PPX that are likely attributed to postsynaptic D_2 receptor activation are yawning in rats (0.025-0.1 mg/kg, s.c.), reversal of haloperidol-induced catalepsy in rats (ED_{50} = 4.4 mg/kg, s.c.), dose-dependent induction of gnawing in rats (0.03 - 3 mg/kg, s.c.), and stimulation of locomotor activity in reserpinized mice (9 mg/kg, i.p.).

The primary *in vivo* neurochemical effects of PPX appear to result from stimulation of presynaptic D_2 autoreceptors which reduces dopamine turnover. PPX decreased DA synthesis as measured by inhibition of DOPA accumulation in striatum and limbic system after γ-butyrolactone lesions of dopaminergic pathways:

	ED_{50}
striatum	0.13 mg/kg, s.c.
limbic forebrain	0.05 mg/kg, s.c.

The effect of PPX in the striatum was blocked by haloperidol indicating a D_2 receptor-mediated action. The more potent, but not statistically significant, effect in the limbic forebrain was suggested to be due to D_3 activation. No pharmacological evidence was provided in support of this contention. A PPX-induced decrease in dopamine release was also demonstrated in α-methyltyrosine-treated rats (ED_{50} = 0.04 mg/kg, s.c.) and by *in vivo* microdialysis.

Evidence for activation of DA autoreceptors by PPX was also obtained in electrophysiology studies where decreases in the firing rate of nigrostriatal (SNPC) and mesolimbic (VTA) neurons were observed:

	ED_{50}
SNPC	0.066 mg/kg, i.v.
VTA	0.082 mg/kg, i.v.

In anterior caudate neurons, PPX stimulated the firing of postsynaptic neurons at higher doses (10 mg/kg, i.v., increased firing by 60%). This was suggested to be a D_3 effect since other D_2-preferring agonists did not affect firing.

A.2. Efficacy in Parkinson's Disease Models

PPX (0.01 - 1 mg/kg, s.c.) caused contralateral turning in rats with 6-hydroxydopamine (6-OHDA)-induced lesions of the medial forebrain bundle. The ED_{50} (0.026 mg/kg, s.c.) indicated that PPX was equipotent to apomorphine (ED_{50} = 0.03 mg/kg, s.c.). Maximal effects of PPX occurred between 80-140 min, whereas the duration of action for apomorphine was ≤ 80 min. The effect was completely blocked by haloperidol, and partially blocked by the D_1 antagonist SCH 23390.

In the MPTP-induced Parkinson's-disease model in primates, PPX (0.03-0.1 mg/kg, i.m.) dose-dependently reversed parkinson-like symptoms (ED_{50} = 0.045 mg/kg, i.m.). A dose of 0.06 mg/kg relieved virtually all of the symptoms. In a second experiment, an oral dose of 0.075 mg/kg reversed Parkinsonian symptoms for 5-24 hr. Several other Parkinson's agents did not consistently affect symptomology ($\leq$ 2 mg/kg biperiden, p.o., <300 mg/kg amantadine, p.o., $\leq$ 2 mg/kg bromocriptine, p.o.). L-DOPA/carbidopa (15 mg/kg, p.o.) was effective for 2 hrs (Table A.2.a). When tested in combination with the monoamine oxidase inhibitor l-deprenyl (Eldepryl, 0.2 mg/kg, i.m.), the effectiveness of PPX (10-120 µg/kg, i.m.) was not potentiated.

Tab. A.1.a.

Substance	Optimal efficacy from (mg/kg)	Duration of action	Side effects at high dosage
Combination L-dopa (+ benserazide and carbidopa)	15 p.o.	1 - 2 h	salivation motor restlessness
Biperidene (Akineton)	up to 2.0		
Amantadine (PK-Merz)	up to 300	unsatisfactory effect	
Bromocriptine (Prävidel)	up to 2.0		
B-HT 920	0.05 p.o.	2 - 5 h	sedation, ataxia
SND 919 Y	0.075 p.o.	2 - 24 h	occasional salivation
	0.05 i.m.		raised reactivity

Tab. 9: Effect of antiparkinsonian drugs and agents under development on MPTP-induced Parkinson's disease in monkeys.

A.3. Neuroprotection

The sponsor proposes a labeling claim suggesting neuroprotective effects of pramipexole based on data from three preclinical models:

1. Prevention of post-ischemic retrograde degeneration of nigrostriatal dopamine neurons following transient forebrain ischemia (Bilateral Carotid Artery Occlusion Model, BCAO) in gerbils

2. Attenuation of methamphetamine-induced nigrostriatal dopaminergic neurotoxicity in mice

3. Attenuation of L-DOPA neurotoxicity *in vitro*

In the gerbil transient forebrain ischemia study, pramipexole (1 mg/kg, p.o., b.i.d. for 28 days beginning on the day of surgery) attenuated by 40% the loss of tyrosine hydroxylase(TH)-positive neurons in the substantia nigra (Fig. A.3.a.1). A much smaller degree of protection was afforded in the CA1 region of the hippocampus (cresyl-violet staining), and statistically significant in only a preliminary experiment (Fig. A.3.a.2). Details regarding the timing of drug administration relative to the ischemic insult were not provided. In the *in vivo* methamphetamine neurotoxicity study, four daily doses pramipexole (1 mg/kg, p.o.) beginning 1 hr after the last methamphetamine injection (10 mg/kg, i.p., every two hrs for four doses) completely prevented the loss of TH-positive neurons in the substantia nigra of mice five days after methamphetamine dosing (Fig. A.3.a.3). The proposed protective mechanism is prevention by pramipexole of methamphetamine-induced elevations in dopamine turnover which, if not prevented, would lead to tissue damage *via* the generation of oxygen-derived free radicals. In the *in vitro* experiment, nanomolar concentrations of pramipexole prevented the loss of TH-positive cells due to micromolar concentrations of L-DOPA in primary cultures of rostral mesencephalic tegmentum cells (Fig. A.3.a.4). Preliminary evidence suggested the involvement of a heat-sensitive trophic factor in the protective effect of pramipexole.

The gerbil BCAO transient forebrain ischemia model is an acceptable preclinical efficacy screen for drugs proposed in the treatment of stroke. The clinical relevance of the *in vivo* methamphetamine and *in vitro* L-DOPA neurotoxicity models is not established. The results from the ischemia study would provide some preclinical support for a clinical trial proposal, although only one of the two regions examined appeared to be significantly protected. The potential clinical relevance of these findings is further compromised since no mechanistic basis of protection was evaluated. For instance, the observed protection may simply be a consequence of the hypothermic effects of pramipexole, and not related to inhibition of dopamine release. Thus, a labeling claim suggesting that pramipexole "reduces dopamine-induced neuronal degeneration", which has significant and far-reaching clinical implications, is not supported by these preclinical findings.

FIGURE 8. Dose-response for pramipexole's effect on the loss of tyrosine hydroxylase-positive neurons 28 days following a 10-min BCO in the gerbil. Data given as mean ± SEM.

A.3.a.1

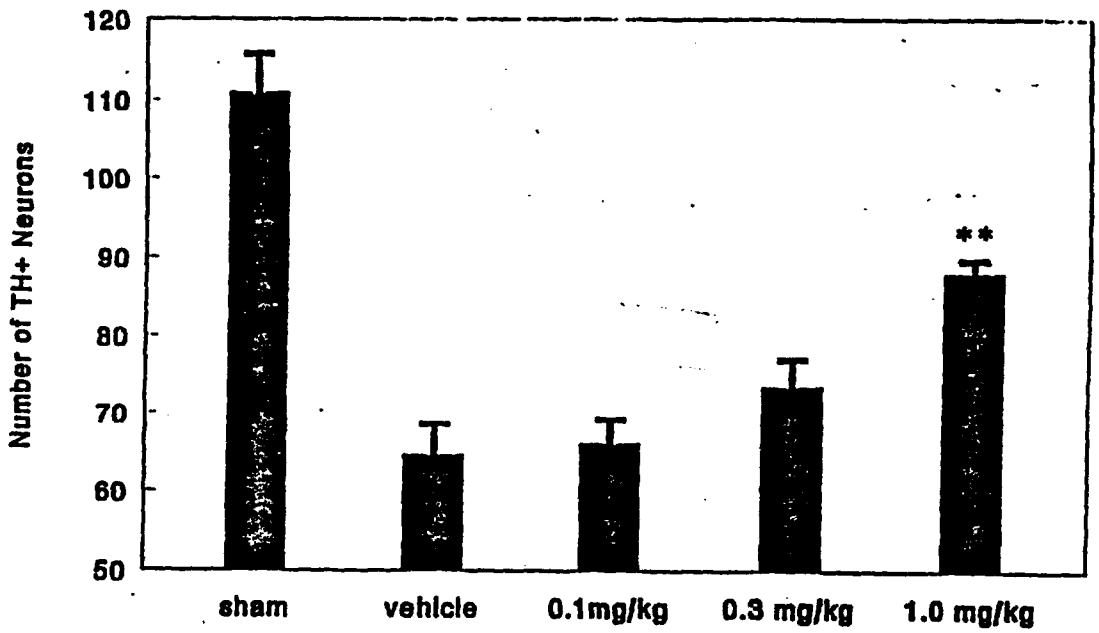


FIGURE 9. Dose-response of pramipexole's effect on neuronal damage in the CA_1 region of the hippocampus 28 days following a 10-min BCO in the gerbil. Data given as mean ± SEM.

A.3.a.2

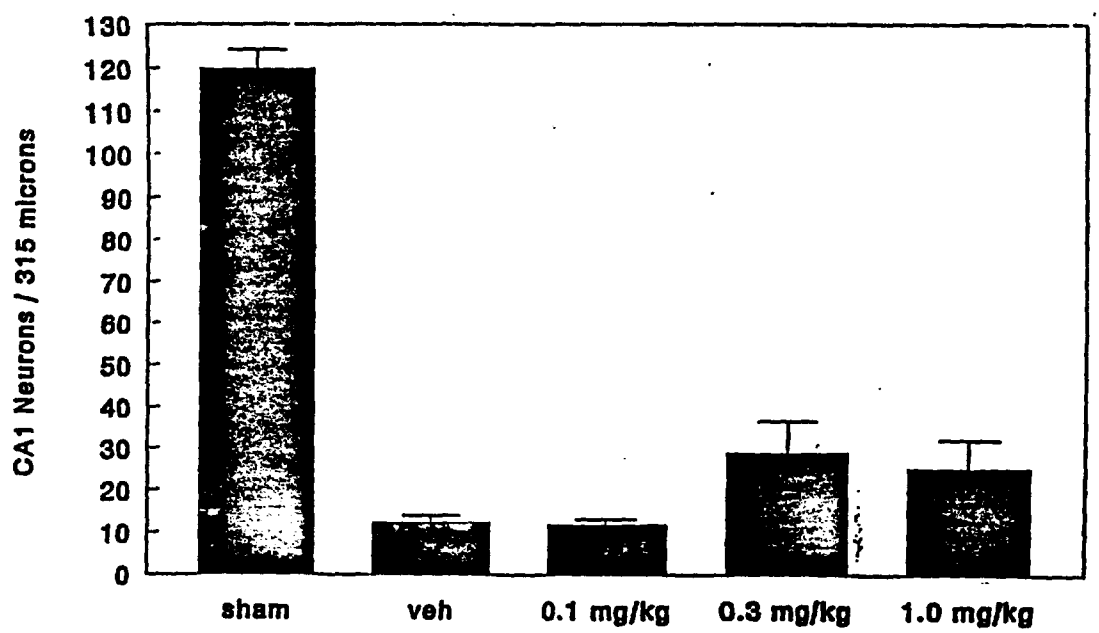


Fig. A.3.a.3

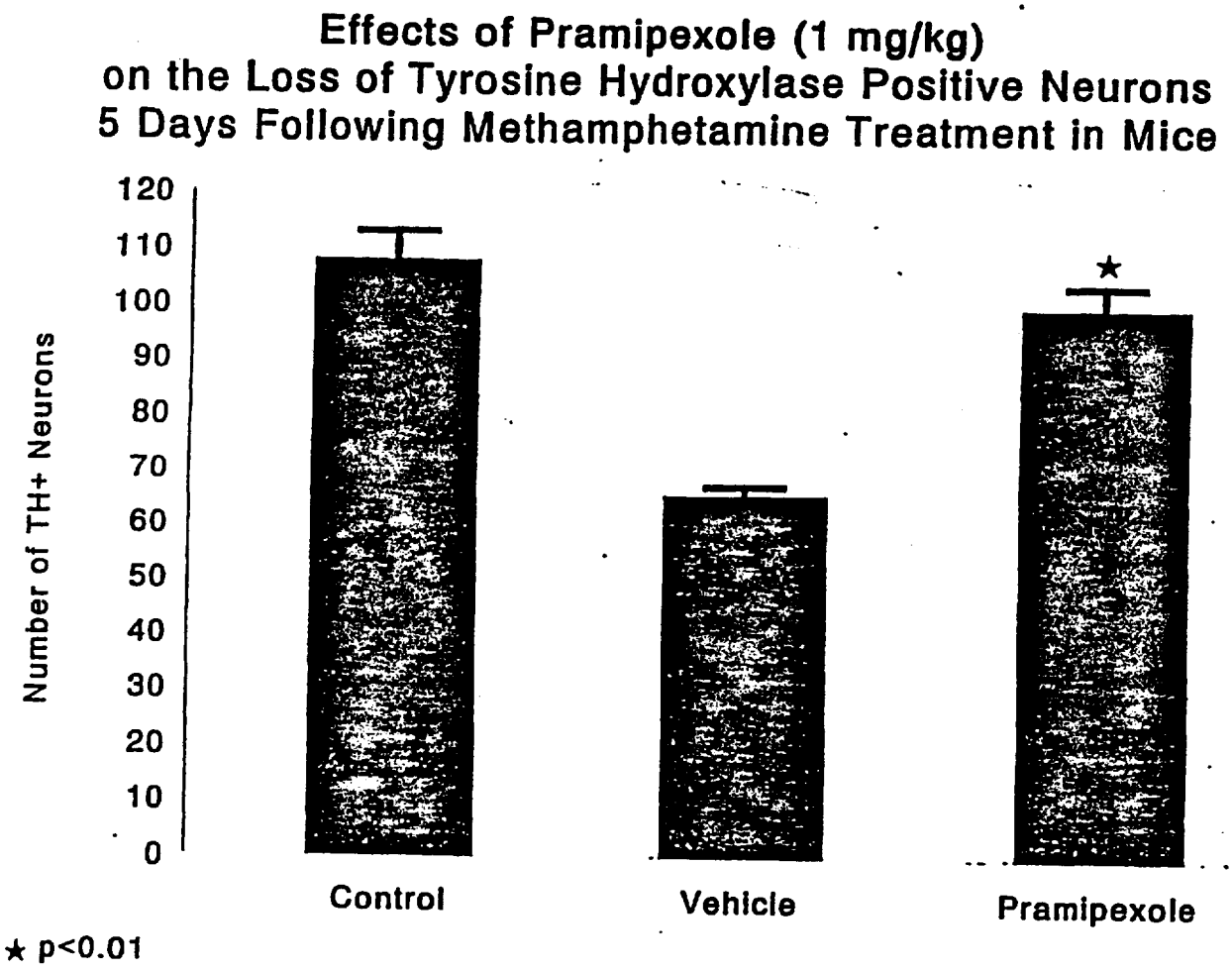
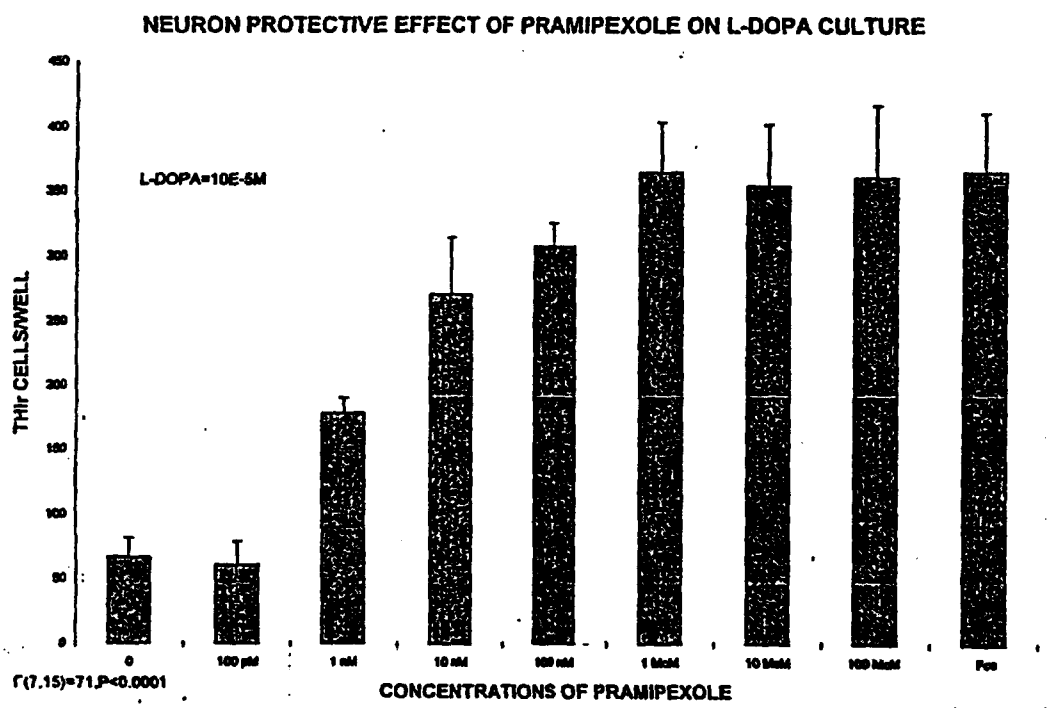

Effects of Pramipexole (1 mg/kg)
on the Loss of Tyrosine Hydroxylase Positive Neurons
5 Days Following Methamphetamine Treatment in Mice
Number of TH+ Neurons
120
110
100
90
80
70
60
50
40
30
20
10
0
Control
Vehicle
Pramipexole
★ p<0.01

FIGURE # A3.a.4.

Dose-dependent neuroprotective effects of pramipexole in an L-dopa toxicity model of THIR cells. Data are mean and S.E. for at least two experiments. Procedures for culture methodology, immunostaining and cell count assessment are described in the Methods. Immediately following plating, RMT cultures were exposed to various concentrations of pramipexole with or without L-dopa (10 μM) for 72 hrs and THIR cells were counted.



A.4. Other Indications

The sponsor has submitted several preclinical studies to demonstrate the efficacy of PPX in other indications including anxiety, depression and schizophrenia. These studies are not considered relevant to the present application and were not reviewed.

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B. SAFETY PHARMACOLOGY

B.1. Central Nervous System Effects

Aside from the aforementioned behavioral changes, relatively few significant CNS effects were induced by acute treatment with PPX. Ataxia did not occur in mice at PPX doses of 0.003-10 mg/kg, p.o., or 0.001-100 mg/kg, s.c. Doses of 0.3-3 mg/kg, s.c., did not lower the threshold for pentylenetetrazol-induced seizures in mice. Monkeys were slightly sedated by doses of 100-150 µg/kg, i.m. and 300 µg/kg, p.o. REM and non-REM sleep in rats was suppressed by 0.3 mg/kg, p.o. A biphasic effect on sleep was observed in cats; low doses (0.1 mg/kg, p.o.) increased non-REM sleep initially, followed by reduction in REM and non-REM sleep. Higher doses (0.3 mg/kg) completely suppressed sleep. PPX decreased body temperature in mice by 2°C with an ED_{50} of 0.23 mg/kg, s.c.

B.2. Cardiovascular/Respiratory Effects

In anesthetized cats, PPX (0.03-1 mg/kg i.v.) caused a slight, transient (2-3 min), non-dose-dependent decrease in blood pressure and a slight bradycardia at 1 mg/kg, but did not alter respiration. In anesthetized rabbits, 0.03 mg/kg, i.v. decreased blood pressure, and 0.1 mg/kg decreased both pressure and heart rate. The cardiovascular effects of 0.3 mg/kg PPX were blocked with dopamine antagonists. In spontaneously hypertensive rats (SHRs), 0.001-0.03 mg/kg, i.v., PPX lowered blood pressure by a D_2-receptor mechanism. Higher doses (0.1-1 mg/kg, i.v.) increased blood pressure by a peripheral α_2-receptor mechanism. After oral administration of 3 and 30 mg/kg PPX to SHRs, a slight bradycardia was the only effect observed. In a study with anesthetized SHRs, PPX (0.04-8.8 mg/kg, i.v.) decreased blood pressure and the effect could be blocked by either a D_1 or D_2 antagonist.

A special series of studies were conducted in rhesus monkeys to evaluate the cardiovascular effects of pramipexole in combination with other drugs used in Parkinson's disease (i.e., Sinemet and Eldepryl; reviewed inder IND 34,850). In a pilot study, a dose of 0.05 mg/kg p.o., but not 0.1 mg/kg, lowered blood pressure for up to 6 hrs. Doses of 0.005-0.1 mg/kg produced a non-dose-dependent bradycardia, although the duration of effect increased with dose (6-24 hr). In the combination study, slight (non-significant) decreases in heart rate, diastolic blood pressure, and mean arterial blood pressure following 0.05 mg/kg PPX, p.o., were not potentiated by either Sinemet (100 mg/kg L-DOPA/10 mg/kg carbidopa, p.o.) or Eldepryl (0.2 mg/kg, p.o.).

B.3. Gastrointestinal Effects

Like other dopamine agonists, PPX induced emesis in dogs (ED_{50}s = 0.0067 mg/kg, p.o., and 0.0052 mg/kg, s.c.). The effect was blocked with a dopamine antagonist. PPX inhibited gastrointestinal transit in mice (ED_{50} = 0.033 mg/kg, p.o.).

B.4. Renal Effects

Conflicting results were obtained in assessments of the renal effects of PPX in rats. In conscious rats, PPX (0.3 mg/kg, p.o.) produced a moderate decrease in urinary volume; electrolyte excretion was not significantly affected. In a study from an independent investigator with anesthetized normotensive (WKY) and spontaneously hypertensive (SHR) rats (Kaneko, et al., J. Auton. Pharmacol., 10(suppl. 1):s53, 1990), PPX (0.04-8.8 mg/kg, i.v.) increased urine volume and Na excretion. The low dose effects of PPX were antagonized by a D_1 antagonist and the high dose effects by a D_2 antagonist. The contrasting effects of PPX in conscious and anesthetized animals may have been due to the anesthesia, PPX dose, strains of rats, or the use of water-loading in the former, but not the latter study. The effectiveness of the D_1 antagonist against PPX in this study suggest that the renal effects of PPX may be mediated by D_1 receptors, and additional biochemical data support this hypothesis.

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C. TOXICOLOGY

C.1. Acute Toxicology

Conducted by:

Sponsor Volume: 1.31

These studies complied with GLP

Summary

Acute toxicology studies were conducted in mice, rats and dogs. Animals were observed for up to 14 days following treatment. The lethality of PPX was approximately 10-fold higher in mice and 4-fold higher in rats by the intravenous versus oral route of administration. Common signs of toxicity were exophthalmus, piloerection, tremors/convulsions, ataxia and hypomotility, nervousness/agitation and hypermotility, and tachypnea or dyspnea. Most deaths following i.v. treatment occurred shortly after dosing, whereas delayed deaths were more common following oral administration. The primary sign at autopsy of animals that died following drug treatment was hemocongestion of large organs. Animals that were sacrificed at the end of the study did not show any consistent pathologies. The dog studies were limited by the pronounced emetic effect of PPX.

C.1.a. Acute Oral Toxicity in Mice

Doses: 1400, 2000 mg/kg n = 10 (5M, 5F)

Results:

	# deaths	
	1400 mg/kg	2000 mg/kg
0-6 hr	2	3
6-24 hr		3
1-7 days	1	2

Signs: exophthalmos, piloerection, tremors/convulsions, hypomotility

LD_{50}: ca. 1700 mg/kg

C.1.b. Acute Intravenous Toxicity in Mice

Doses: 100, 125, 160, 200 mg/kg n = 10 (5M, 5F)

Results:

	# deaths			
	100 mg/kg	125 mg/kg	160 mg/kg	200 mg/kg
0-6 hr	0	0	6	7

Signs: exophthalmos, convulsions, tachypnea

LD_{50}s: male: 155, female: 188, m+f: 169

C.1.c. Acute Oral Toxicity in Rats

Doses: Study I: 100, 200 mg/kg n = 10 (5M, 5F)
II: 200, 400, 560, 800 mg/kg n = 10 (5M, 5F)

(In study I, animals were housed in plastic cages, and deaths were attributed to choking on bedding. In study II, the animals were housed in suspended cages)

Results:

	# deaths					
	100 mg/kg	200 mg/kg	200 mg/kg	400 mg/kg	560 mg/kg	800 mg/kg
0-6 hr					1	3
6-24 hr						
1-2 days	1	1				
2-7 days	2	4	1		2	2
7-14 days						1

Signs: exophthalmos, chewing, ataxia, automutilation

LD_{50s}:

	0-24 hr	> 24 hr
male:	> 800	> 800
female:	> 852	> 548
m + f:	> 957	> 809

C.1.d. **Acute Intravenous Toxicity in Rats**

Doses: Study I: 100, 140 mg/kg n = 10 (5M, 5F)
II: 200, 400, 560, 800 mg/kg n = 10 (5M, 5F)

(In study I, animals were housed in plastic cages, and deaths were attributed to choking on bedding. In study II, the animals were housed in suspended cages)

Results:

	# deaths				
	100 mg/kg	140 mg/kg	140 mg/kg	180 mg/kg	225 mg/kg
0-6 hr					7
6-24 hr		1			
1-2 days	2	1			
2-5 days	2	3			

Signs: exophthalmos, dyspnea, convulsions, ataxia, hypomotility
Autopsy: pulmonary hemocongestion
LD_{50}: ca. 210 mg/kg

5. **Acute Oral Toxicity in Beagles**

Doses: 0.001, 0.01, 0.1, 1.0 mg/kg; n = 1/sex/dose

Results: 0.01-1 mg/kg caused emesis; 1 mg/kg caused mydriasis and decreased food intake

6. **Acute Intravenous Toxicity in Beagles**

Doses: 1, 3, 5, 10 µg/kg; n = 1/sex/dose

Results: 3 µg/kg caused salivation; doses $\geq$ 3 µg/kg in females and $\geq$ 5 µg/kg in males caused emesis

C.2. Chronic Toxicology

C.2.a. 52-Week Toxicity Study in the Rat

Conducted by:

Document #'s:

Upjohn TR 7219-94-067

Sponsor Volumes: 1.34-1.36

This study complied with GLP

Significant notation:

The sponsor has attached an Amendment (no. 2) to the original report. The basis for the amendment was a discrepancy in the terminology used by histopathologists evaluating the data from the 52-week rat chronic toxicity study and the 2-year rat carcinogenicity study. Briefly, mammary gland changes were observed in female rats from the mid- (3.0 or 2.0 mg/kg) and high- (15.0 or 8.0 mg/kg) dose groups of both studies. In the 52-week study, the changes were described as an "increase in mammary gland acini (control: 13/20, low dose: 6/20, mid dose: 17/19, high dose: 20/20) with concurrent hypertrophy and/or hyperplasia of the glandular epithelium (controls 0/20, low dose: 0/10, mid dose: 8/19, high dose: 19/20)...". In the 2-year rat carcinogenicity study, these changes were designated as a "change in the normal glandular growth pattern", according to the work of Cardy ("Sexual dimorphism of the normal rat mammary gland", Vet Pathol, 28:139-145, 1991). Consequently, the histopathology slides from the 52-week rat study were re-evaluated using the terminology of Cardy. Diagnoses that were originally described as "increase in glandular acini" were changed to "proliferation of glandular epithelium". Original diagnoses of "hypertrophy" or "hyperplasia" were changed to "mixed tubuloalveolar/lobuloalveolar pattern" or "lobuloalveolar pattern." According to the redefinition, only one case of mammary gland hyperplasia (alveolar) was identified in the 52-week rat study (1 LDF).

Summary:

Pramipexole was administered in the diet to Wistar rats (Chbb:THOM) for 52 weeks at dose of 0, 0.5, 3.0 and 15.0 mg/kg. Toxicology dosage groups were composed of 20 rats/sex; a satellite group of 7 rats/sex/dose were used for toxicokinetic analysis. Administration of the lowest test dose resulted in slight behavioral activation in both sexes, and decreased body weight gain, cholesterol and triglycerides in females. Body weight gain was reduced in both sexes by the mid and high doses. The female clinical chemistry changes were more evident at the mid and high doses. In addition, sporadic, modest elevations in transaminases, alkaline phosphatase and urea, and decreases in serum potassium occurred at the mid and high doses,

generally more frequently in females than in males. Slight thrombocytopenia (MD, HD) and slight-to-moderate increase in the granulocyte/lymphocyte ratio were evident in females. Organ weight changes were reduced liver weights in HDM, and reduced thymus weights in MDF and HDF. Ovarian weights were increased at all dosage levels, and enlarged corpora lutea were observed at the mid and high dose. Histopathological changes in the uteri (dilatation, serous contents, pyometra) and mammary glands (the above-mentioned glandular pattern changes) were also evident in MDF and HDF. Leydig cell hyperplasia occurred only in PPX-treated males, but the incidence was highest at the low dose level. Eleven animals (4 control, 7 PPX-treated) were identified with tumors, none of which could be clearly attributed to PPX treatment. One control and one LDM had Leydig cell adenoma.

Toxicokinetic analyses suggested that PPX concentrations tended to increase dose-proportionally in females, but were greater than dose-proportional in males. This resulted in higher plasma levels in HDM compared to HDF at week 26 and 52.

The "No Toxic Effect" level was considered as 0.5 mg/kg. The plasma levels measured at 1 hr after the start of the light phase during week 26 and 52 at this dose (4.0 - 6.5 ng/ml) approximate the steady-state Cmax in humans administered the projected maintenance dose of 1.5 mg PPX, t.i.d (5.5-7.2 ng/ml).

Methods:

Dosages: 0.5, 3.0, 15.0 mg/kg (Batch II)

Route of Administration: Drug-in-diet

Species/Strain/Number: Rat/Wistar (Chbb:THOM)

80 males, 80 females for toxicology
21 males, 21 females for plasma toxicokinetics

Mean initial weights: males: 296.1g
females: 193.8g

Dosages/Group Designation:

Group	Dosage (mg/kg/day)	Number of animals	
		males	females
0 (control)	0	20	20
1 (low dose=LD)	0.5	20	20
2 (middle dose=MD)	3.0	20	20
3 (high dose=HD)	15.0	20	20
4 (for determination	0.5	7	7
5 of plasma con-	3.0	7	7
6 centrations only)	15.0	7	7

Parameters monitored/Intervals:

Clinical	-	daily
Body weight	-	weekly
Food consumption	-	weekly
Water consumption	-	weekly (weeks 14, 26, 36, 48)
Spontaneous Activity	-	during weeks 1, 17, 34,49 for a 22-hr period
Ophthalmology	-	weeks -1 & 51 (groups 0 and 3); weeks 12 & 25 (3 only)
Hematology	-	weeks -2, 6, 13, 27, 39, 52

Erythrocytes	Leucocytes
Haemoglobin	Differential blood count
Haematocrit	Thrombocytes
MCV, MCH, MCHC	Thromboplastin time (TPT)
Reticulocytes	

Clinical Chemistry - weeks -2, 6, 13, 27, 39, 52

GPT	Glucose
GOT	Sodium
Alkaline phosphatase	Potassium
Bilirubin	Calcium
Cholesterol	Chloride
Triglycerides	Inorganic phosphate
Urea	Protein
Creatinine	Protein electrophoresis

Urinalysis - weeks 12, 25, 38, 42, 50 (groups 0 and 3)
weeks 38, 42 (groups 1 and 2)

Specific gravity	Blood	Nitrite
pH	Ketone bodies	Examination of
Protein	Bilirubin	sediment
Glucose	Urobilinogen	

Plasma Conc - weeks 1, 26, 52 at hrs 1 and 8

Organ Weights - termination

Brain
Pituitary gland
Salivary glands (Glandula submaxillaris et sublingualis major)
(Parotid gland if required)
Thyroid gland
Thymus
Heart
Lungs
Liver
Spleen
Kidneys
Adrenal glands
Gonads
Prostate

Histopathology

Tongue
Cervical lymph nodes
Both pinnae with ear tattoo
Trachea and larynx (latter not sectioned)
Oesophagus
Aorta
Sternum
Pancreas
Stomach
Small intestine (duodenum, jejunum, ileum)
Large intestine (caecum, colon, rectum)
Mesenteric lymph nodes
Urinary bladder
Seminal vesicles
Uterus (incl. cervix uteri and vagina)
Mammary tissue
Skin
Skeletal muscle (M. semimembranosus)
Femur with stifle joint
Sciatic nerve
Spinal cord
Injection site (parenteral studies)

Results:

Mortality:

Group	0		1		2		3	
Sex	m	f	m	f	m	f	m	f
Died	0	2	2	0	0	0	2	1
Sacrificed	1	0	0	0	0	0	1	0
Total	1	2	2	0	0	0	3	1
%	5	10	10	0	0	0	15	5

No deaths could be directly attributed to the drug. Six animals (2 CON, 1 LD, 3 HD) died under anesthesia for blood sampling, and 1 LDM had abscess-forming pneumonia. One sarcoma-bearing control male, and one cachectic HDM were sacrificed.

Clinical: increased activity - MD, HD (both sexes); effect more evident in females (wk 1,17, 34, 49)

Body Weight Gain:

MDM - sig. reduction - weeks 10, 11
HDM - sig. reduction - weeks 1-32, and 39

All F groups - sig. reduction throughout study

Food Intake: During week 1, food intake was decreased in MDM, HDM, and all treated females. The animals recovered during week 2, and some significant increases were recorded over the course of the study in MDM and all female groups. The diet delivered the targeted drug dose generally within 2%.

Water Intake: No drug-related effects

Ophthalmology: No drug-related oculotoxic effects were apparent. Cataracts and corneal abnormalities (opacity, calcium deposits) appeared to be spontaneous lesions.

Hematology:

Significant mean changes were noted on various parameters over the course of the study, but few clearly dose- or time-related effects were evident.

granulocyte/lymphocyte ratio- gradual increase in F

decrease RBC - dose-dep. in F (wk 13)
MDF (wk 6)
HDF (wk 6, 39, 52)

decrease Hb - MDF (wk 6, 13)
HDF (wk 13

decrease Hct - dose dep in all F (wk 13)
MDF (wk 6)
HDF (wk 52)

decrease platelets - MDF (all times except wk 39)
HDF (all times)

decrease lymphocytes - LDF (wk 6)
MDF (wk 6, 27, 52)
HDF (wk 6, 27, 39, 52)

To assess the relative magnitude and frequency of thrombocytopenia in individual female rats, the occurrence of platelet count decreases on the order of 20% and 40% were noted:

	Control	LD	MD	HD
week 6	-	1, 0	1, 0	2, 0
" 13	-	-	1, 0	-
" 27	1, 0	2,0	5, 1	6, 0
" 39	0, 1	7, 0	5, 0	9, 1
" 52	2, 2	7, 0	8, 1	5, 4

first number = # of animals with 20% reduction; second number = # of animals with 40% reduction

As shown, the number of female rats with reduced platelet counts tended to increase with time and dose. However, there was not a clear worsening in all animals with time.

In males, no clear dose or time dependent effect on reduction of platelet counts was evident. Generally, 2-4 animals in each group including controls had marginal reductions in platelets. However, platelets in one MD male were reduced by 67% at week 52.

Clinical Chemistry:

The most dramatic, clearly dose-related effect was decreased cholesterol in females. The mean elevations in SGPT and SGOT in females were significant ($p<0.05$), but marginal; only sporadic instances of significant individual elevations (2X control values) were recorded. By week 52, no elevations were evident in PPX-treated female rats. At week 52, SGPT and SGOT levels were elevated in 1 LD and 1 HD male rats, and SGPT was elevated 1 MD male. Serum bilirubin levels fluctuated in all dosage groups throughout the study.

increased SGPT	-	MDF (wks 6-27) HDF (wks 6-39) MDM (wk 6) LDM, MDM (wk 27)
increased SGOT	-	MDF, HDF (wks 6-52)
increased AP	-	MDF, HDF (wks 6-52)
decreased cholesterol	-	dose-dep decrease in females, marked at HD; (wk 6-52) no changes in males
decreased triglycerides	-	all females, not dose-dep (largest effect in MD); (wk 6-52) MDM, HDM - small effect
increased urea	-	MDF, HDF (wk 6-52) MDM (wk 13, 27, 39)
decreased K	-	dose-dep decrease in females (wk 6-52); HDM (wk 6-52)

Protein Analysis:

The noted changes were generally within the normal range. Individual variations that were outside of the normal range at week 52 were elevated γ-globulin in 1 LDM and increased α_2-globulin in 1 HDF.

decreased total protein	-	MDF, HDF (wk 39 & 52) MDM (wk 39)
decreased albumin	-	MDF, HDF (wk 6-52)

		-	HDM (wk 52)
	increased globulin	-	MDF, HDF (wk 6-52)
	decreased globulin	-	MDM (wk 39)
	increased γ-globulin	-	MDF, HDF (wk 6-52) HDM (wk 13, 27, 52 MDM (wk 27)
	decreased γ-globulin	-	LDM (wk 39)
	decreased α_1-globulin	-	LDF (wk 52) MDF (wk 13, 39, 52) HDF (wk 39, 52)
	decreased α_2-globulin	-	MDM (wk 27) HDM (wk 27, 39)
	increased α_2-globulin	-	LDM (wk 39)
	increased β-globulin	-	MDF,HDF (wk 39, 52)
Urinalysis:			
	blood/RBCs	-	MDF, HDF (also found in some controls, LDM, MDM)

Organ Weights:

↓ liver	-	HDM
↓ thymus	-	MDF, HDF
↑ ovary	-	LDF, MDF, HDF

Gross Pathology:

Premature decedents:	-	no drug-related findings
Survivors:		
uterine dilatation	-	2/20 LDF 5/20 MDF 6/19 HDF
ovarian size increase	-	14/20 MDF 18/19 HDF
thymus, small	-	3/19 HDF

Histopathology:

Males:

Leydig cell, hyperplasia	-	10 LDM 7 MDM 2 HDM
adenoma	-	1 ConM 1 LDM
kidney, pyelonephritis	-	2 MDM, 1 HDM

Females:

corpora lutea, enlarged	-	2 CON 0 LD 18 MD 19 HD
pyometra	-	1 MD 5 HD
adrenals, decreased lipids/ birefringent substances		3 HD
kidney, pyelonephritis		1 HDF
uterus, dilatation	-	similar incidence rate (10-25% in all groups)
squamous metaplasia	-	4 HDF
glandular cystic metaplasia	-	1 MDF 1 HDF
pyometra	-	1 MDF 5 HDF
bladder, squam. metaplasia	-	1 HDF
mammary gland	-	see discussion of amendment

Neoplasia:

A total of eleven animals were diagnosed with tumors during the study. The tumors are known to occur spontaneously in Wistar rats. No clear pattern of frequency or distribution was identified; thus, the tumors were not clearly related to PPX administration (Tab. C.2.a.1).

Incidence of tumor types, listed according to animal number and primary site per group and sex (G 59 - SND 919 CL 2Y, feed, rat, 52 weeks)

Study group	0		1		2		3	
Sex*	m	f	m	f	m	f	m	f
Heart								
Neurilemmoma+							316	
Testis								
Leydig cell adenoma	008++u		116u++					
Pituitary gland								
Adenoma nos.		058		159				
		064						
		065						
Cervical lymph node(s)								
Malignant lymphoma					204			
Thymus								
Malignant lymphoma					204			
Skin/subcutis								
Fibrosarcoma								
Sarcoma nos.	015						369	
Brain								
Granular cell tumor			151					

*m = male, f = female
+ = according to the classification of Alison et al.[1]
++u = unilateral

Plasma Concentrations:

In females, plasma concentrations of PPX were proportional to dose. In males, plasma concentrations were greater than dose-proportional. The plasma concentrations of PPX in males 1 hr after dosing appeared to be much higher during week 26 and 52 compared to week 1. Plasma concentrations in males 8 hrs after dosing were highest during week 26 compared to weeks 52 and 1. In females, time-related differences were not marked (Tab. C.2.a.2).

Table [redacted]. Rat Mean Plasma Pramipexole Concentrations (ng/mL) in the 52-Week Toxicity Study*

C.2.a.2.

Sex	Dose (mg/kg)	Week			Mean
		1	26	52	
1 Hour After Start of Light Phase					
Female	0.5	4.79	6.45	5.04	5.43
	3	22.45	36.24	25.25	27.98
	15	176.77	189.74	163.49	176.67
Male	0.5	1.87	4.10	4.02	3.33
	3	13.33	32.74	37.23	27.77
	15	174.46	385.39	332.98	297.61
8 Hours After Start of Light Phase					
Female	0.5	2.37	5.09	2.72	3.39
	3	11.74	21.65	10.18	14.52
	15	39.72	99.93	56.29	65.31
Male	0.5	1.41	2.65	2.53	2.20
	3	12.08	21.82	22.20	18.70
	15	87.15	219.94	136.04	147.71

* [18] arithmetic means

C.2.b. 52-Week Chronic Toxicity Study in Rhesus Monkey

Conducted by :

Document #(s):

Upjohn TR 7219-94-065

Sponsor Volumes: 1.39-1.41

This study complied with GLP

Summary:

Pramipexole was administered by gavage at doses of 0, 0.1, 0.5 and 2.0 mg/kg/day to rhesus monkeys (4/sex/dose) for 52 weeks. Few notable drug-related toxicities were apparent, but dosing was limited to 2.0 mg/kg because of drug-induced injurious behavior in the animals during the early phase of the study. The most significant drug-related effect was bradycardia with increased R-R and Q-T intervals recorded during weeks 29/30, 36/37, and 47/48 at 1.5 to 6 hrs post-dose; however, this effect was only observed in mid-dose males. One death, a low-dose female, occurred late in the study; death did not appear to be drug-related. Behavioral changes (agitation, jumping, swinging, gripping) occurred early in the study but diminished over the course of treatment. Body weight and food consumption were not affected by PPX. There were no treatment-related hematological or urinary changes, and only some modest changes in clinical chemistry were noted. Organ weights were not altered and no histopathological findings were attributed to PPX. Plasma concentrations of PPX were measured 2, 4, 6 and 24 hrs after drug treatment during weeks 1, 26, and 50. Monkey plasma concentrations 2 hrs after dosing were approximately 2- (low test dose) to 80-fold (high test dose) higher than the human $Cmax_{ss}$ following the projected human PPX maintenance dose of 1.5 mg, t.i.d. (4.0-6.5 ng/ml). Thus, oral administration of 0.1-2.0 mg/kg/day PPX for 52 weeks does not produce significant pathologic effects in monkeys.

Methods:

Dosages: 0.1, 0.5, 2.0 mg/kg/day (Batch II)

Low dose is two times the expected human dose (at the time of study initiation). The high dose was selected as the highest tolerable dose based on a range-finding study.

Route of Administration: oral (gastric intubation after feeding)

Species/Number: Rhesus monkeys (16 males, 16 females)

Mean initial weights:

males:	4.3 to 6.5 kg
females:	3.8 to 6.2 kg

Toxicokinetic Analyses:

Blood was sampled during weeks 1, 26 and 50 at 2, 4, 6 and 24 hrs after drug administration. (Note: The analysis was by an RIA method rather than the HPLC/EC method used in rodent studies.)

Parameters monitored/Intervals:

Clinical	-	daily
Body weight	-	weekly
Food consumption	-	weekly
Fecal Occult Blood	-	predose and wks 13, 26, 40 and 52
Hematology	-	predose and wks 6, 13, 26, 39 and 52

- hemoglobin concentration (Hb)
- mean cell volume (MCV)
- red blood cell count (RBC) and derived indices:
  mean cell hemoglobin (MCH)
  packed cell volume (PCV)
  mean cell hemoglobin concentration (MCHC)
- thrombin time (TT)
- prothrombin time (PT)
- partial thromboplastin time (PTT)
- total and differential white blood cell count (WBC)
- reticulocytes
- platelets
- blood sedimentation rate

With the exception of thrombin time (TT), prothrombin time (PT), and partial thromboplastin time (PTT), all the above parameter were examined on blood collected in EDTA anticoagulant.

Thrombin time (TT), prothrombin time (PT), and partial thromboplastin time (PTT) was determined on blood collected into trisodium citrate (0.11 mol/l, ratio 1:9).

- rib and bone marrow (beyond the requirements of the study protocol)
- salivary gland (submaxillary)
- sciatic nerve
- seminal vesicle
- skeletal muscle
- skin and mammary gland
- spinal cord (cervical)
- spleen
- sternum and bone marrow
- stomach
- testes
- thymus
- thyroids (with parathyroids)
- tongue
- trachea
- urinary bladder
- uterus
- all unusual lesions

The above tissues were transferred to the study sponsor for further processing and examination.

Histopathology was conducted by the sponsor.

Statistics

Body weight, food consumption and organ weight comparisons were made by one-way ANOVA and Newman-Keuls test for multiple comparisons. Hematology, clinical chemistry, ECG, BP, and organ/body weight ratios were compared by one-way ANOVA based on ranks, and Newman-Keuls test for multiple comparisons. Plasma concentration data were evaluated by ANOVA to assess the dose-proportionality relationship.

Results:

Mortality: One LDF died on day 364 of study. Signs of a persistent bacterial infection (chronic purulent pericarditis and pleuritis), but no signs of systemic toxicity were present.

Clinical Signs:

Dose-related increases in agitation occurred during the first months of the study. The effect was most prominent the night of the first administration as indicated by the presence of wounds caused by thrashing in cages. In the following weeks, the behavioral changes (jumping, swinging, gripping) that started 3-4 hrs after treatment and persisted for several hours diminished, such that during the final months of treatment these behaviors did not occur.

Body Weight Gain:

No statistically significant changes were observed (Fig. C.2.b.1).

Food Intake:

Occasional statistically significant effects were observed, but no clear drug-related trends (Fig. C.2.b.2).

Ophthalmology:

According to the sponsor, no treatment-related ocular changes occurred, but a number of notations appeared in the Pathologists report (i.e., visible cribrosum plate, pale optic disc). These findings were discussed with Dr. Tony Carreras of HFD-540 who concurred with the sponsor's conclusion.

Fig. C.2.b.1

Figure 1

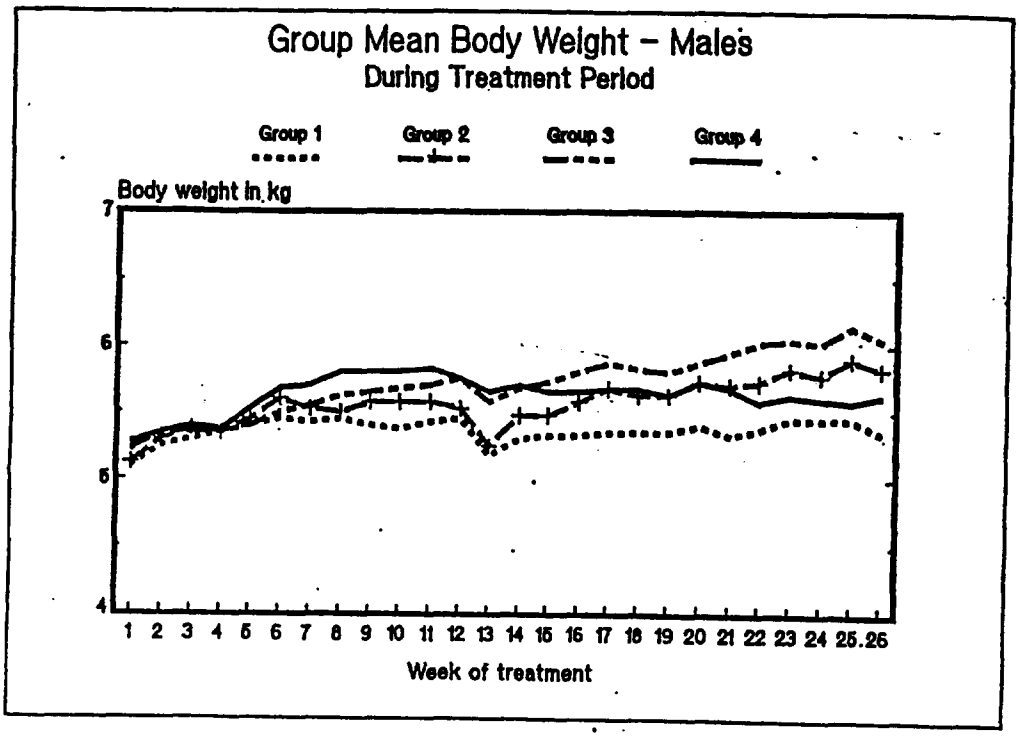


Figure 1 (cont.)

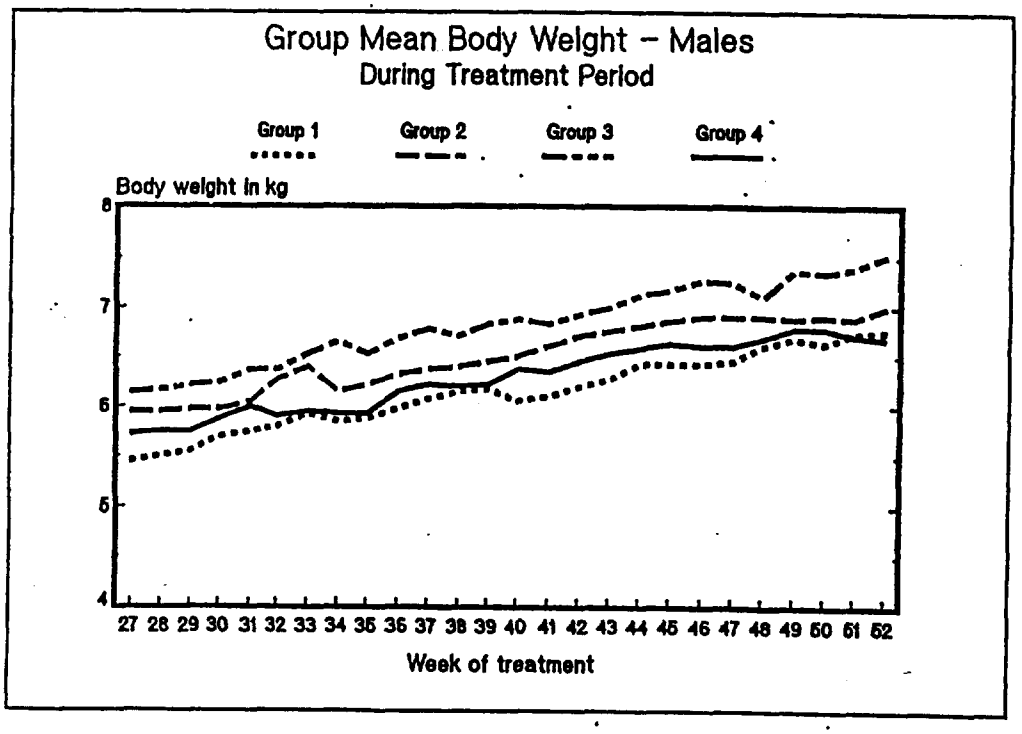


Figure C.2.b.1 (cont.)

Figure 2

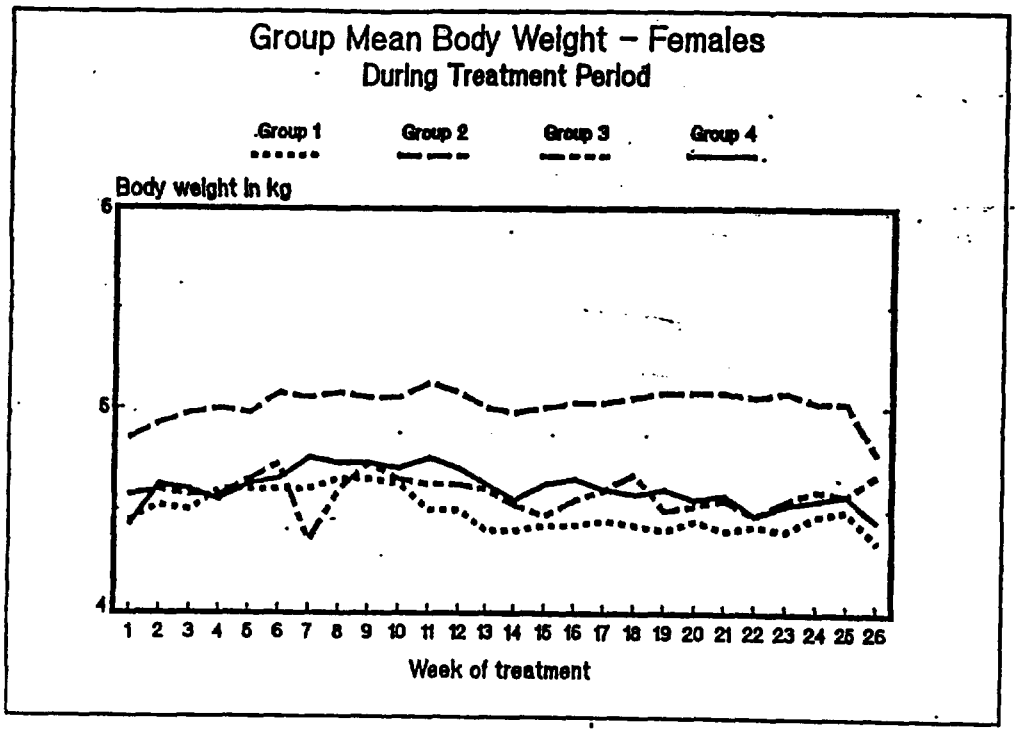


Figure 2 (cont.)

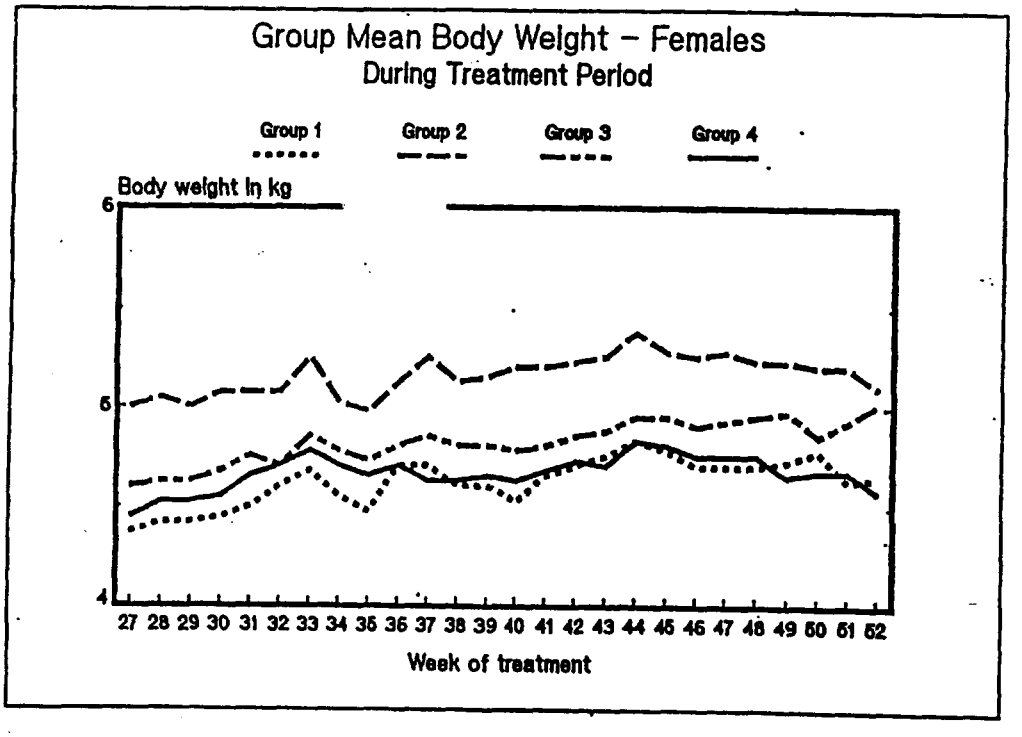


Figure C.2.b.2.

Figure 3

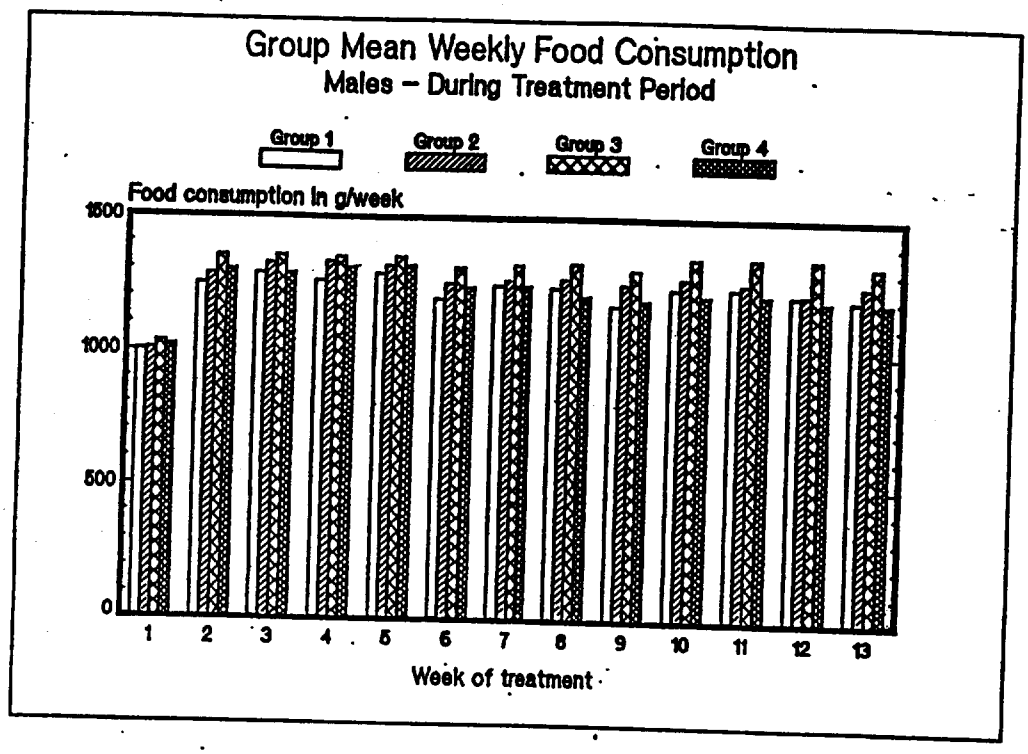


Figure 3 (cont.)

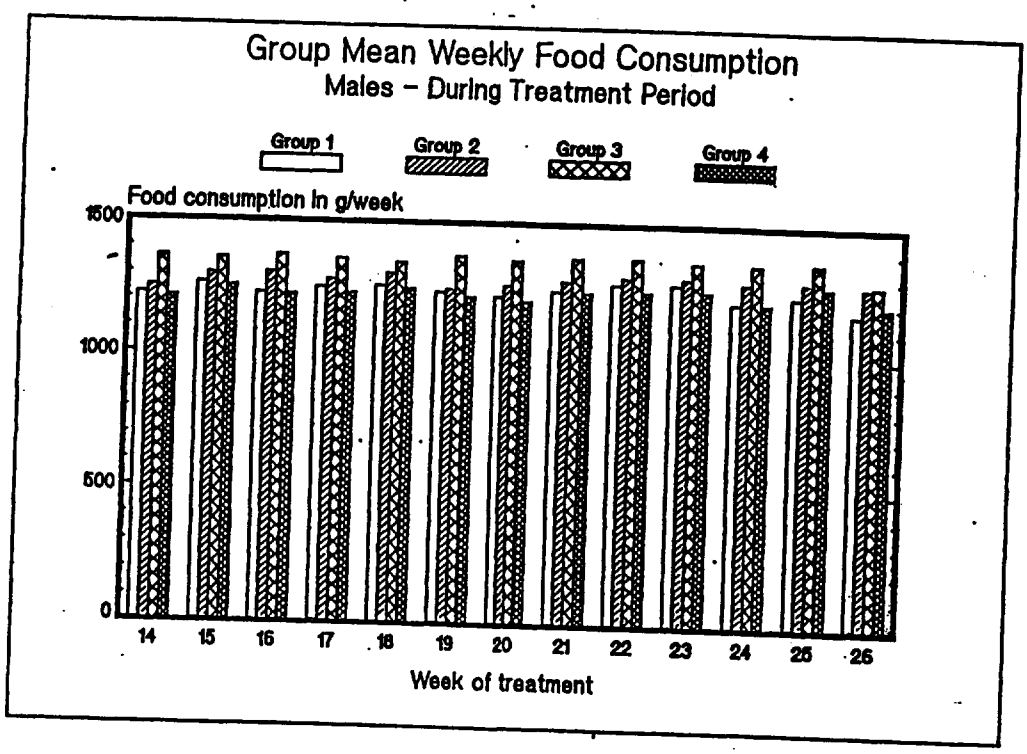
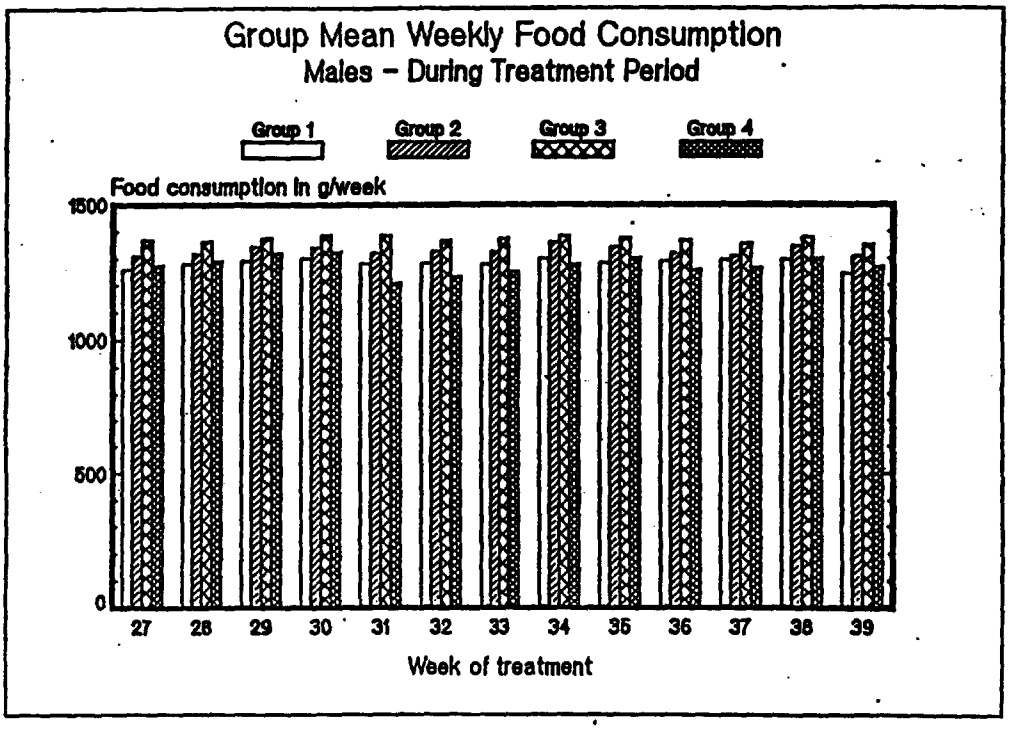


Fig. C.2.b.2. (cont.)

Figure 3 (cont.)



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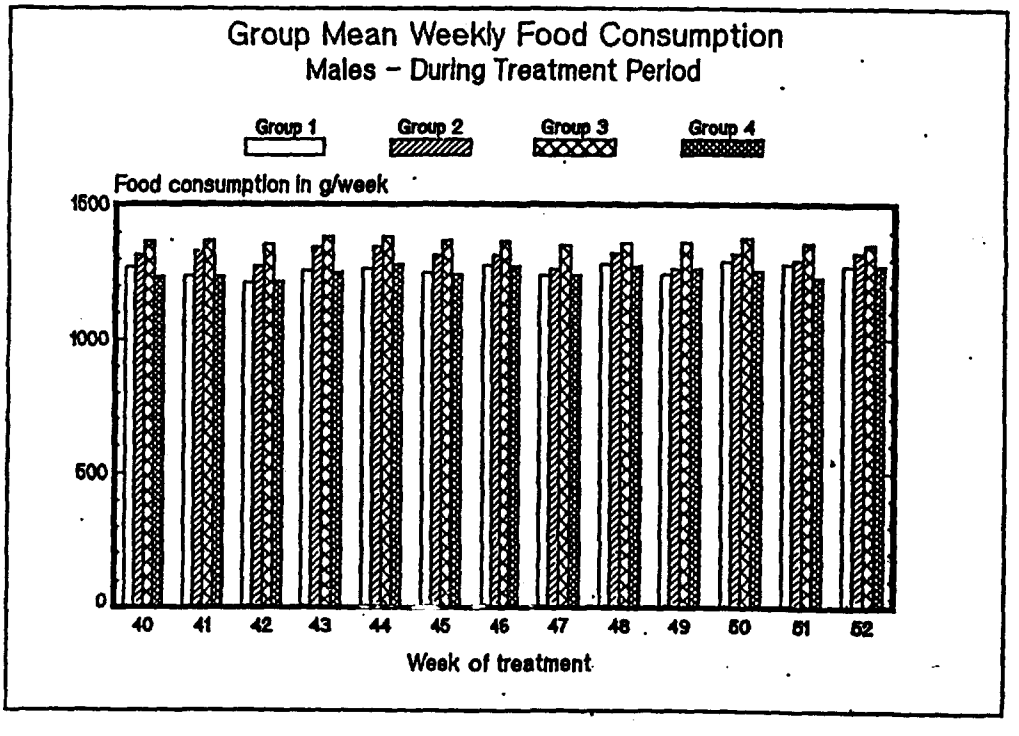


Figure C.2.b.2. (cont.)

Figure 4

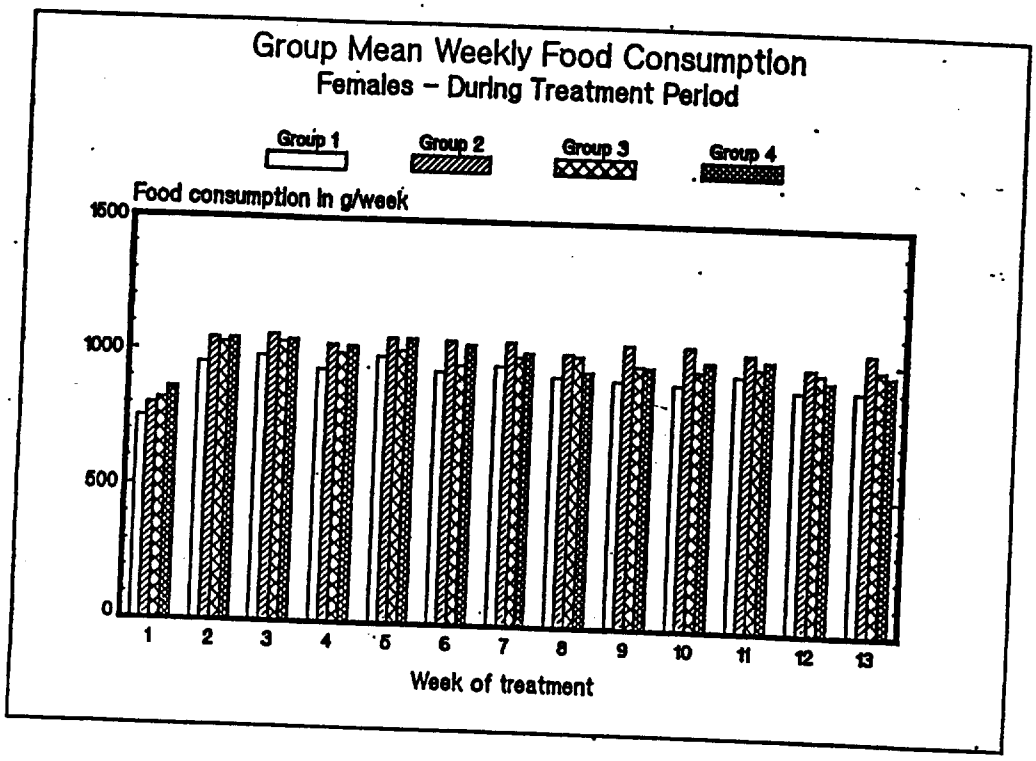


Figure 4 (cont.)

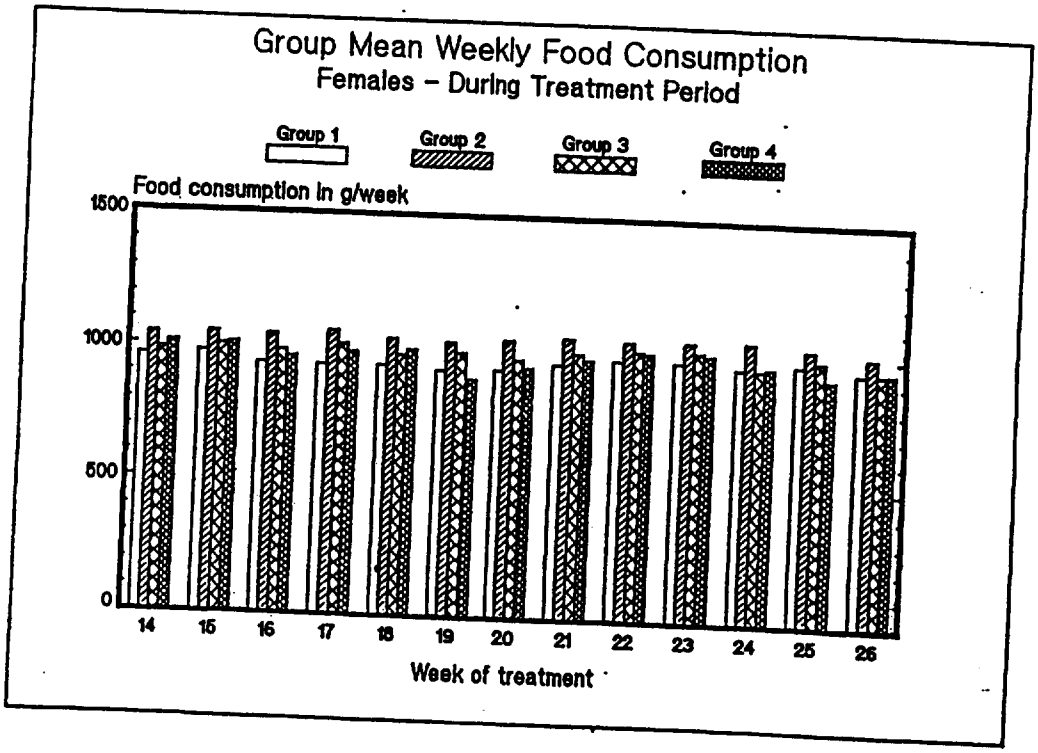
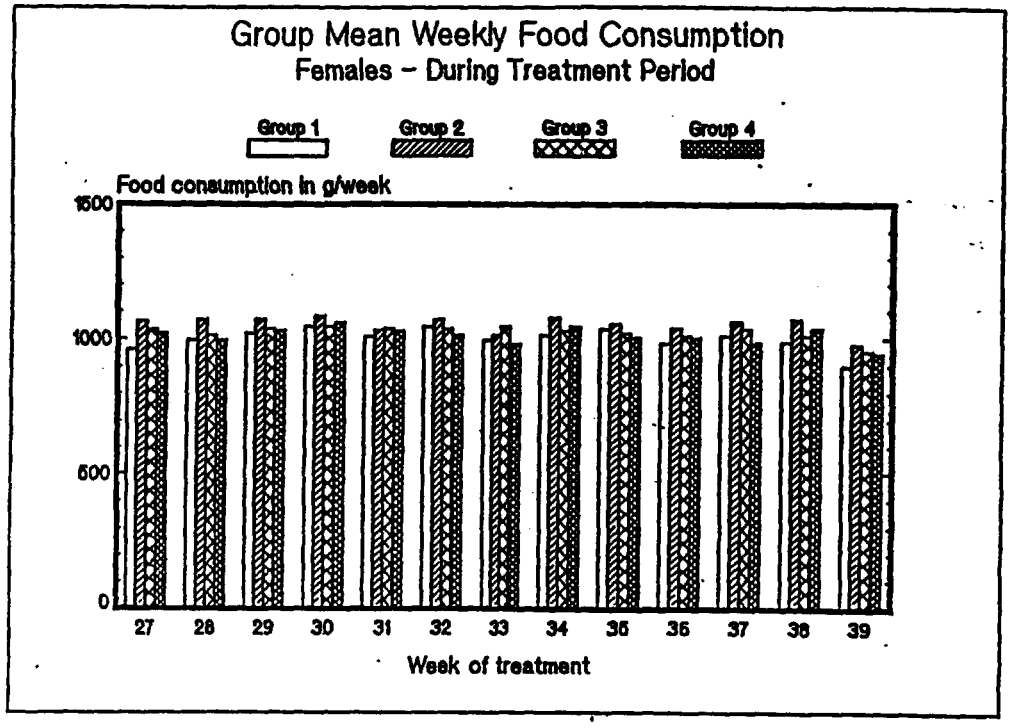


Figure C.2.b.2. (cont.)

Figure 4 (cont.)



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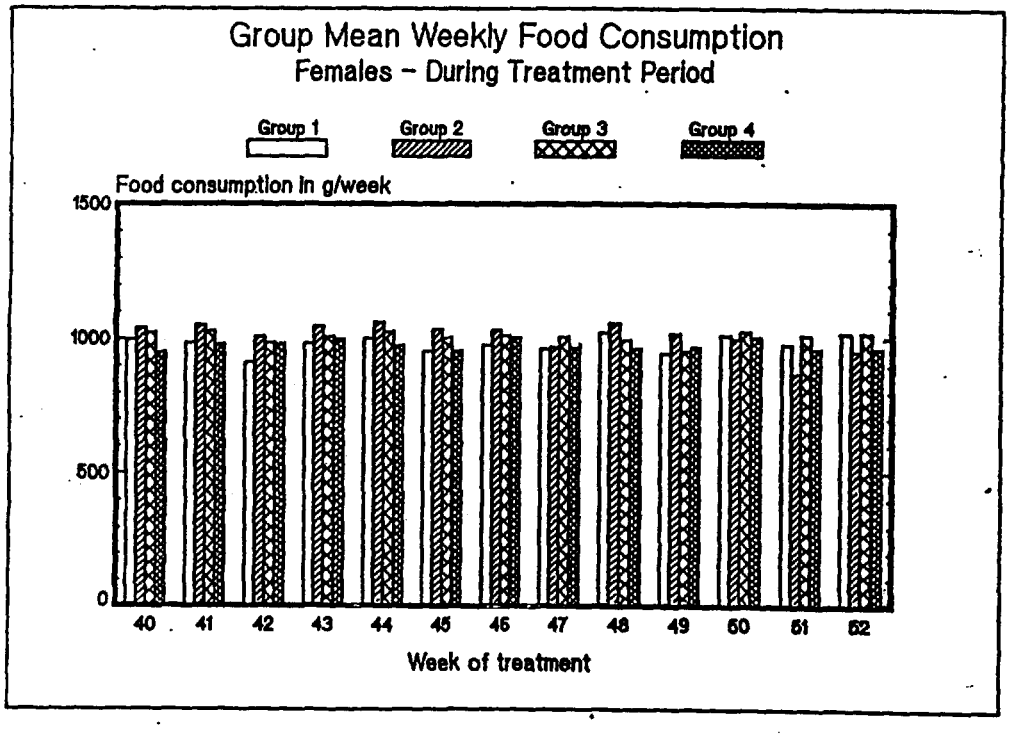


Hematology:

Group variations:

There were occasional statistically significant events, but no clear drug-related trends and variances were within a normal range.

increase PT	-	MDF (wk 39)
decrease PT	-	MDF (wk 52)
increase PTT	-	LDM (wk 26) MDM (wks 6, 13, 26, 39) HDM (wks 26, 39) MDF (wks 39, 52)

Individual variations:

decrease RBC (RBC range 5-8)	-	2 0F (wk 52) 1 LDM (wks 26, 52) 1 MDM (wk 26) 1 HDM, 1 HDF (wk 52)
decrease WBC (range = 17-23 x 10^9/L)	-	2 0F (wk 52) 1 LDM (wk 0, 26) 1 LDF (wk 0, 13, 26, 39, 52) 1 HDM (wk 0, 6, 39)
increase WBC	-	1 LDM (wk 6)
increase Baso % ($\geq$ 4)	-	1 MDM (wk 6) 1 MDF (wk 6) 1 HDF (wk 6)
increase Eos % ($\geq$ 10-m, 8-f)	-	1 LDF (wk 6), 1 LDF (wk 26)
decrease Lymphos % ($\leq$ 25)	-	1 0F (wk 26) 1 LDF (wk 52) 1 MDM (wk 6) 1 MDF (wk 6, 26) 1 MDF (wk 26) 1 HDF (wk 13)

Clinical Chemistry

Group variations:

There were occasional statistically significant events, but no clear drug-related trends.

Individual variations:

Listed are variations that occurred outside of a reference range (in parentheses) in drug-treated animals only.

increase LDH (3x con & predose)	-	1 HDF (wk 13)
increase AP (2x pre & >1000)	-	1 LDM (wks 13, 26) 1 LDF (wk 52)
increase BUN (2x con & predose)	-	4 LDM (wk 52) 3 MDM (wk 52) 2 HDM (wk 52)
(no corresponding increases in creatinine)		
increase CPK	-	At week 52, several PPX-treated and contol animals had levels that were more than 3x higher than predose levels.

Urinalysis:

Hemoglobin was detected most frequently and in relatively greater amounts in HDF at most time points. However, at week 52 no Hb was detected in samples from this group.

Cardiovascular Measurements:

The most significant cardiovascular effect was bradycardia with a corresponding increase in R-R interval. The effect was most evident in animals of the mid-dose group. During week 29/30, heart rate was reduced at 1.5-6 hrs post-dose in MDM, but the effect was statistically significant only at 6 hr. Significant bradycardia occurred at 1.5 hr in MDM during week 36/37 and 47/48, and 6 hr post-dose in MDF during week 36/37.

Significant effects on blood pressure were decreases in systolic, diastolic, and mean arterial pressures at 6 hr postdose in HDF during weeks 29/30, and an increase in mean arterial pressure in LDF at 1.5 hr postdose during weeks 47/48. Significant pressure elevations were detected in females of all dosage groups at 24 hrs postdose in weeks 36/37, but this may have been the result of subnormal pressures in control animals.

Other significant effects on ECG recordings were:

increase Q-T -	MDM, 3 hr	(wk 29/30)
	MDM, 1.5 hr	(wk 36/37)
	L,M&HDM, 1.5 hr	(wk 47/48)
decrease QRS -	HDF, 3 hr	(wk 29/30)
	HDM, 6 hr	(wk 47/48)

Although predose recordings were not taken, the noted cardiovascular effects appeared to be drug-related since readings were normal 24 hrs postdose.

Organ Weights:

No clear drug-related changes occurred. There was a nearly significant increase in testes weight in MDM, and a nearly significant decrease in adrenal weights in HDF.

Histopathology:

Findings observed only in drug-treated animals were:

testes:	reduced spermiogenesis	-	1 LDM
			2 HDM
epididymis:	reduced sperm number	-	2 LDM
			2 HDM
spleen:	focal fibrosis	-	1 MDM
	reduced follicle size	-	1 LDM

The male reproductive effects were attributed to sexual immaturity.

Myelogram:

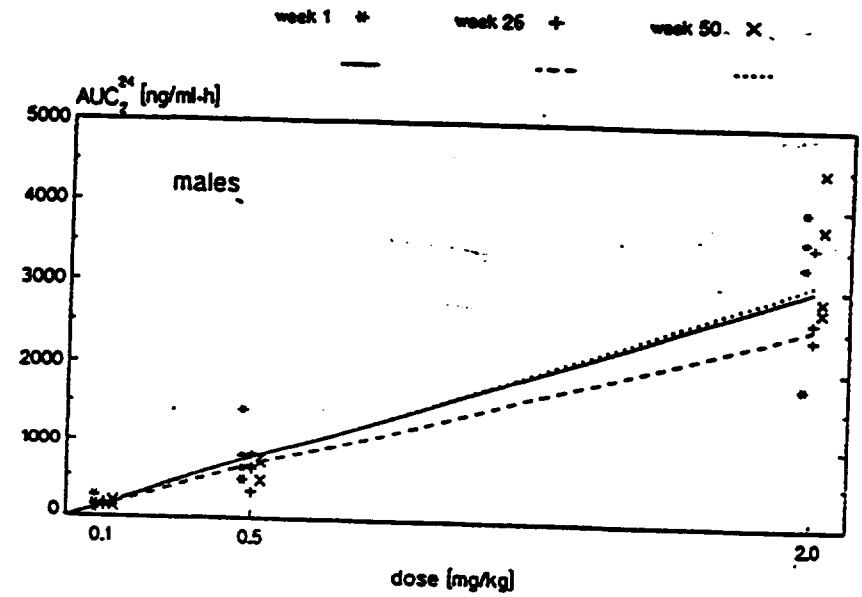
No drug-related changes in the erythropoietic or granulopoietic system were evident.

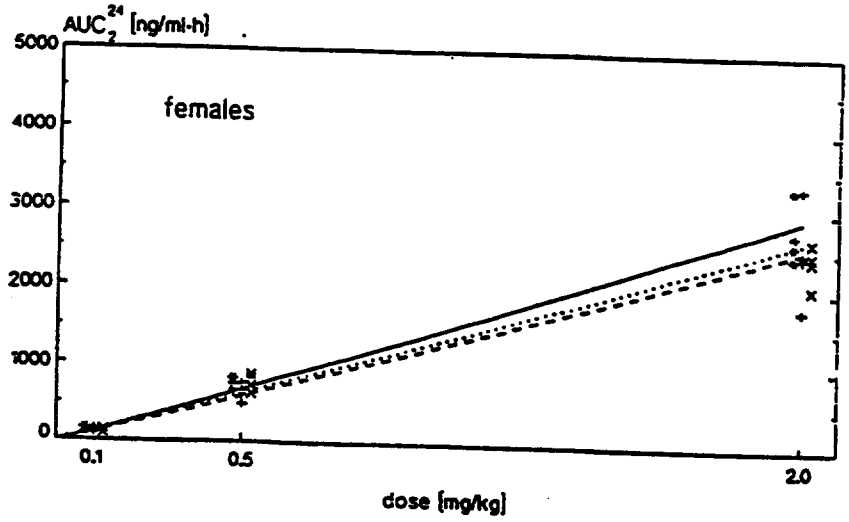
Plasma Concentrations:

PRAM concentartions in monkey plasma were determined by RIA at 2, 4, 6 and 24 hrs postdose during weeks 1, 26 and 50. Increases in plasma concentrations and AUCs were approximately dose-proportional. ANOVA indicated that significantly higher concentrations were present in males at the 6 and 24 hr time points, and also according to AUC. There were no suggestions of drug accumulation (Fig. C.2.b.3, Tab. C.2.b.1).

Figure C.2.b.3

Fig.5: SND 919 CL2 Y , 52-week toxicity (gavage) in the monkey
AUC HLD project no. 059-018





U-1159

Tab. C.2.b.1.

Plasma Concs

Tab. #: SND 919 CL 2 Y / rhesus monkey / 52-week oral toxicity /

Mean plasma concentrations [ng/ml]

HOURS	SEX	DOSE	WEEK 1	WEEK 26	WEEK 50	MEAN
2	Female	0.1	12.325	15.525	10.963	12.938
		0.5	60.613	98.746	73.575	77.644
		2	199.100	397.000	235.237	277.112
	MALE	0.1	8.637	19.450	9.250	12.446
		0.5	66.258	85.096	55.213	68.856
		2	209.375	421.800	316.875	316.017
4	FEMALE	0.1	11.212	10.088	9.000	10.100
		0.5	68.563	64.150	63.350	65.354
		2	221.517	275.062	208.700	235.093
	MALE	0.1	12.633	15.075	15.238	14.315
		0.5	66.138	62.100	58.325	62.188
		2	223.000	288.437	297.312	269.583
6	FEMALE	0.1	8.000	6.762	7.112	7.292
		0.5	53.058	37.721	52.338	47.706
		2	202.500	146.562	159.187	169.417
	MALE	0.1	11.450	9.200	11.875	10.842
		0.5	54.183	35.638	43.754	44.525
		2	238.042	161.250	238.538	212.610
24	FEMALE	0.1	0.775	0.637	1.087	0.833
		0.5	3.900	3.238	4.058	3.732
		2	12.563	12.400	18.042	14.335
	MALE	0.1	2.325	1.187	1.212	1.575
		0.5	8.575	3.175	4.262	5.337
		2	14.896	19.904	18.800	17.867

Tab. #: SND 919 CL 2 Y / rhesus monkey / 52-week oral toxicity /

Mean AUC (2 - 24 hours) data [ng/ml·h]

AUC

SEX	DOSE	WEEK 1	WEEK 26	WEEK 50	Mean
Female	0.1	121.725	109.063	109.875	113.554
	0.5	763.421	633.392	760.175	718.996
	2	2780.195	2524.350	2406.887	2570.478
Male	0.1	169.329	152.287	169.387	163.668
	0.5	817.542	594.246	647.767	686.518
	2	3169.855	2790.212	[illegible]	[illegible]

C.3 Reproductive Toxicology

Conducted by :

These studies complied with GLP

C.3.a. Segment I in Rats: Fertility and Reproduction

Document #(s):

Upjohn TR 7219-94-077

Sponsor Volume: 1.42

Summary:

Pramipexole was administered by gavage at doses of 0, 0.1, 0.5 and 2.5 mg/kg/day to Wistar (Chbb:THOM) rats (24/sex/dose). Males were treated for 70 days prior to mating, and sacrificed after mating. Females were treated for 14 days prior to mating. One half of the females were treated through gestation, and sacrificed on day 22 for delivery of pups by Caesarean section. The remaining females littered spontaneously and drug treatment was continued through the weaning period (21 days).

Overt drug-related changes were restlessness and agitation with the middle and high doses, and decreased body weight gain and food intake at the high dose. No reproductive toxicities (abnormalities in mating, pregnancy or pup development) were apparent in animals of the low-dose group, or the mid-dose animals (dams and pups) delivered by Caesarean section. Significant toxicities were evident in the high-dose treatment group. Irregular estrus (prolongation by 1-2 days) occurred in about one-half of the HDF; hence, a longer mating period was required for successful insemination. In addition, the numbers of corpora lutea, implantations, pregnant females and females that successfully delivered were markedly reduced. Teratogenic effects of pramipexole were not evident, but one case of micrognathia inferior occurred in an MD pup. The teratogenicity data are limited by the low number of evaluable pups. Body weight development was impaired in pups from the mid- and high dose dams, but statistical evaluation of the high dose pup data was not possible due to the low number of reared pups. The sponsor suggests this impairment may have been due to drug-induced CNS stimulation in the dams resulting in reduced suckling opportunities. An alternative possibility is that inhibition of prolactin secretion by PPX reduced milk production in dams. Other developmental parameters, including fertility, were not affected by PPX. Histopathological findings in F_0 animals were prostate edema in one male subject from each dosage group, and hydronephrosis in one MD and one HD dam. The analysis of the testes may be considered inadequate since tissue fixation was in formalin rather than Bouin's solution. Plasma concentrations were not measured in this study. Thus, prampipexole produces significant reproductive toxicity, most evident as a reduction in successful pregnancies at a dose of 2.5 mg/kg. In view of the established role of prolactin in the

maintenance of pregnancy in the rat, and the probability that this dopamine agonist inhibits prolactin secretion, it is likely that the infertility is due to effects in the dam. However, additional studies are necessary to determine the source of infertility.

Methods:

Dosages: 0.1, 0.5, 2.5 mg/kg/day (Drug Lot: Batch III; prepared in distilled water)

Low dose is five times the expected human dose (at the time of study initiation). The high dose was selected as the highest tolerable dose based on a range-finding study.

Route of Administration: oral (gavage)

Species/Number: 96 males and 96 nulliparous females

Mean initial weights/age:

males:	218 g / 8 weeks
females:	209 g / 11 weeks

Parameters monitored/Intervals:

Clinical	-	daily
Body weight	-	weekly in males; daily in females
Food consumption	-	weekly

At Termination -

Males: Testes and epididymis were weighed, fixed in 7.5% formalin, and stored.

Females: Gross pathology, numbers of fetuses (viable and dead), corpora lutea, and resorptions. Non-pregnant females were excluded from mean calculations.

Fetuses: (C-section group) Live/dead, sex, external, skeletal (2/3 of subjects), and visceral (1/3 of subjects) abnormalities.

Pups: (rearing group) Live/dead, body weight, sex, gross abnormalities, functional/maturational parameters (erection of pinnae, fur growth, eye opening, etc.). At weaning, four pups (2 male, 2 female) were retained for additional developmental tests (simming, Preyer reflex, pupillary reflex, water T-maze), and fertility testing at 10 weeks. All pups were examined for pathological changes.

Statistics

Statistical comparisons were made by Bartlett test, one-way ANOVA, Newman-Keuls or Dunnett's test for multiple comparisons, and Chi-square and Fisher's exact test.

Results:

Effects in Males:

Mortality: none

Clinical Signs:

Dose-dependent increases in the severity and duration of restlessness and agitation were evident in MD and HD males.

Body Weight Gain:

Significantly decreased in the HD groups during weeks 1-10 (Fig. C.3.a.1).

Food Intake:

Significantly decreased in the HD groups during week 1, and increased during weeks 2-3 (Fig. C.3.a.2).

Copulation:

One control and one MD male did not copulate.

Necropsy:

Prostate edema occurred in one male from each dose group (LD, MD, HD). One control male had unilateral testicular hypoplasia, but there were no significant differences in testicular weights among treatment groups.

Effects in Females:

Mortality: none

Clinical Signs:

Dose-dependent increases in the severity and duration of restlessness were evident MD and HD during the entire treatment period.

Body Weight Gain:

Mean body weight was significantly reduced in the HD group during week 1 of treatment. After mating, the only significant effect on body weight was a slight decrease in the HD C-section group (Fig. C.3.a.3).

Food Intake:

Decreased in the HD group during week 1, and in the LD group during week 2.

Estrous Cycle:

A dose-dependent increase in estrous cycle irregularities was evident (2 LDF, 3 MDF, 13 HDF). For 4 HD females, two estrous cycles were required for successful insemination (Tab. C.3.a.1).

Gestation (Tab. C.3.a.2):

C-section group: Of 12 rats per dose group, 1 MD and 10 HD animals were not pregnant. Body weight and food consumption did not differ among groups.

Spontaneous delivery group: Seven of 12 dams in the HD group did not become pregnant. Body weight did not differ significantly among groups . Food consumption was significantly reduced throughout lactation in the HD group, and during week 1 of lactation in the LD group.

Necropsy: One MD and 1 HD dam had unilateral hydronephrosis.

Effects on fetuses and pups:

C-section group: Only 2 of 12 HD dams were pregnant, and only one had viable fetuses. There were no statistical variations among control, LD and MD litters; the HD group was not included in the analyses because of the low survivor number. The number of implantations in the HD group is clearly lower than in other groups. There were no dose-related trends in the incidence of malformations or skeletal and visceral variations, although one case of micrognathia inferior was found in an MD pup (Tables C.3.a.3-5).

Spontaneous delivery group: Significant reductions in weight were recorded in HD pups at birth, day 4 and day 21, and in MD pups at day 21. Body weight gain from days 1-4 and days 4-21 was also significantly reduced in MD and HD pups (Tables C.3.a.6-7; Fig.C.3.a.4).

The only other notable difference in tests of pup maturation and behavior was a slight (insignificant) delay in eye-opening in MD and HD pups. No drug-related pathological changes were identified in pups (Table C.3.a.8). In fertility studies of the F1 generation, no overt fertility impairments were apparent. Body weights of the F_1 MD and HD dams were reduced during their gestational period, but body weight gain during gestation did not differ among groups of F_1 offspring (Fig. C.3.a.5).

C.3.a.1

Fig. C.3.a.1

[redacted] Males- Bodyweight

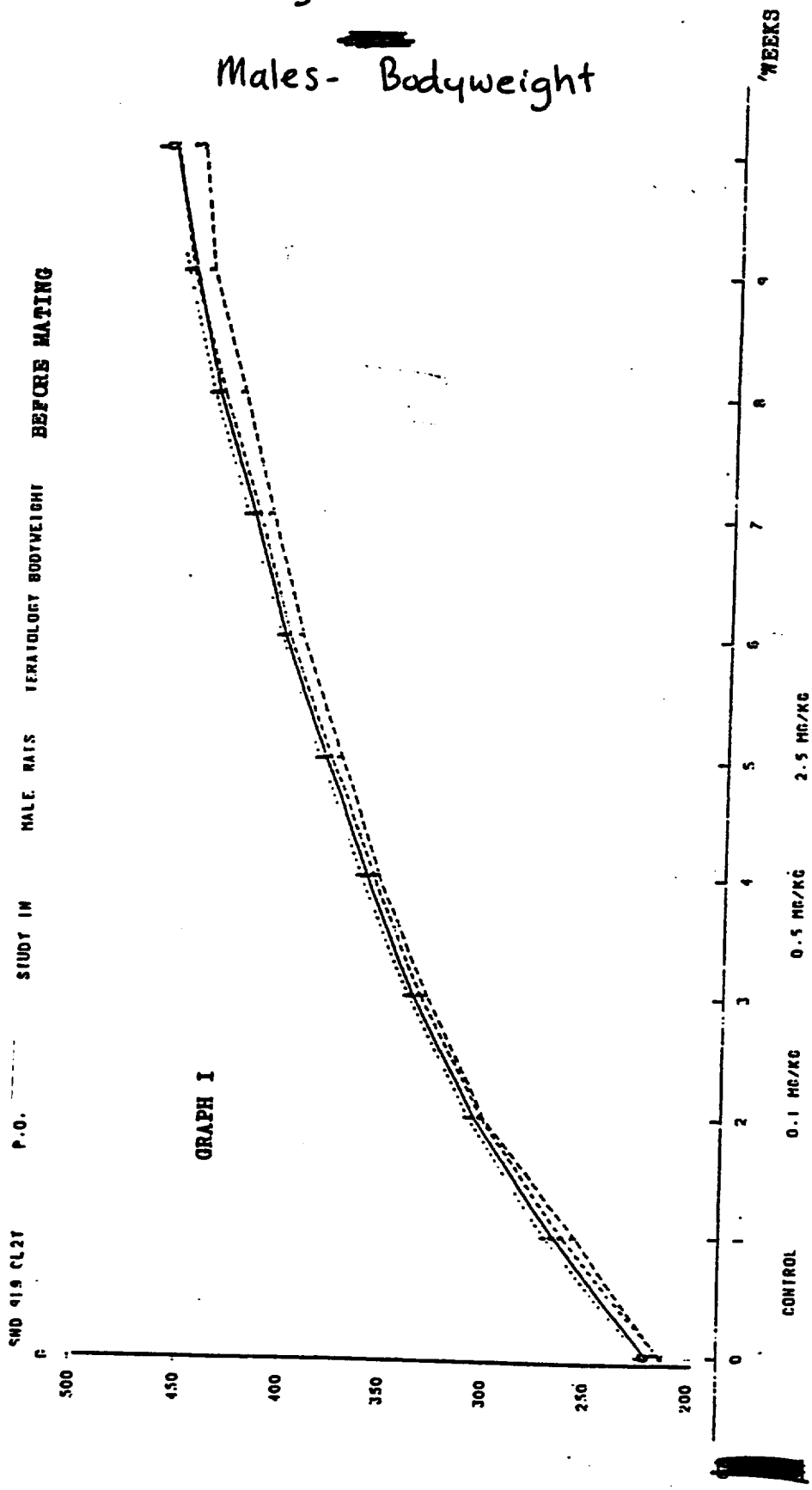


Figure C.3.a.2.

Males - Food Consumption

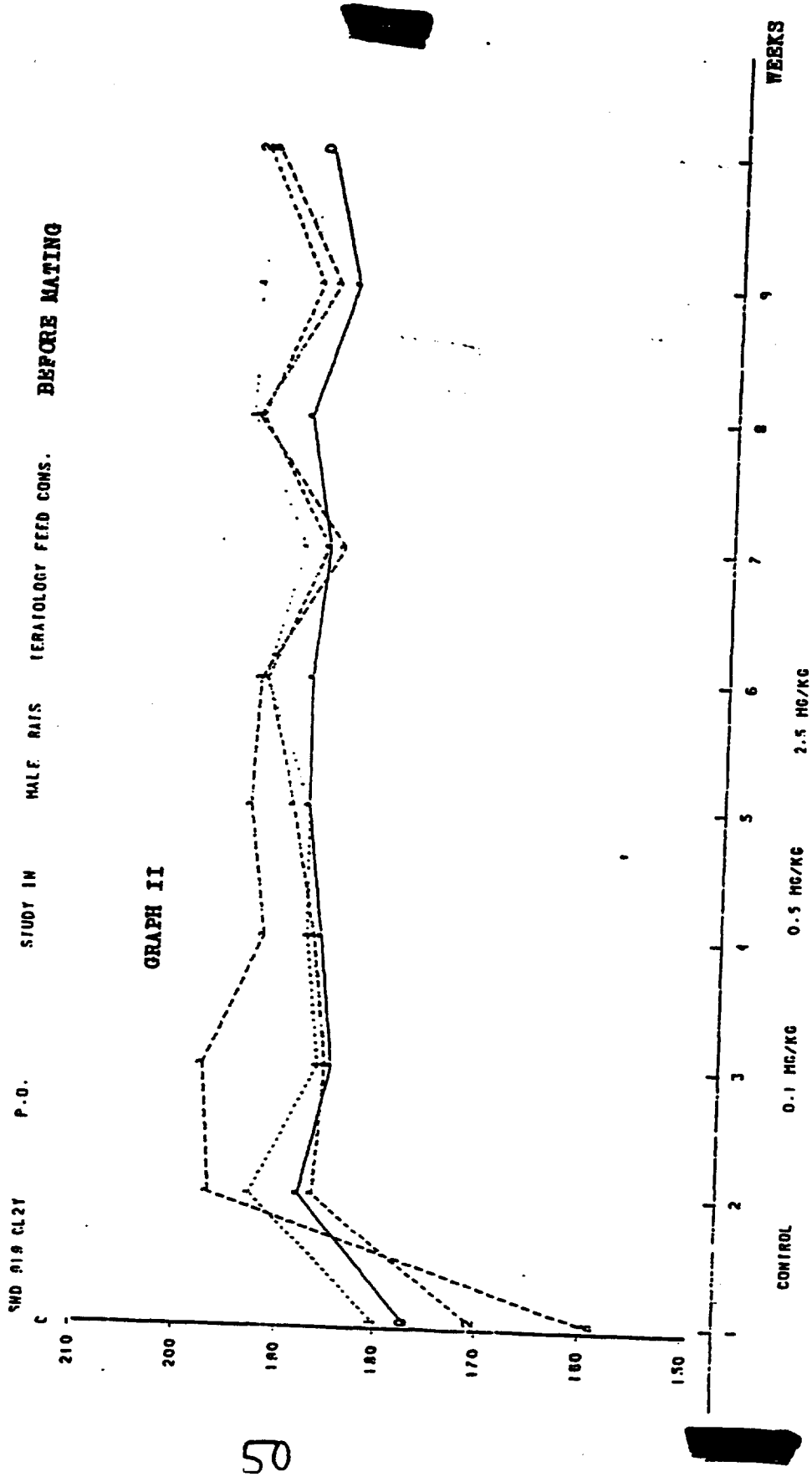


Fig. C.3.a.3

Females - Bodyweight

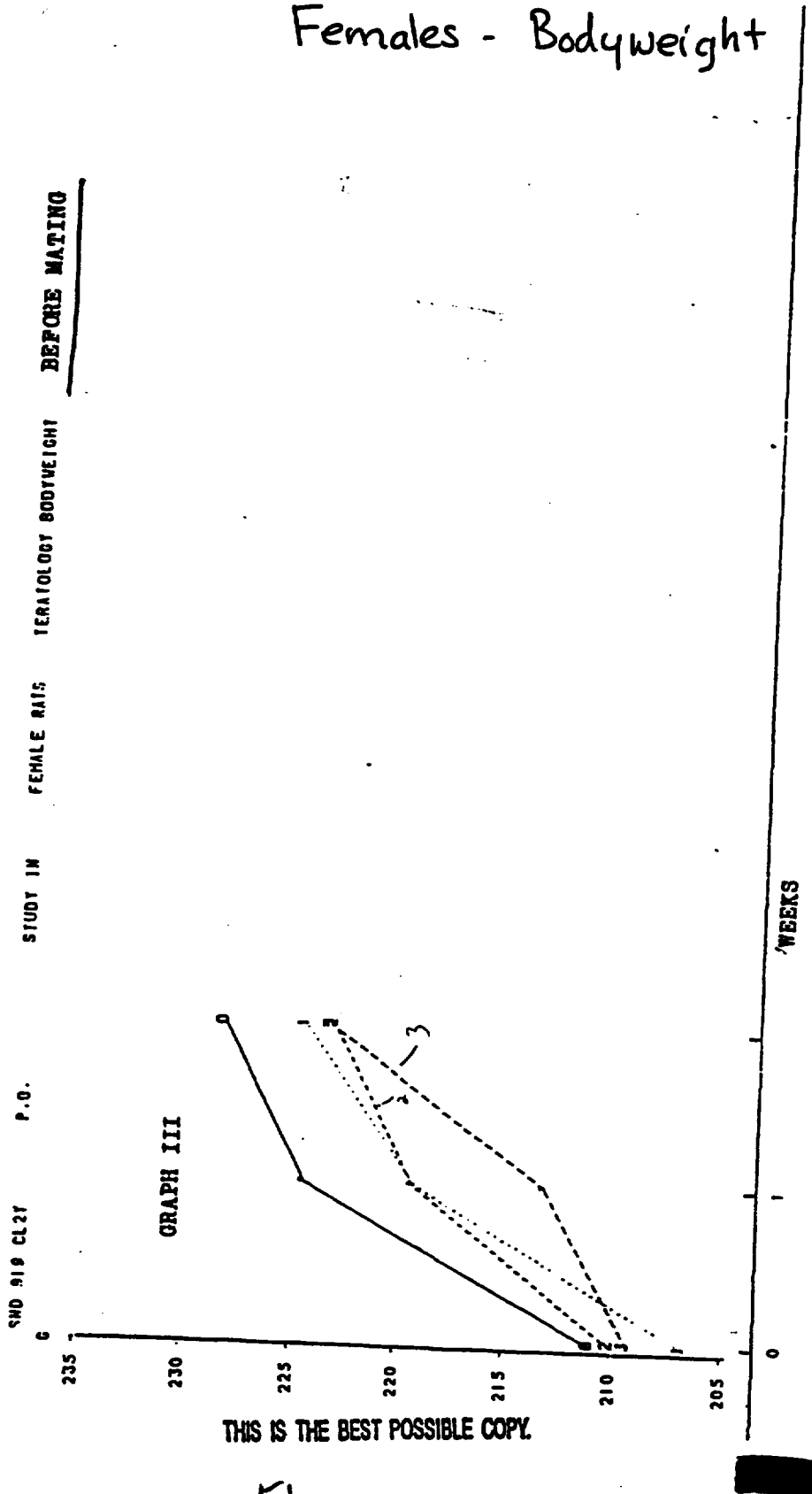


Fig. C.3.a.3. (cont.)

Females - Bodyweight

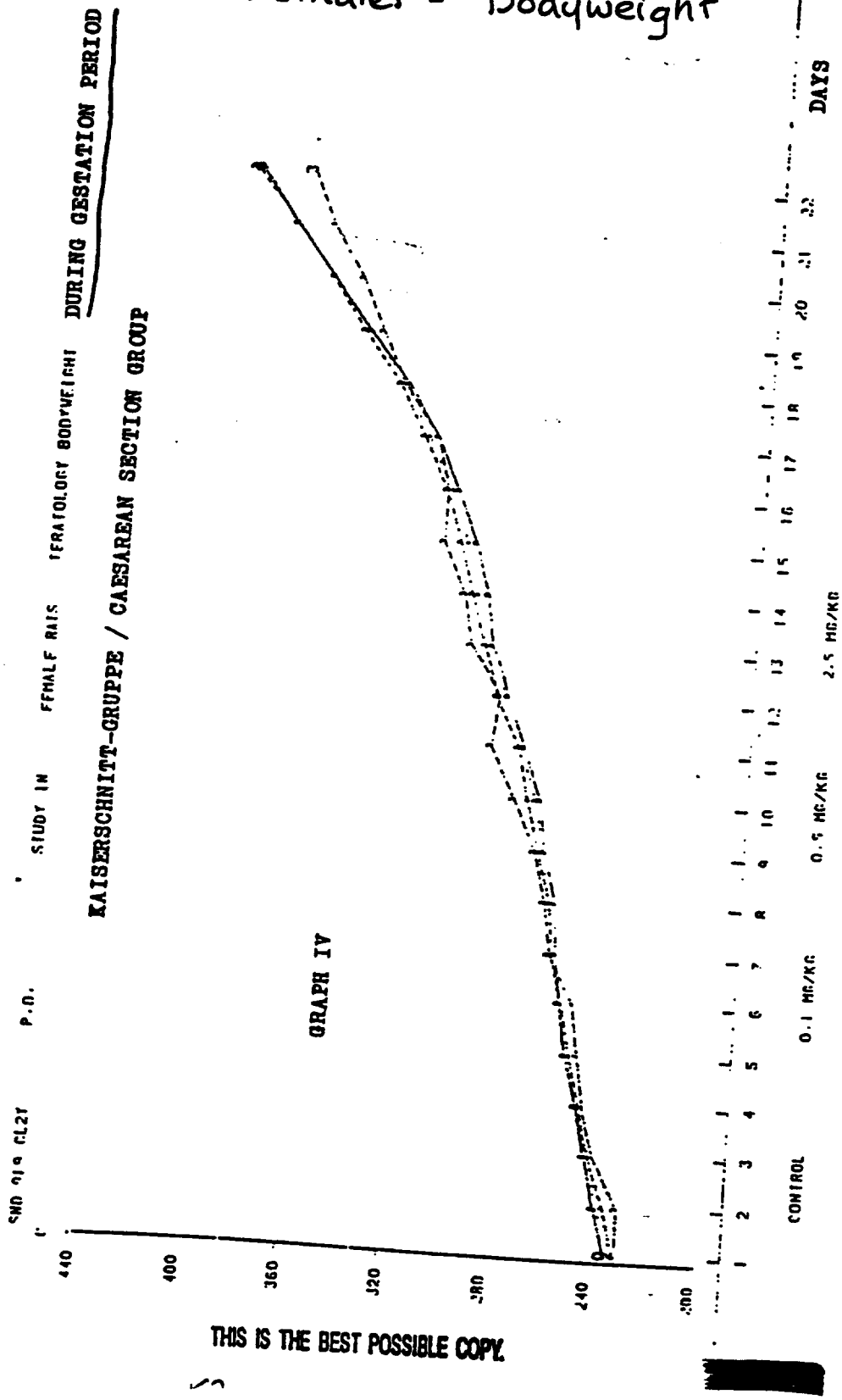
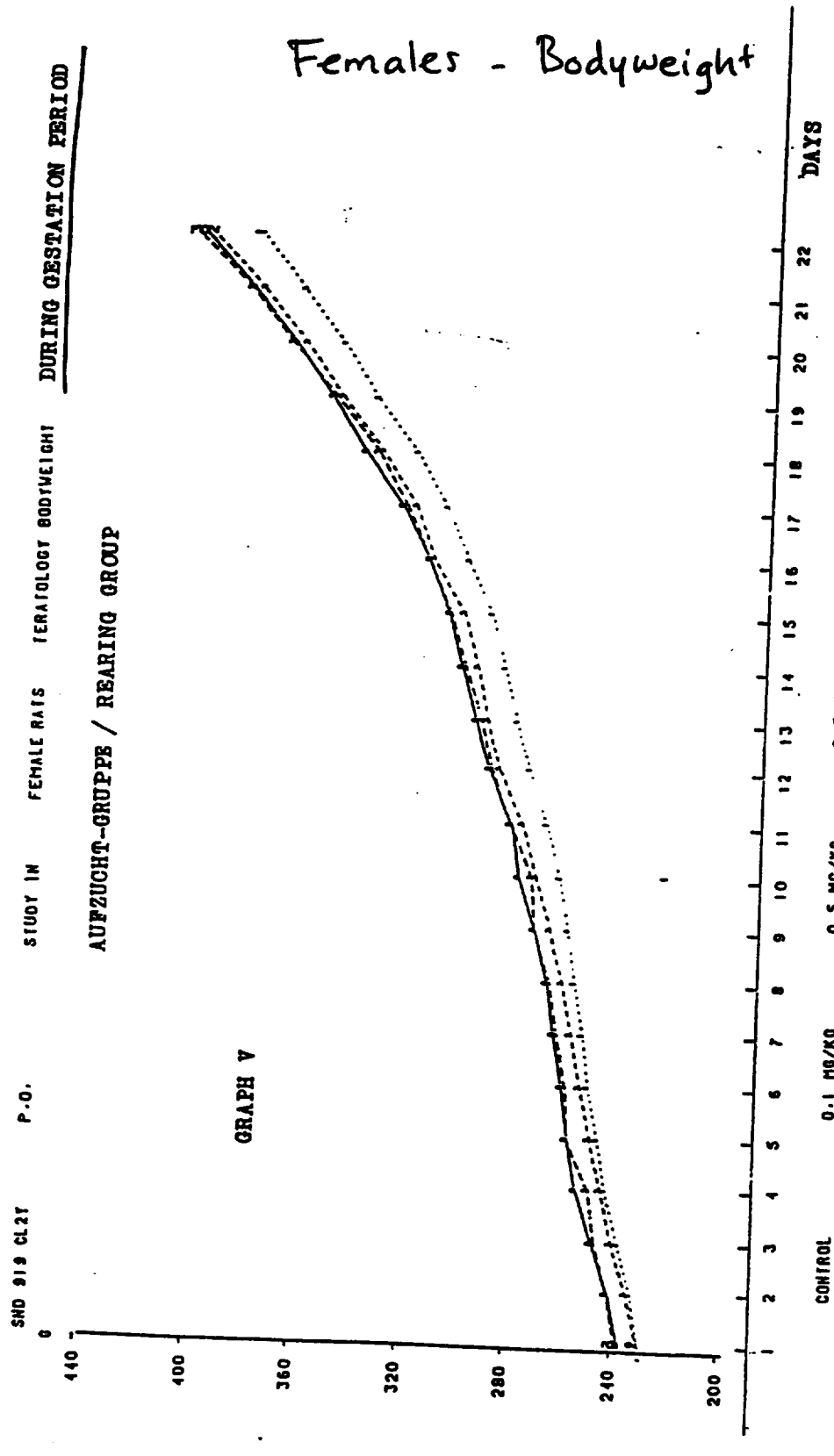


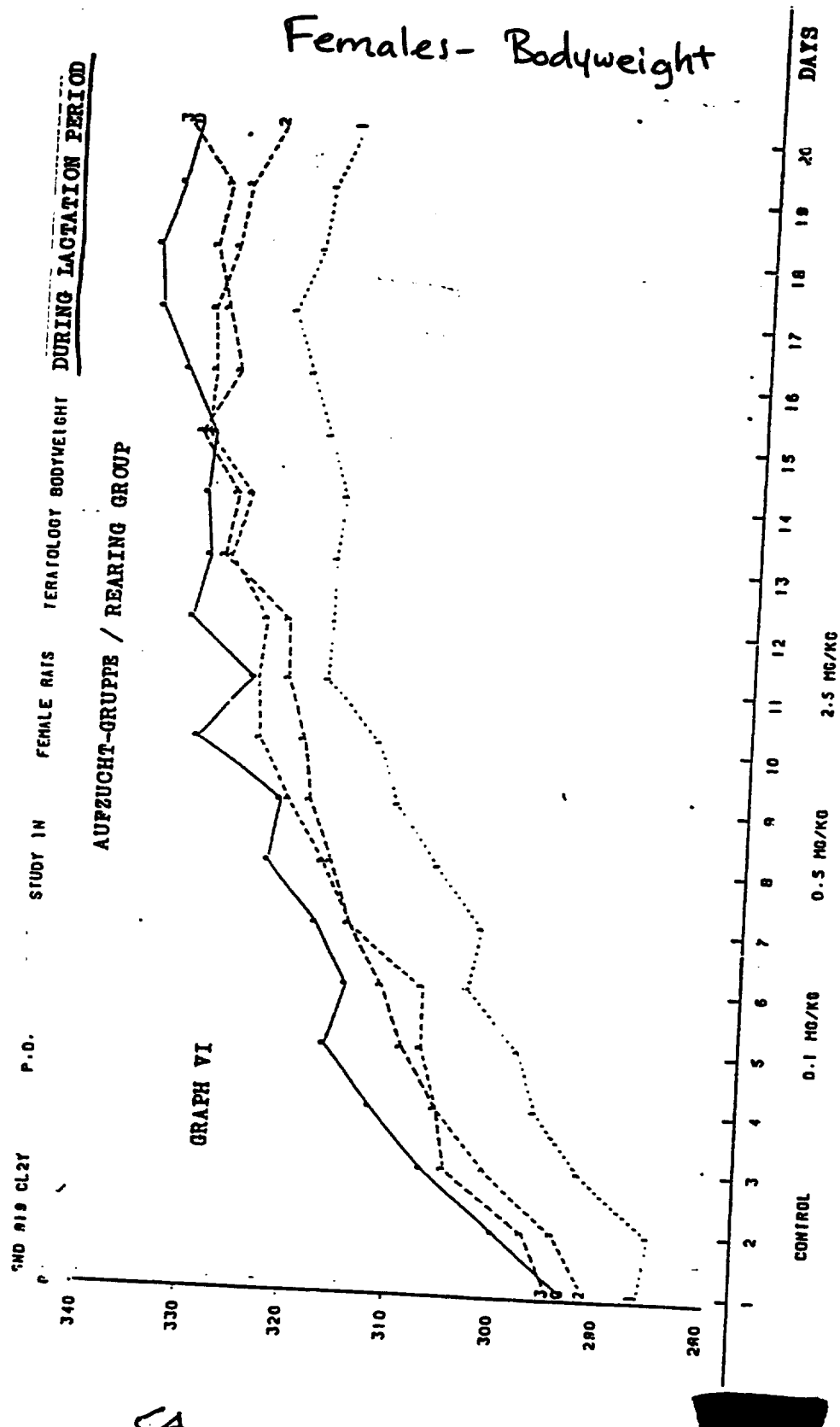
Fig. C.3.a.3.(cont.)

Females - Bodyweight



· Fig. C.3.a.3. (cont.)

Females- Bodyweight



Tab. # C.3.a.1

SND 919 CL 2 Y

RATS

LENGTH OF ESTROUS CYCLE DURING ADMINISTRATION PERIOD

DOSE	NO. OF ANIM.	REGULAR (4 DAYS)	<4 DAYS	>4 DAYS	IRREGULAR <AND >4 DAYS
CONTROL	24	24	0	0	0
0.1 MG/KG	24	22	0	2	0
0.5 MG/KG	24	21	0	3	0
2.5 MG/KG	24	11	0	12	1

SND 919 CL 2 Y

Tab. # C.3.a.2.

RATS

MATING PERFORMANCE

GROUP	NO. OF RATS WITH POSITIVE SMEARS AT "n" - DAYS AFTER PAIRING													NO. OF PREGNANT ANIMALS		
	n=1	2	3	4	5	6	7	8	9	10	11	12	TOTAL	SACRIFICED AT DAY 22	ALLOWED TO PRODUCE	TOTAL
	1	6	7	9												
0.1 MG/KG	8	6	4	6									23	12	11	23
0.5 MG/KG	4	7	8	4									24	12	12	24
2.5 MG/KG	7	6	5	2	2		1		1				23	11	11	22
													24	2	5	7

C.3.a.3

Tab. [redacted]

REPRODUCTION TOXICOLOGY

RATS

'STUDY NO. : R02

SUM VALUES CAESAREAN SECTION GROUP

	CONTROL	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
TOTAL NUMBER OF ANIMALS	12	12	12	12
MATERNAL MORTALITY	0	0	0	0
TOTAL RESORPTIONS	0	0	0	1
NATURAL DELIVERIES	0	0	0	0
ANIM. WITH VIABLE FET.	12	12	11	1
CORPORA LUTEA	191	186	171	34
IMPLANTATIONS	185	172	157	24
VIABLE FETUSES	174	162	146	10
MALE IN %	47	48	51	50
FEMALE IN %	53	52	49	50
DEAD FETUSES	0	0	0	0
RESORPTIONS	11	10	11	13
EARLY IN %	64	70	55	93
LATE IN %	36	30	45	7
MALFORMATIONS	1	0	1	0
VARIATIONS	15	15	8	0

C.3.a.4.

Tab. [redacted]

REPRODUCTION TOXICOLOGY

SPEC. / RATS SEGM. 1 /STUDY NO. : R02

LITTER DATA MEAN VALUES — CAESAREAN SECTION GROUP

		CONTROL	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
WEIGHT / FETUS (G)	MW	5.81	5.25	5.26	5.25
	SD	0.19	0.22	0.38	0.00
PLAC. WEIGHT/ FETUS (G)	MW	0.44	0.41	0.40	0.44
	SD	0.08	0.02	0.04	0.00
CORPORA LUTEA / DAM	MW	15.9	15.5	15.5	23.0
	SD	1.6	1.6	1.4	0.0
IMPLANTATIONS / DAM	MW	15.4	14.3	14.3	13.0
	SD	1.7	1.9	1.6	0.0
VIABLE FETUSES / DAM	MW	14.5	13.5	13.3	10.0
	SD	1.7	1.7	1.7	0.0
DEAD FETUSES / DAM	MW	0.0	0.0	0.0	0.0
	SD	0.0	0.0	0.0	0.0
RESORPTIONS / DAM	MW	0.9	0.8	1.0	3.0
	SD	1.1	0.9	0.8	0.0
MALFORMATIONS / DAM	MW	0.1	0.0	0.1	0.0
	SD	0.3	0.0	0.3	0.0
VARIATIONS / DAM	MW	1.3	1.3	0.7	0.0
	SD	1.5	1.5	1.3	0.0
VIABLE FET. IN % IMPL.	MW	97.2	96.9	96.9	76.9
	SD	3.4	2.8	2.3	0.0
RESORPTIONS IN % IMPL.	MW	2.8	3.1	5.1	23.1
	SD	3.4	2.8	2.3	0.0
PRE IMPLANTAT. LOSS %	MW	1.6	3.7	4.1	43.5
	SD	1.8	4.4	4.6	0.0
POST IMPLANTAT. LOSS %	MW	2.8	3.1	5.1	23.1
	SD	3.4	2.8	2.3	0.0
MALFORM. IN % VIAB. FET.	MW	0.1	0.0	0.1	0.0
	SD	0.6	0.0	0.7	0.0
VARIAT. IN % VIAB. FET.	MW	10.7	9.8	3.7	0.0
	SD	10.4	10.8	8.8	0.0

CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

Study No.: R 02

Tab. C.3.a.5.

RATS

FINDINGS IN FETUSES	CAESAREAN SECTION GROUP			
	Contr.	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
TOTAL NO. OF FETUSES EXAMINED	174	162	146	10
FOR SKELETAL DIAGNOSIS	115	108	105	7
FOR VISCERAL DIAGNOSIS	59	54	41	3
EXTERNAL				
POLYDACTYLIA RIGHT FOREPAW	1	0	0	0
MICROGNATHIA INFERIOR	0	0	1	0
SKELETAL				
RUDIMENTARY 13TH RIB	7	9	4	0
ADDITIONAL 14TH RIB	2	1	0	0
GENERAL INCOMPLETENESS OF OSSIFICATION	0	0	1	0
VISCERAL				
DILATATION OF RENAL PELVIS (UNI- OR BILATERAL)	6	5	3	0
RUNTS	0	0	1	0
ADDITIONAL FINDINGS IN STERNEBRAE				
POORLY OSSIFIED STERNEBRA V	8	4	3	0
POORLY OSSIFIED STERNEBRAE II, IV, V	1	0	0	0
POORLY OSSIFIED STERNEBRAE I, II, V	0	1	0	0
POORLY OSSIFIED STERNEBRAE II, III, IV, V	0	0	1	0

Tab. C.3.a.6.

STUDY.NO.: R02

RATS

/ LITTER DATA
SUM VALUES

BEARING GROUP

	/CONTR.	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
TOTAL NUMBER ANIMALS	11	12	11	12
MATERNAL MORTALITY	0	0	0	0
ABORTIONS	0	0	0	0
PREGNANT ANIMALS	11	12	11	5
STILLBIRTHS	1	0	1	0
VIABLE PUPS DAY 1	158	160	157	75
MALE IN %	51.27	46.25	51.59	48.00
FEMALE IN %	48.73	53.75	48.41	52.00
VIABLE PUPS DAY 4	156	157	156	75
VIABLE PUPS DAY 4*	88	96	88	40
VIABLE PUPS DAY 7	88	96	88	40
VIABLE PUPS DAY 14	88	96	88	40
VIABLE PUPS DAY 21	88	96	88	40
MORT. IN PUPS 1 - 4	2	3	1	0
MORT. IN PUPS 4* -21	0	0	0	0
MALFORMATIONS	0	1	0	0
VARIATIONS	0	0	0	0

*AFTER LITTER REDUCTION

Tab. C.3.a.7.

STUDY.NO.: R02

RATS

LITTER-DATA
MEAN-VALUES

REARING GROUP

		/CONTR.	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
	MW	22.00	22.00	22.00	22.00
GESTATION PERIOD OF DAMS	SD	0.00	0.00	0.00	0.00
NUMB. OF ANIM.	N	11.00	12.00	11.00	5.00
(G) TAG 1	MW	6.12	6.05	6.04	(*) 5.77
WEIGHT/PUP AT (G) DAY 1	SD	0.18	0.30	0.30	0.19
(G) TAG 4	MW	7.74	7.72	7.42	** 6.62
WEIGHT/PUP (G) DAY 4	SD	0.26	0.39	0.75	0.35
(G) TAG 4=	MW	7.90	7.91	7.57	** 6.90
WEIGHT/PUP (G) DAY 4=	SD	0.26	0.30	0.75	0.33
(G) TAG 21	MW	42.63	40.59	*** 36.60	*** 20.91
WEIGHT/PUP (G) DAY 21	SD	2.18	3.15	2.62	5.14
(G) TAG 1-4	MW	1.62	1.61	** 1.28	*** 0.84
BODYW. INCR. (G) DAY 1-4	SD	0.36	0.47	0.51	0.38
(G) TAG 4=-21	MW	34.72	32.68	** 29.03	*** 14.01
BODYW. INCR. (G) DAY 4=-21	SD	2.67	4.00	2.48	4.49
TAG 1	MW	14.36	13.33	14.27	15.00
VIABLE PUPS/ DAM DAY 1	SD	1.03	2.27	3.04	1.41
TAG 1	MW	0.09	0.00	0.09	0.00
DEAD PUPS / DAM DAY 1	SD	0.30	0.00	0.30	0.00
TAG 4	MW	14.18	13.08	14.18	15.00
VIABLE PUPS/ DAM DAY 4	SD	0.98	2.23	3.03	1.41
TAG 4=	MW	8.00	8.00	8.00	8.00
VIABLE PUPS/ DAM DAY 4=	SD	0.00	0.00	0.00	0.00
TAG 21	MW	8.00	8.00	8.00	8.00
VIABLE PUPS/ DAM DAY 21	SD	0.00	0.00	0.00	0.00
% TAG 1-4	MW	1.23	1.80	0.61	0.00
PUPS LOSS % DAY 1-4	SD	2.78	3.28	2.01	0.00
% TAG 4=-21	MW	0.00	0.00	0.00	0.00
PUPS LOSS % DAY 4=-21	SD	0.00	0.00	0.00	0.00
	MW	0.00	0.08	0.00	0.00
MALFORMATIONS / DAM	SD	0.00	0.29	0.00	0.00
	MW	0.00	0.00	0.00	0.00
VARIATIONS / DAM	SD	0.00	0.00	0.00	0.00
TAG 1	MW	0.00	0.64	0.00	0.00
MALF. % VIAB. PUPS / DAY 1	SD	0.00	2.22	0.00	0.00
TAG 1	MW	0.00	0.00	0.00	0.00
VARIAT. % VIAB. PUPS/ DAY 1	SD	0.00	0.00	0.00	0.00

** = $p < 0.01$

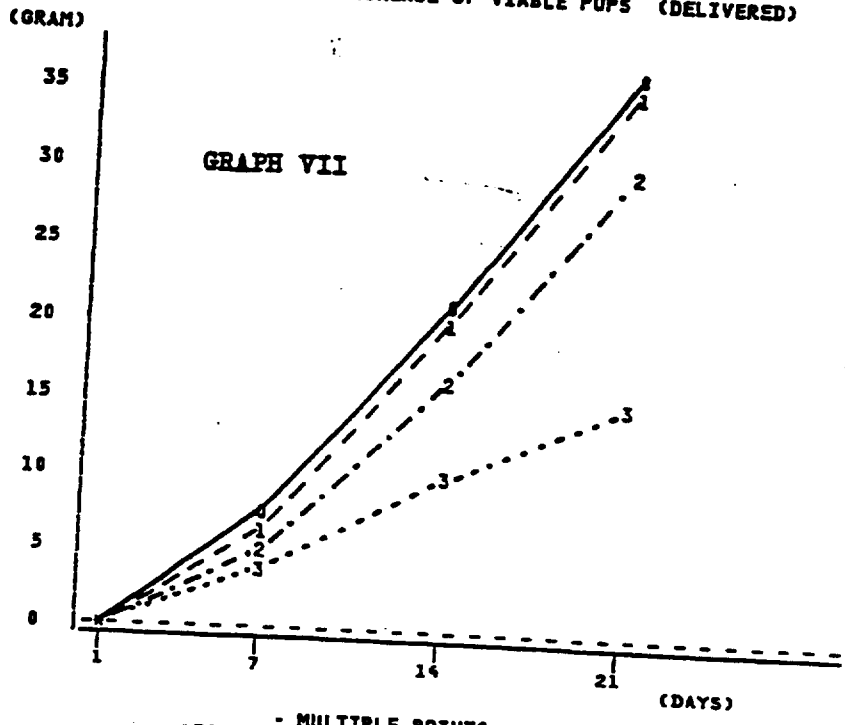
*** = $p < 0.001$

CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

.Fig. C.3.a.4.

SUBST./COMP. : SMD 919 CL2Y SPEC. : RATS
STUDY NO. : R82

MEAN BODY WEIGHT INCREASE OF VIABLE PUPS (DELIVERED)



MULTIPLE POINTS
-CONTR 1: 0.1 MG/KG 2: 0.5 MG/KG 3: 2.5 MG/KG

Study No.: R 02

SND 919 CL 2 Y

Tab. C.3.a.8.

NATS

SEGM. 1

OBSERVATIONS OF F_1-OFFSPRING IN SPONTANEOUS DELIVERY GROUP

RESULTS IN PER CENT

DOSE	EVALUATED LITTERS	ERECTION OF PINNAE		FUR GROWTH		RUNNING WITH RAISED VENTER		ERUPTION OF MAXILLARY INCISORS		EYE OPENING		
		TAG / DAY		TAG / DAY		TAG / DAY		TAG / DAY		TAG / DAY		
		4	5	6	7	12	13	12	13	15	16	17
CONTROL	11	3.4	93.2	-	100.0	100.0	100.0	100.0	100.0	28.4	80.7	100.0
0.1 MG/KG	12	3.1	95.8	-	100.0	100.0	100.0	100.0	100.0	17.7	74.0	98.0
0.5 MG/KG	11	9.1	98.9	-	100.0	100.0	100.0	100.0	100.0	2.3	67.0	100.0
2.5 MG/KG	5	2.5	100.0	-	100.0	100.0	100.0	100.0	100.0	10.0	57.5	100.0

Fig. C.3.a.5.

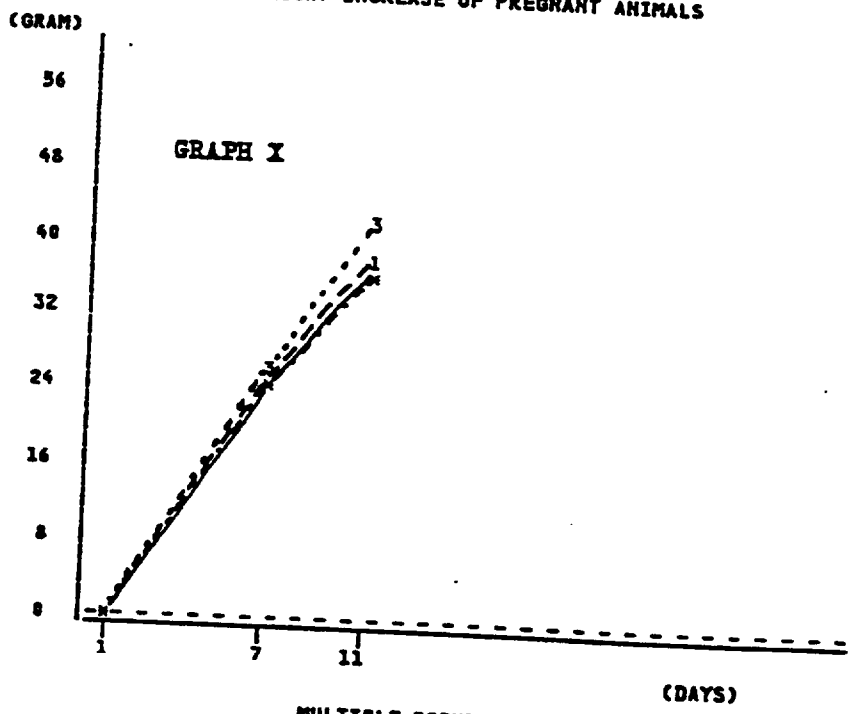
SUBST./COMP. : SND 919CL2Y
STUDY NO. : R03 SEGM. 1 SPEC. : RATS

BODY WEIGHT OF PREGNANT ANIMALS (G)(DAYS 1, 7, 11) F_1-GENERATION
MITTELWERTE / MEAN VALUES

		N	1	7	11
CONTROL	MW	10	238.2	261.8	274.4
	SD		13.0	12.1	9.3
0.1 MG/KG	MW	11	228.5	252.8	267.4
	SD		12.8	18.9	24.2
0.5 MG/KG	MW	11	216.8*	240.8*	253.1(*)
	SD		17.1	19.1	28.4
2.5 MG/KG	MW	4	196.8***	223.3**	237.8*
	SD		25.9	27.8	34.6

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

MEAN BODY WEIGHT INCREASE OF PREGNANT ANIMALS



MULTIPLE POINTS
CONTR 1: 0.1 MG/KG 2: 0.5 MG/KG 3: 2.5 MG/KG

Tab. C.3.a.9

SUBST./COMP. : SND 919CL2Y
STUDY NO. : R03
SEGM. 1
SPEC. : RATS

LITTER DATA
SUM VALUES F_1-GENERATION
SACRIFICED DAY 16-16)

	CONTROL	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
TOTAL NUMBER OF ANIMALS	11	12	11	5
MATERNAL MORTALITY	0	0	0	0
TOTAL RESORPTIONS	0	0	0	0
NATURAL DELIVERIES	0	0	0	0
ANIM. WITH VIABLE FET.	10	11	11	4
CORPORA LUTEA	155	171	163	68
IMPLANTATIONS	129	160	149	57
VIABLE FETUSES	122	146	139	54
RESORPTIONS	7	14	10	3

Tab. C.3.a.10

SUBST./COMP. : SND 919CL2Y SPEC. : : RATS
STUDY NO. : R83 SEGM. 1

LITTER DATA F_1-GENERATION
MEAN VALUES
SACRIFICED DAY 14-16)

		CONTROL	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
CORPORA LUTEA / DAM	MW	15.5	15.5	14.8	15.0
	SD	2.0	1.9	1.3	1.4
IMPLANTATIONS / DAM	MW	12.9	14.5	13.5	14.3
	SD	4.1	2.9	3.1	1.5
LIFE EMBRYOS / DAM	MW	12.2	13.3	12.6	13.5
	SD	4.2	3.1	3.4	1.3
RESORPTIONS / DAM	MW	0.7	1.3	0.9	0.8
	SD	1.3	1.9	1.0	1.0
LIFE EMBRYOS IN % IMPL.	MW	98.4	96.3	95.9	97.5
	SD	4.4	5.9	4.2	3.5
RESORPTIONS IN % IMPL.	MW	1.6	3.7	4.1	2.5
	SD	4.4	5.9	4.2	3.5
PRE IMPLANTAT. LOSS %	MW	10.9	1.5	3.8	3.8
	SD	10.1	6.2	7.8	1.7

CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

C.3.b. Segment I in Rats: Fertility and Reproduction (Follow-up Study)

Document #(s):

Upjohn TR 7219-94-078

Sponsor Volume: 1.43

Summary:

In the previous Segment I study in rats, daily treatment of females with 2.5 mg/kg PPX before and during gestation, and of males for 10 weeks before copulation significantly reduced the pregnancy rate. These studies did not determine the source of this impairment (i.e., male or female). Because of the well-established role of prolactin in the maintenance of rat pregnancy, and the ability of dopamine agonists to inhibit prolactin, it is reasonable to suspect that the female is the source of impairment. The present study was designed to provide evidence of this phenomenon by mating PPX-treated males with untreated females, and PPX-treated females with untreated males. A control group of untreated males and females, and a positive control group of treated males and females were also evaluated. PPX (2.5 mg/kg) was administered according to a schedule similar to that of the initial study. Males were sacrificed after copulation, and females were sacrificed on day 22 of gestation. In addition to the reproductive assessments, toxicokinetics and prolactin levels were also determined.

The main finding of the study was that the number and percentage of pregnant rats were significantly reduced in treated females regardless of whether the male partners had been treated. As in the preceding Segment I study, estrus was prolonged, and the total number of implantations in PPX-treated females was markedly reduced. Thus, the fertility impairment appears to result from an effect in the females rather than males. These findings were anticipated since pramipexole lowers serum prolactin as demonstrated in this study. The toxicokinetic analysis indicated that exposures in the pregnant rats at 2 hrs after dosing were higher than anticipated steady-state human levels (7-8 ng/ml). No adverse effects on litter parameters, and no teratogenic effects of PPX were evident. However, as in the preceding study, a low number of viable offspring from the treated groups limited the teratology information.

Methods:

Dosages: 2.5 mg/kg/day (Drug Lot: Batch VI; prepared in distilled water)

Route of Administration: oral (gavage)

Species/Number: 96 male and 96 nulliparous females

Allocated to four groups (24/sex):

Group 0: control male; control female
1: treated male; treated female
2: treated male; untreated female
3: treated female; untreated male

Mean initial weights/age:

males:	269g / 8 weeks
females:	203 g / 11 weeks

Parameters monitored/Intervals:

Clinical	-	daily
Body weight	-	weekly in males; daily in females
Food consumption	-	weekly

At Termination -

Males: Sacrificed after successful mating. Testes and epididymis were weighed, fixed in 7.5% formalin, and stored.

Females: Sacrificed on day 22 of gestation. Gross pathology, numbers of fetuses (viable and dead), corpora lutea, and resorptions. Ovaries were fixed in 7.5% formalin, and stored.

Fetuses: Live/dead; sex; one-half were examined for skeletal abnormalities, and one-half were examined for visceral and cephalic abnormalities.

Histopathology:

Fixed organs were embedded in paraplast. Sections were stained with hematoxylin-eosin.

Toxicokinetics:

Plasma levels were determined at sacrifice two hours after the last dose in 10/sex treated animals from the test groups (1-3), and in 5/sex control animals (group 0).

Prolactin determinations:

Serum prolactin levels were measured at sacrifice two hours after the last dose in 10 treated and 10 untreated animals per sex.

Statistics

Litter data were statistically evaluated using the Bartlett test, one-way ANOVA, Newman-Keuls test, Fisher's exact test, and the exact Wilcoxon test. Serum prolactin levels were evaluated using the Wilcoxon Rank Sum Test.

Results:

Effects in Males

Mortality: none

Clinical Signs:

Restlessness was observed from 1-8 hrs after treatment.

Body Weight Gain:

Slight significant decrease in PPX-treated groups during week 2 (Fig. C.3.b.1).

Food Intake:

Significantly decreased in treated groups during week 1; significantly increased at later time points.

Necropsy:

No gross pathological changes were evident in any male rats. No significant differences in testicular weights among treatment groups were apparent.

Effects in Females

Mortality: none

Clinical Signs:

Restlessness was observed from 0.5-8 hrs after treatment.

Body Weight Gain:

Body weight and body weight gain was significantly reduced in the PPX-treated groups during the first 2 weeks of treatment. No consistent effects on body weight in the treated animals occurred during gestation (Fig. C.3.b.2).

Food Intake:

Significantly increased in treated groups during week 2 prior to mating and during week 1 of gestation. During weeks 2 and 3, intake was significantly increased only in group 1.

Fig. C.3.b.1.

Dept.Exp.Path.and Tox.
Report/Study No.: R 39

Male - Bodyweight

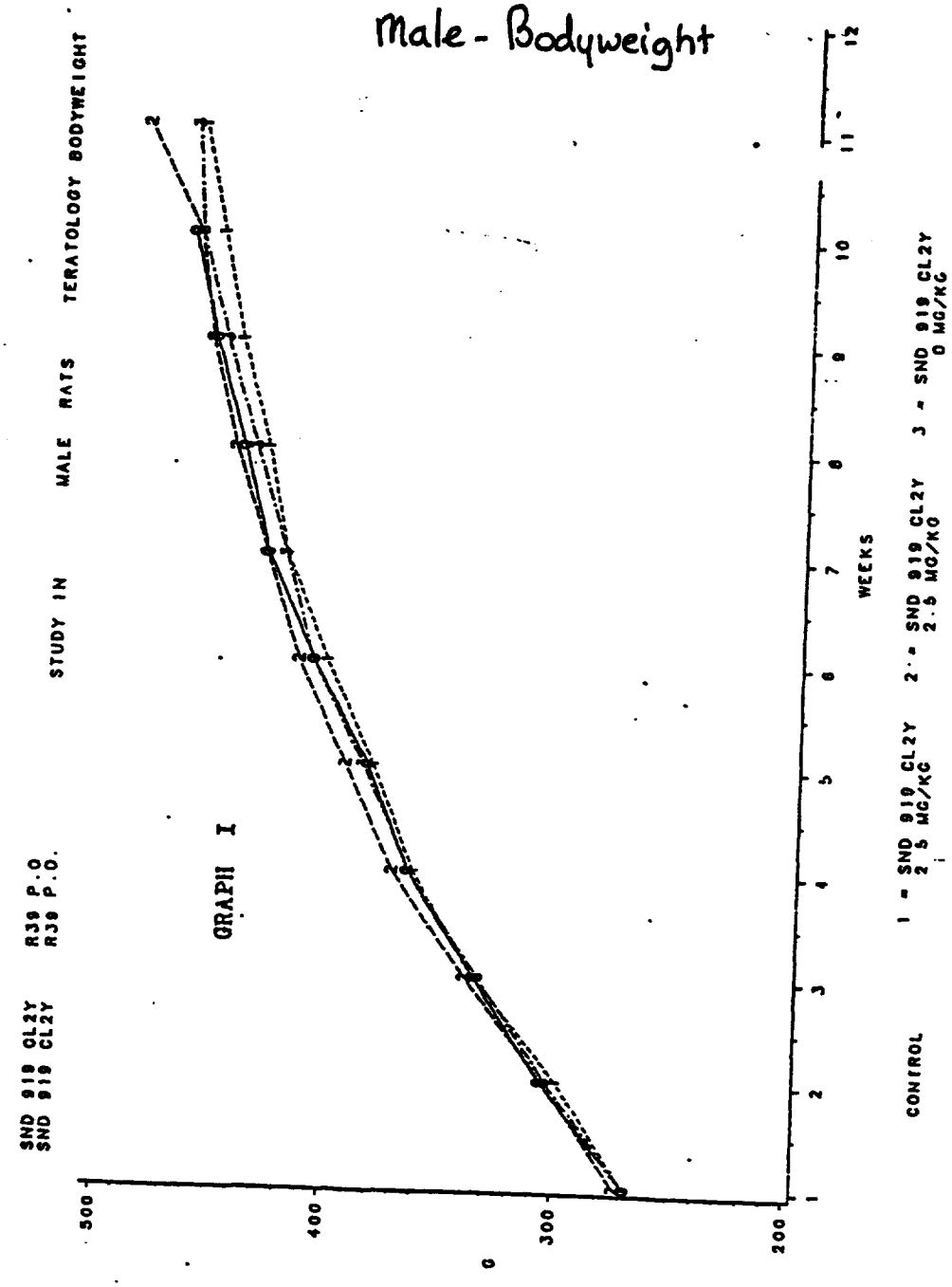
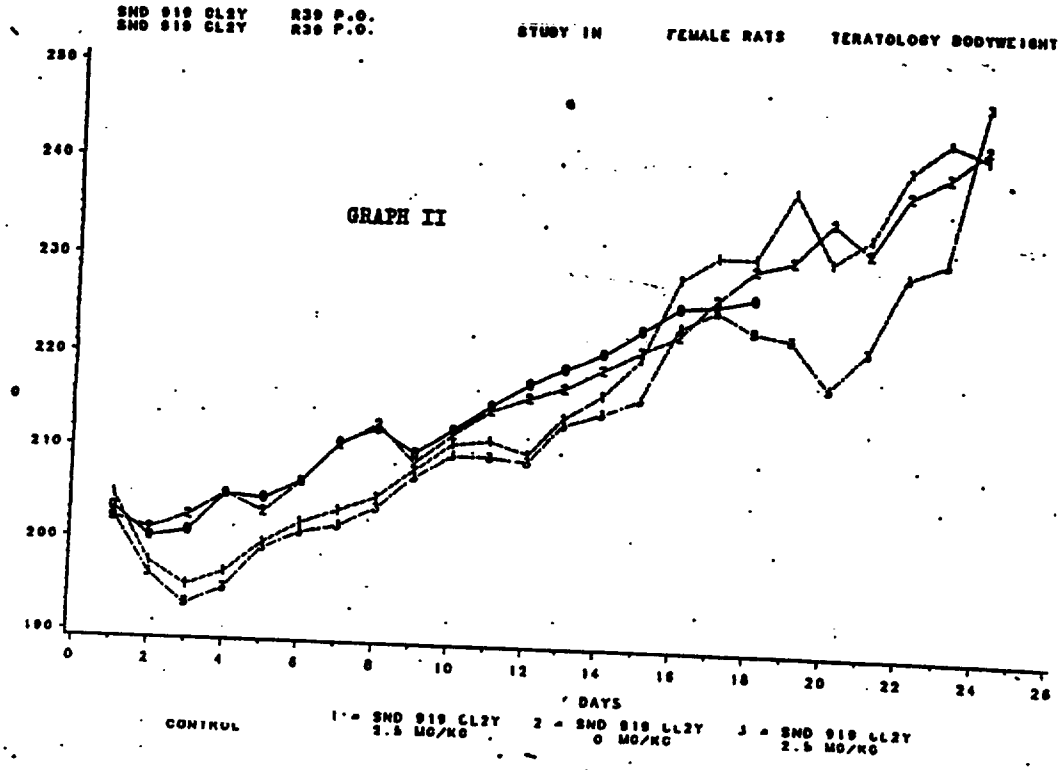
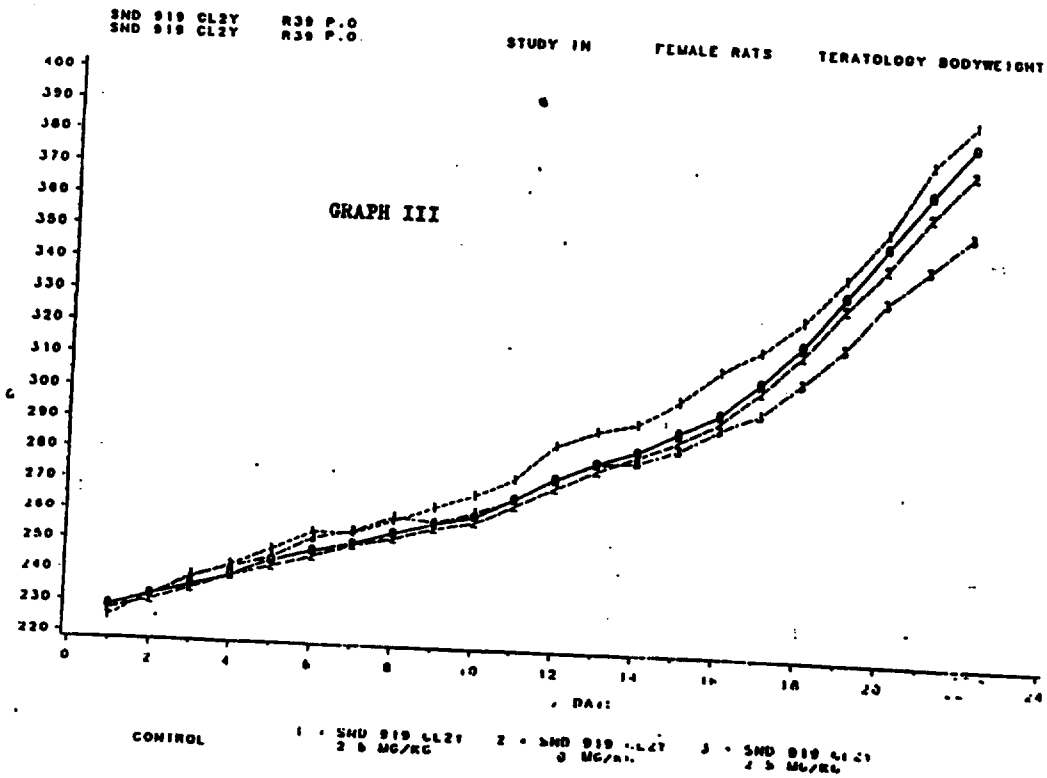


Fig. C.3.b.2.
Female - Bodyweight

Premating



Gestation



Estrous Cycle:

The estrus cycle was prolonged by 1 or 2 days in 13 of 24 females from each of the two drug-treated groups.

Conception:

Successful matings occurred in most groups within the first four days of mating. An additional cycle was required in 5 of 48 treated pairs. Two treated pairs did not successfully mate.

Fertility:

Successful pregnancies were recorded in 46 of 48 females of the untreated groups, and in 7 of 47 females of the treated groups.

Necropsy:

No gross pathological changes were found in any female rats, and there were no significant differences in ovary weights among treatment groups.

Effects on litter parameters

One group 3 female had a total resorption. The total number of implantations and pregnant dams in the PPX-treated groups was significantly reduced compared to controls (Tab. C.3.b.1). There were no significant differences among groups in the number of corpora lutea, fetuses (viable or dead), or resorptions per dam (Tab. C.3.b.2). Some differences in group means occurred when the dam with the total resorption was included in the calculation.

Effects on fetuses

The low pregnancy rate in PPX-treated animals provided a small number of fetuses for this assessment. No drug-related skeletal or visceral abnormalities were identified by the sponsor. The incidence of an additional rib in fetuses of PPX-treated dams (4/25 = 16% in Group 3 fetuses; 4/40 = 10% if PPX-treated fetuses are pooled; Tab. C.3.b.3) appears elevated relative to historical control data compiled by

Histopathology

No drug-related lesions of the testes or epididymis were identified. Treated females (33/48) had an abnormally high number of corpora lutea and low number of follicles.

Tab. C.3.b.1

REPORT/STUDY NO. : R39

(SND 919 CL2Y , P.O. , RAT , SEGMENT I)

	CAESAREAN SECTION				
	CONTROL	2.5 MG/KG	0 MG/KG	2.5 MG/KG a)	2.5 MG/KG b)
TOTAL NUMBER OF ANIMALS	24	24	24	24	24
MATERNAL MORTALITY	0	0	0	0	0
TOTAL RESORPTIONS	0	0	0	1	0
NATURAL DELIVERIES	0	0	0	0	0
ANIM. WITH VIABLE FET.	23	2	23	4	5
CORPORA LUTEA	355	32	345	65	87
IMPLANTATIONS	339	31	333	56	70
VIABLE FETUSES	330	31	308	53	53
MALE IN %	51	55	50	45	45
FEMALE IN %	49	45	50	55	55
DEAD FETUSES	0	0	0	0	0
RESORPTIONS	9	0	25	3	17
EARLY IN %	89	0	68	100	100
LATE IN %	11	0	32	0	0
MALFORMATIONS	1	0	0	0	0
VARIATIONS	42	3	38	8	8

a) = excluding, b) = including dam no.317 with total resorptions

Tab. C.3.b.2

REPORT/STUDY NO. : R39

(SND 919 CL2Y , P.O. , RATTE / RAT , SEGMENT I)

LITTER DATA MEAN VALUES
CAESAREAN SECTION

		CONTROL	2.5 MG/KG	0 MG/KG a)	2.5 MG/KG a)	2.5 MG/KG b)
WEIGHT / FETUS (G)	MW	5.20	4.93	5.24	5.07	5.07
	SD	0.22	0.44	0.24	0.34	0.34
PLAC. WEIGHT/ FETUS (G)	MW	0.42	0.40	0.41	0.43	0.43
	SD	0.04	0.02	0.05	0.07	0.07
CORPORA LUTEA / DAM	MW	15.4	16.0	15.0	16.3	17.4
	SD	1.5	2.8	2.4	1.8	2.7
IMPLANTATIONS / DAM	MW	14.7	15.5	14.5	14.0	14.0
	SD	1.7	3.5	2.3	4.8	4.1
VIABLE FETUSES / DAM	MW	14.3	15.5	13.4	13.3	10.6
	SD	1.7	3.5	2.7	4.3	7.0
DEAD FETUSES / DAM	MW	0.0	0.0	0.0	0.0	0.0
	SD	0.0	0.0	0.0	0.0	0.0
RESORPTIONS / DAM	MW	0.4	0.0	1.1	0.8	3.4
	SD	0.7	0.0	1.3	1.5	6.1
MALFORMATIONS / DAM	MW	0.1	0.0	0.0	0.0	0.0
	SD	0.2	0.0	0.0	0.0	0.0
VARIATIONS / DAM	MW	1.8	1.5	1.7	2.0	~~2.0~~
	SD	2.2	0.7	1.2	2.4	2.4
VIABLE FET. IN % IMPL.	MW	99.3	100.0	95.6	98.8	84.8
	SD	2.1	0.0	4.2	4.6	39.6
RESORPTIONS IN % IMPL.	MW	0.7	0.0	4.4	1.2	15.2
	SD	2.1	0.0	4.2	4.6	39.6
PRE IMPLANTAT. LOSS %	MW	2.0	1.8	0.9	7.0	11.4
	SD	2.7	3.6	2.9	14.2	13.4
POST IMPLANTAT. LOSS %	MW	0.7	0.0	4.4	1.2	15.2
	SD	2.1	0.0	4.2	4.6	39.6
MALFORM. IN % VIAB. FET.	MW	0.1	0.0	0.0	0.0	0.0
	SD	0.8	0.0	0.0	0.0	0.0
VARIAT. IN % VIAB. FET.	MW	17.2	18.1	22.0	14.5	14.5
	SD	13.0	0.5	11.0	20.1	20.1

CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

a) = excluding, b) = including dam no.317 with total resorptions

Tab. C.3.b.3

Dept. Exp. Path. and Tox.
Report/Study No.: R 39

SHD 919 CL 2 % EFFECTS ON FETUSES RATS

SUM VALUES

	CONTR.	2.5 MG/KG	0 MG/KG	2.5 MG/KG
SKELETAL EXAMINATION				
NO. OF FETUSES EXAMINED	160	15	147	25
NO. OF FETUSES WITH MALFORMATIONS	1	0	0	0
NO. OF FETUSES WITH VARIATIONS	22	0	13	5
VISCERAL EXAMINATION				
NO. OF FETUSES EXAMINED	170	16	161	28
NO. OF FETUSES WITH MALFORMATIONS	0	0	0	0
NO. OF FETUSES WITH VARIATIONS	20	3	25	3
TYPE OF MALFORMATIONS				
CLEFT VERTEBRAE	1	0	0	0
TYPE OF VARIATIONS				
DUMB-BELL SHAPED VERTEBRAE	5	0	0	0
SHORT 13TH RIB (UNI- OR BILAT.)	16	0	13	1
ADDITIONAL 14TH RIB (PUNCTUAL)	0	0	0	4
GENERAL INCOMPLETENESS OF OSSIFICATION	1	0	0	0
DILATATION OF RENAL PELVIS (UNI- OR BILATERAL)	20	3	25	3
RUNTS	0	1	0	0
ADDITIONAL SKELETAL FINDINGS				
UNOSSIFIED STERNEBRA V	0	1	2	1
POORLY OSSIFIED STERNEBRA V	27	2	15	0
POORLY OSSIFIED STERNEBRAE IV+V	1	0	0	0

Tab. C.3.b.4.

SKELETAL ANOMALIES ALL STUDIES

		FETAL INCIDENCE (%)			LITTER INCIDENCE (%)		
		AVG	S.D.	MAX	AVG	S.D.	MAX
STERNEBRAE							
1st fused to Manubrium		0.002	0.03	0.47	0.018	0.27	4.00
Multiple fusions		0.031	0.17	1.71	0.259	1.19	9.09
Agenesis		0.004	0.04	0.58	0.041	0.43	4.76
Split		0.126	0.51	5.88	0.540	2.19	21.74
Misaligned		0.471	1.44	10.19	2.990	7.37	47.37
Asymmetric		0.027	0.17	2.04	0.262	1.76	22.73
Duplicated		0.004	0.06	0.88	0.030	0.45	6.67
Misshapen		0.064	0.40	4.76	0.439	2.54	27.78
RIBS							
Agenesis		0.056	0.26	2.96	0.422	1.80	12.00
Branched/split		0.002	0.03	0.40	0.002	0.03	0.40
Cervical		0.394	0.75	5.00	2.814	4.80	25.00
Fused		0.034	0.13	0.68	0.287	1.11	5.88
Hypoplastic		0.926	2.81	21.64	2.778	8.53	61.90
Intercostal		0.004	0.06	0.84	0.025	0.37	5.56
Misshapen		0.270	0.96	7.50	1.628	5.42	42.11
Supernumerary		3.199	5.30	25.14	14.776	22.97	77.78
Wavy		0.409	2.00	28.40	1.461	3.18	20.00
Bent		0.050	0.31	3.49	0.332	2.31	29.41
PELVIC GIRDLE							
Pelvic bone:	Agenesis	0.003	0.05	0.72	0.023	0.33	5.00
	Misaligned	0.002	0.02	0.26	0.037	0.39	4.17
Ilium:	Misshapen	0.003	0.05	0.72	0.025	0.37	5.56
Ischium:	Hypoplastic	0.013	0.10	1.20	0.110	0.87	10.00
SHOULDER GIRDLE							
Scapula:	Misshapen	0.006	0.07	0.82	0.076	0.66	6.67
APPENDICULAR SKELETON							
Forelimb							
Long bone:	Hypoplastic	0.006	0.09	1.41	0.041	0.61	9.09
	Misshapen	0.001	0.02	0.28	0.020	0.29	4.35
Metacarpal:	Agenesis	0.012	0.11	1.37	0.090	0.82	10.00
	Hypoplastic	0.021	0.14	1.36	0.136	0.95	10.00
Phalanx:	Misaligned	0.002	0.04	0.54	0.023	0.33	5.00
	Agenesis	0.003	0.04	0.59	0.019	0.28	4.17
	Clubbed	0.006	0.09	1.41	0.041	0.61	9.09
	Fused	0.004	0.05	0.82	0.030	0.45	6.67
Hindlimb							
Long bone:	Small	0.006	0.09	1.41	0.041	0.61	9.09
	Hypoplastic	0.002	0.03	0.47	0.002	0.03	0.47
	Misshapen	0.005	0.04	0.47	0.041	0.41	4.35
Metacarpal:	Agenesis	0.004	0.06	0.88	0.030	0.45	6.67
Phalanx:	Agenesis	0.024	0.22	2.37	0.158	1.43	16.00
	Clubbed	0.006	0.09	1.41	0.041	0.61	9.09
	Supernumerary	0.005	0.07	1.03	0.018	0.27	4.00
	Misaligned	0.044	0.65	9.73	0.169	0.51	27.59

Serum Prolactin levels

A marked lowering of serum prolactin was recorded in most PPX-treated rats (Tab. C.3.b.5).

Influence of SND 919 Cl2 on Serum Prolactin Levels in Rats

Groups	Dose	Sex	Animal-No.	Prolactin (ng/ml)
0/3	Control	m	054	120.87
			059	133.72
			065	99.95
			068	28.11
			069	34.57
			351	31.30
			355	77.08
			357	357.44
			358	53.22
			362	103.99
			Median	88.52
			NI	10
1/2	2.5 mg/kg SND 919 Cl2	m	154	< 0.39
			156	< 0.39
			263	0.71
			265	0.72
			268	< 0.39
			269	< 0.39
			270	1.43
			271	3.01
			272	10.37
			274	2.19
			Median	0.71 ***
			NI	10
0/2	Control	f	009	252.09
			015	186.42
			019	15.35
			021	409.13
			205	272.42
			207	294.12
			209	287.99
			215	238.15
			218	91.73
			223	195.20
			Median	245.12
			NI	10
1/3	2.5 mg/kg SND 919 Cl2	f	112	< 0.39
			113	< 0.39
			114	< 0.39
			115	< 0.39
			118	236.64
			119	< 0.39
			312	< 0.39
			316	< 0.39
			317	72.26
			318	< 0.39
			Median	< 0.39 ***
			NI	10

*** = p < 0.001

Toxicokinetics

Plasma concentrations of PPX were determined 2 hrs after dosing. Levels were higher in females than in males (Tab. C.3.b.6).

group no.	mean ± SD	
	females	males
1	158.3 ± 47.18	74.7 ± 23.74
2	-	85.0 ± 34.83
3	164.1 ± 40.95	-

The plasma concentrations of SND 919 CL 2 Y in female animals were clearly higher than in males.

For both sexes, there was no relevant difference between the results from different groups (females: group no. 1 vs. no 3, males: group no. 1 vs. no. 2).

C.3.c. Segment II in Rats: Reproduction and Teratogenicity

	Main Study	PK Study
Document #(s):	Upjohn TR 7219-94-074	Upjohn TR 7256-94-027
Sponsor Volume:	1.43	1.59

Summary:

Pramipexole was administered by gavage at doses of 0, 0.1, 0.5 and 1.5 mg/kg/day to Wistar rats (36/dose) from day 7 to 16 of gestation. Twenty-four rats per group were sacrificed on day 22 for delivery of pups by Caesarean section. The remaining females (12/dose) littered spontaneously and raised the pups to weaning (21 days). A supplementary toxicokinetic study was conducted in 6 pregnant females/dose. Animals were treated on days 7-12, and plasma samples collected at 1, 2, 4 and 24 hrs post-treatment on day 12.

Overt drug-related changes were restlessness and agitation with the middle and high doses, and decreased body weight gain and food intake at the high dose. With respect to reproductive toxicities, a very clear threshold effect was apparent; the MD group was virtually devoid of toxicities, and very pronounced toxicities were evident at the HD. Significant embryolethality occurred with the high dose as only 7 of 32 pregnant females had viable offspring. The other 25 pregnancies were classified as complete "early" resorptions. No clear drug-related effects on fetal maturation and development, or skeletal/visceral abnormalities were apparent. As in the previous studies, the teratology information is limited by the low number of evaluable pups. One case each of anal atresia (LD), sirenomelia (LD), and cleft vertebra (MD) were noted in pups from PPX-treated dams. Since impairment of body weight development and delayed eye-opening in pups from drug-treated dams did not occur in this study, as they had in the previous Segment I study, it is reasonable to conclude that these impairments were due to drug administration during lactation. Drug exposure in the LD group approximated exposure of humans receiving the projected PPX maintenance dose of 1.5 mg, t.i.d.

Methods:

Dosages: 0.1, 0.5, 1.5 mg/kg/day (Drug Lot: Batch I - main study, Batch IV - PK study; prepared in distilled water) from day 7 to day 16 (inclusive) of gestation in main study, and day 7-12 in PK study.

Low dose is 10 times the expected human dose (at the time of study initiation). The high dose was is somewhat lower than the dose used in a pilot study, in which significant signs of CNS toxicity were observed in dams administered 2.5 mg/kg.

Route of Administration: oral (gavage)

Species/Number: 144 inseminated females for main study, 24 for PK study

Approximate initial weight/age: 230 g / 12 weeks

Parameters monitored/Intervals:

Clinical	-	daily
Body weight	-	days 1, 7-16, and 22 of gestation, and days 1, 6, 13, and 20 of lactation
Food consumption	-	weekly
Plasma Concs	-	1, 2, 4, 24 hrs postdose on day 12 (HPLC-EC)

Termination:

Caesarean Section: 24 dams/group were sacrificed on day 22 of gestation. Non-pregnant females were excluded from mean calculations. The number of corpora lutea, fetal viability/loss, and implantation sites were determined. Dams were autopsied. Fetuses were sexed, and examined for skeletal or visceral and cephalic abnormalities.

Spont. delivery: 12 dams/group delivered pups and raised them to weaning. Litter parameters (size, live/still births, gross abnormalities) were recorded, and functional/behavioral/maturational tests were conducted. Pups were sacrificed and autopsied during the fourth week.

Statistics

Statistical comparisons were made by Bartlett's test, one-way ANOVA, Newman-Keuls test for multiple comparisons, and Chi-square and Fisher's exact test.

Results:

Effects on Dams

Mortality: One MD dam died apparently from choking on bedding

Clinical signs:

In the main study, restlessness and agitation at MD and HD, and one HD dam had vaginal bleeding. In the TK study, sedation was noted at the HD, and 5/6 HD dams had vaginal bleeding.

Body Weight Gain:

Significantly decreased in the HD groups from beginning of treatment through gestation (Fig. C.3.c.1).

Food Intake:

Significantly decreased in HD group during week 2 and 3 of gestation. No differences among groups occurred during the lactation period.

Gestation:

21 of 144 females were not pregnant (CON: 7; LD: 3; MD: 8; HD: 3). 25 of 32 pregnant HD dams (18 C-section, 7 spontaneous delivery) had complete resorptions.
In the PK study, all HD dams had complete resorptions.

Necropsy: No pathologies were found in the dams.

Effects on fetuses and pups

C-section group: The total litter resorption by 18 of 22 pregnant dams in the HD group resulted in some significant differences in mean litter values. There were no significant differences in mean fetal or placental weights, or in the incidence of external, skeletal, visceral or cephalic abnormalities (Tab. C.3.c.1-3), although some rare malformations were noted in pups of PPX-treated dams (one case of anal atresia at LD, one case of sirenomelia with gastroschisis at LD, and one case of cleft vertebra at MD).

Spontaneous delivery group: The mean number of live pups per dam was significantly reduced in the HD group because 7 of 10 pregnant animals had total resorptions (Tab. C.3.c.4-5). There was a dose-dependent trend, but no significant increase in pup body weight development through weaning (Fig. C.3.c.2). No functional, behavioral or maturational impairments, or structural abnormalities were evident in the pups (Tab. C.3.c.6-7).

Plasma Concentrations (Satellite Study)

Except for 24 hrs after the 0.1 mg/kg dose, PPX was detectable in plasma. The highest concentrations were noted 1 hr after dosing. Increases in AUC were generally dose proportional. PK parameters ($C_{1\,hr}$, AUC_{1-24}) associated with the lowest test dose approximated those of humans receiving the projected PPX maintenance dose of 1.5 mg, t.i.d. ($Cmax_{ss}$ = 5.4 - 7.2 ng/ml, AUC_{0-8} = 34.7 - 47.5)

Fig. C.3.c.1.

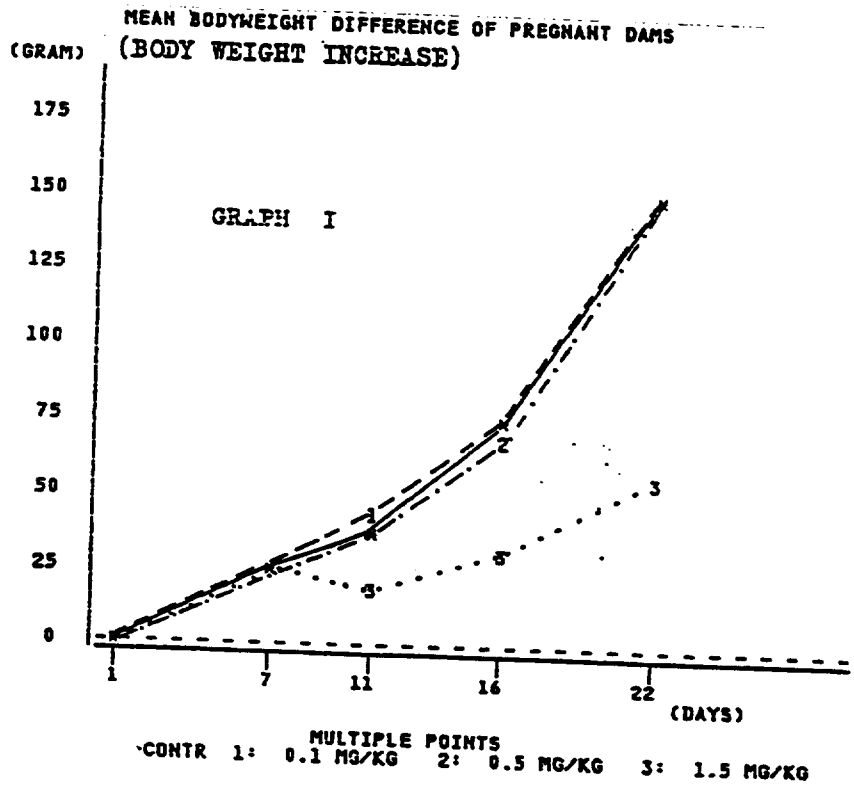
RATS

SEGM. 2

BODYWEIGHTS OF PREGNANT DAMS (G)
MEAN VALUES

CAESAREAN SECTION GROUP

		N	1	7	11	16	22
CONTROL	MW	19	222.4	246.8	262.7	296.1	373.8
	SD		10.7	12.9	13.3	15.7	27.3
0.1 MG/KG	MW	21	224.3	250.6	267.7	300.5	376.3
	SD		8.2	9.5	10.0	12.3	24.7
0.5 MG/KG	MW	18	222.7	247.1	257.4	291.1	373.2
	SD		8.6	13.3	14.6	13.9	21.7
1.5 MG/KG	MW	22	222.6	246.6	238.8***	254.1***	280.5***
	SD		8.9	14.2	16.0	22.9	50.0



*** $p < 0.001$

Fig. C.3.c.1.(cont.)

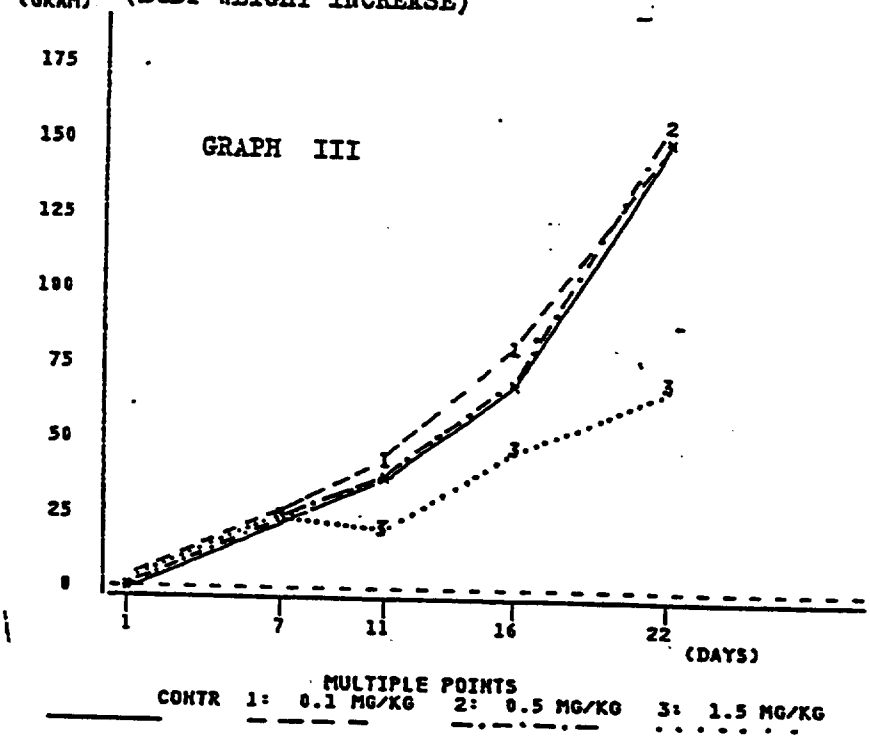
RATS

SEGM. 2

BODYWEIGHTS OF PREGNANT DAMS (G) SPONTANEOUS DELIVERY GROUP
MEAN VALUES

		N	1	7	11	16	22
CONTR CONTROL	MW	10	237.9	259.9	275.2	388.2	388.7
	SD		9.9	18.8	14.4	14.6	24.1
0.1 MG/KG	MW	12	236.0	265.8	281.7	316.2	387.8
	SD		15.4	16.3	18.8	21.8	30.8
0.5 MG/KG	MW	10	237.8	261.7	275.2	388.1	394.1
	SD		9.8	8.6	8.0	8.9	16.6
1.5 MG/KG	MW	10	234.6	261.8	255.0***	275.9***	308.8***
	SD		7.5	8.8	8.6	16.8	52.9

MEAN BODYWEIGHT DIFFERENCE OF PREGNANT DAMS
(BODY WEIGHT INCREASE)



MULTIPLE POINTS
CONTR 1: 0.1 MG/KG 2: 0.5 MG/KG 3: 1.5 MG/KG

*** $p < 0.001$

Tab. C.3.c.1

RATS

SEGM. 2

LITTER DATA
SUM VALUES

CAESAREAN SECTION GROUP

	CONTROL	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
TOTAL NUMBER OF ANIMALS	24	24	24	24
MATERNAL MORTALITY	0	0	0	0
TOTAL RESORPTIONS	0	0	0	18
NATURAL DELIVERIES	0	0	0	0
ANIM. WITH VIABLE FET.	19	21	18	4
CORPORA LUTEA	261	294	247	312
IMPLANTATIONS	240	267	233	311
VIABLE FETUSES	232	250	222	51
MALE IN %	51	54	58	55
FEMALE IN %	49	46	42	45
DEAD FETUSES	0	0	0	0
RESORPTIONS	8	17	11	260
EARLY IN %	50	76	73	100
LATE IN %	50	24	27	0
MALFORMATIONS	0	2	1	0
VARIATIONS	1	6	5	0

Tab. C.3.c.2.

RATS

SEGM. 2

LITTER DATA
MEAN VALUES CAESAREAN SECTION GROUP

		CONTROL	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG	
WEIGHT / FETUS (G)	MW	5.31	5.45	5.38	5.41	
	SD	0.23	0.30	0.22	0.32	
WEIGHT PLAC./ FETUS (G)	MW	0.45	0.49	0.46	0.46	
	SD	0.05	0.10	0.06	0.03	
CORPORA LUTEA / DAM	MW	13.7	14.8	13.7	14.2	
	SD	1.3	2.4	0.6	1.5	
IMPLANTATIONS / DAM	MW	12.6	12.7	12.9	14.1	
	SD	3.0	4.1	2.0	1.5	
VIABLE FETUSES / DAM	MW	12.2	11.9	12.3	2.3	***
	SD	3.0	3.9	2.1	5.1	
DEAD FETUSES / DAM	MW	0.0	0.0	0.0	0.0	
	SD	0.0	0.0	0.0	0.0	
RESORPTIONS / DAM	MW	0.4	0.8	0.6	11.8	***
	SD	0.6	1.2	1.1	5.4	
MALFORMATIONS / DAM	MW	0.0	0.1	0.1	0.0	
	SD	0.0	0.3	0.2	0.0	
VARIATIONS / DAM	MW	0.1	0.3	0.3	0.0	
	SD	0.2	0.5	0.6	0.0	
VIABLE FET. IN % IMPL.	MW	98.8	97.6	98.5	6.0	***
	SD	2.2	3.8	3.5	26.9	
RESORPTIONS IN % IMPL.	MW	1.2	2.4	1.5	94.0	***
	SD	2.2	3.8	3.5	26.9	
PRE IMPLANTAT. LOSS %	MW	2.5	5.1	1.5	0.1	
	SD	8.2	11.0	5.3	0.3	
POST IMPLANTAT. LOSS %	MW	1.2	2.4	1.5	94.0	***
	SD	2.2	3.8	3.5	26.9	
MALFORM. IN % VIAB. FET.	MW	0.0	0.1	0.1	0.0	
	SD	0.0	0.7	0.6	0.0	
VARIAT. IN % VIAB. FET.	MW	0.1	2.1	1.7	0.0	
	SD	1.4	5.5	6.5	0.0	

CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

*** $p < 0.001$

Tab. C.3.c.3.

RATS

SEGM. 2

FINDINGS IN FETUSES	CAESAREAN SECTION GROUP			
	CONTOL	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
EXTERNAL				
ATRESIA ANI	0	1[a]	0	0
SIRENIFORM MALFORM.. OEDEMA, GASTROSCHISIS	0	1[b]	0	0
SKELETAL				
BENT AND SHORTENED LONG BONES, SYNOSTOSIS OF VERTEBRAE AND RIBS	0	1[b]	0	0
SPLIT VERTEBRAL BODY	0	0	1[c]	0
"HOUR-GLASS" SHAPED VERTEBRA	0	1[d]	0	0
VISCERAL				
DILATATION OF RENAL PELVIS	1[e]	5[f]	4[g]	0
DISPLACEMENT OF LEFT KIDNEY	0	0	1[h]	0
ADDITIONAL SKELETAL FINDINGS				
UNOSSIFIED 5TH STERNEBRA	3	3	4	0
REDUCED OSSIFIED 5TH STERNEBRA	2	1	6	0

a FETUS NO 101/14
b FETUS NO 116/2
c FETUS NO 213/5
d FETUS NO 107/7
e FETUS NO 017/3
f FETUS NO 101/4, 106/2, 114/15, 119/12, 124/16
g FETUS NO 210/10, 216/9, 216/11, 219/7
h FETUS NO 209/9

Tab. C.3.c.4.

RATS

SEGM. 2

LITTER DATA
SUM VALUES

SPONTANEOUS DELIVERY GROUP

	CONTROL	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
TOTAL NUMBER OF ANIMALS	12	12	12	12
MATERNAL MORTALITY	0	0	0	1
TOTAL RESORPTIONS	0	0	0	7
PREGNANT ANIMALS	10	12	10	10
VIABLE YOUNG	134	133	138	39
MALE IN %	46	49	41	49
FEMALE IN %	54	51	59	51
DEAD PUPS	0	1	0	0
MALFORMATIONS	0	0	0	0
VARIATIONS	0	0	0	0
PUPS DAY 7	131	130	133	38
PUPS DAY 14	131	130	132	38
PUPS DAY 21	131	130	132	38
MORTALITY IN OFFSPRING	3	3	6	1

Tab. C.3.c.5.

RATS

SEGM. 2

LITTER DATA
MEAN VALUES

SPONTANEOUS DELIVERY GROUP

		CONTROL	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
GESTATION PERIOD OF DAMS	MW	22.0	22.1	22.0	22.0
	SD	0.0	0.3	0.0	0.0
	N	10	12	10	10
WEIGHT / PUP AT DAY 1	MW	5.88	6.24	5.95	6.84
	SD	0.15	0.34	0.26	0.47
WEIGHT / PUP AT DAY 21	MW	29.58	34.76	31.14	32.82
	SD	2.59	6.98	4.83	4.81
BODYW. INCR. DAY 1-21	MW	23.69	28.51	25.19	26.78
	SD	2.56	6.80	4.79	3.88
VIABLE PUPS/ DAM DAY 1	MW	13.4	11.1	13.8	3.9 ***
	SD	1.4	3.3	2.0	6.5
DEAD PUPS / DAM DAY 1	MW	0.0	0.1	0.0	0.0
	SD	0.0	0.3	0.0	0.0
VIABLE PUPS / DAM DAY 7	MW	13.1	10.8	13.3	3.8 ***
	SD	1.2	3.5	2.3	6.1
VIABLE PUPS /DAM DAY 21	MW	13.1	10.8	13.2	3.8 ***
	SD	1.2	3.5	2.2	6.1
PUPS LOSS x DAY 1-21	MW	0.6	0.5	2.2	0.1
	SD	1.6	3.0	2.7	0.3
MALFORMATIONS / DAM	MW	0.0	0.0	0.0	0.0
	SD	0.0	0.0	0.0	0.0
VARIATIONS / DAM	MW	0.0	0.0	0.0	0.0
	SD	0.0	0.0	0.0	0.0
MALFORMATIONS IN x VIAB.P.	MW	0.0	0.0	0.0	0.0
	SD	0.0	0.0	0.0	0.0
VARIATIONS IN x VIAB.PUPS	MW	0.0	0.0	0.0	0.0
	SD	0.0	0.0	0.0	0.0

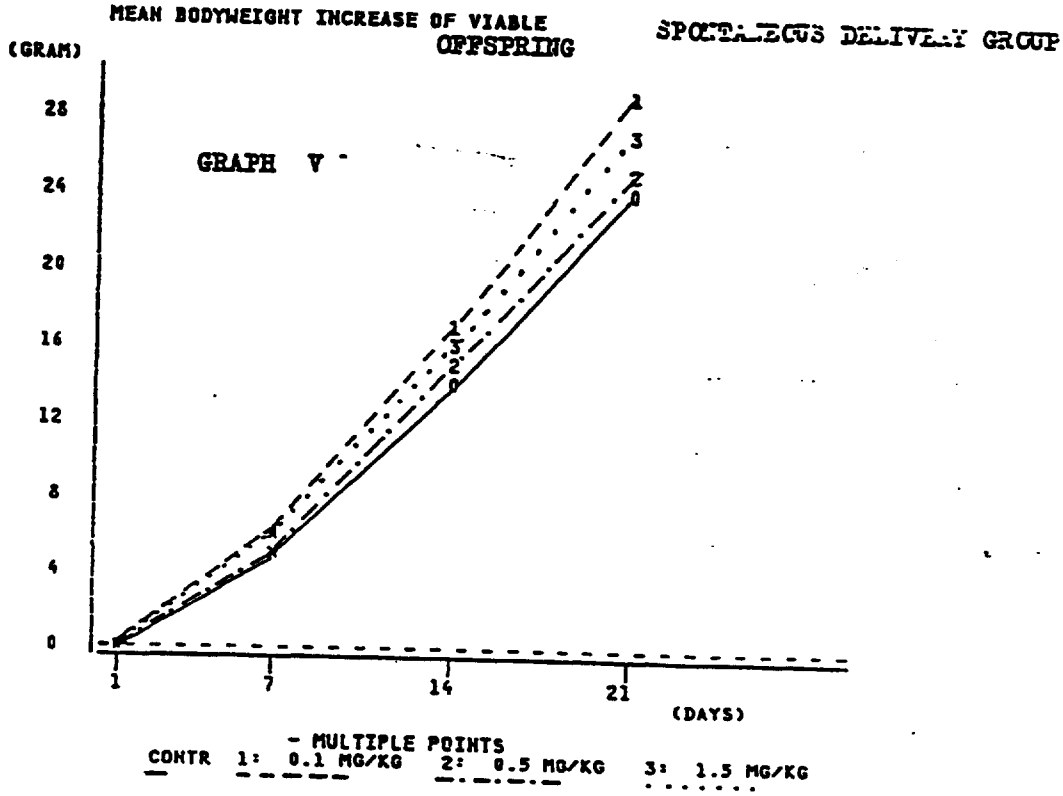
CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

*** $p < 0.001$

Fig. C.3.c 2.

RATS

SEGM. 2



Tab. C.3.c.6

SND 919 CL 2 Y

RATS

SEGM. 2

OBSERVATIONS OF F_1-OFFSPRING IN SPONTANEOUS DELIVERY GROUP

RESULTS IN PER CENT

DOSE	EVALUATED LITTERS	ERECTION OF PINNAE		FUR GROWTH		RUNNING WITH RAISED VENTER		ERUPTION OF MAXILLARY INCISORS		EYE OPENING	
		DAY 4	DAY 5	DAY 6	DAY 7	DAY 12	DAY 13	DAY 12	DAY 13	DAY 15	DAY 16
CONTROL	10	-	96.2	-	100.0	98.5	100.0	95.4	100.0	10.7	67.2
0.1 MG/KG	12	7.6	99.2	6.2	100.0	99.2	100.0	96.2	100.0	22.3	76.9
0.5 MG/KG	10	-	97.0	-	100.0	99.2	100.0	96.2	100.0	12.1	55.3
1.5 MG/KG	3	2.6	100.0	-	100.0	100.0	100.0	97.4	100.0	18.4	81.6

Tab. C.3.c.7

'RATS

SEGM. 2

RESULTS OF FUNCTION AND BEHAVIOUR TESTS IN F_1-OFFSPRING

DOSE	No. OF LITTERS	No. OF ANIMALS	RIGHTING-REFLEX %	PUPILLARY REACTION %	HEARING-TEST %		
					80 Hz	4000 Hz	16000 Hz
CONTROL	10	131	100.0	100.0	100.0	100.0	100.0
0.1 MG/KG	12	130	100.0	100.0	100.0	100.0	100.0
0.5 MG/KG	10	132	100.0	100.0	100.0	100.0	100.0
1.5 MG/KG	3	38	100.0	100.0	100.0	100.0	100.0

Report/Study No.: R 49

C.3.c.8

Table 8: Geometric mean values and ranges of plasma concentrations [ng/ml] and AUC [1-24 h] of SND 919 CL 2 Y in rats on day 12 of gestation after multiple administration by gavage

dose [mg/kg]	hours 1	2	4	24	AUC [ng/ml·h]
0.1	7.32 6.28 - 8.54	5.98 5.53 - 6.46	2.92 2.66 - 3.20	0.00 -	44.78 41.56 - 48.26
0.5	33.25 29.44 - 37.56	26.75 21.24 - 33.68	13.27 9.79 - 17.98	0.63 0.24 - 1.70	213.20 166.08 - 273.67
1.5	77.74 66.81 - 90.46	68.95 51.97 - 91.48	40.10 31.41 - 51.19	1.84 0.55 - 6.14	620.01 514.81 - 746.70

C.3.d. Segment II in Rabbits: Reproduction and Teratogenicity

	Main Study	PK Study
Document #(s):	Upjohn TR 7219-94-073	Upjohn TR 7256-94-026
Sponsor Volume:	1.44	1.59

Summary:

Pramipexole was administered by gavage at doses of 0, 0.1, 1.0 and 10.0 mg/kg/day to pregnant Himalayan rabbits (15-18/dose) from day 6 to 18 of gestation. Fetuses were delivered by Caesarean section on day 29, and maintained in an incubator for 24 hrs. After sacrifice, the offspring were examined for skeletal and visceral abnormalities. A supplemental toxicokinetic study was conducted in 4 rabbits/dose on day 12 of gestation.

Overt drug-related changes were restlessness and agitation with the high dose, and dose-dependent decreases in body weight gain and fecal output. One animal died after the third drug treatment due to cardiovascular collapse. Drug exposure in the LD group was at least equivalent to, and generally exceeded, the exposure of humans receiving the projected PPX maintenance dose of 1.5 mg, t.i.d. Pathological findings in other dams at sacrifice were considered spontaneous findings for this strain. No embryotoxic or fetotoxic effects of pramipexole were identified. Increases in the rate of resorption, which occurred at a very high rate in rats, did not occur in rabbits. No dose-related trends in the incidence of malformations were observed in newborns. Thus, pramipexole appears to be devoid of reproductive toxicities in rabbits at doses up to 10 mg/kg, and at exposures that are well-above expected human exposures.

Methods:

Dosages: 0.1, 1.0, 10.0 mg/kg/day (Drug Lot: Batch I - main study, Batch IV - PK study; prepared in distilled water) from day 6 to day 18 (inclusive) of gestation in the main study, and day 6 to 12 in the TK study.

Low dose is 10 times the expected human dose (at the time of study initiation). The high dose was selected based on a pilot study, in which a reduction in body weight was produced by this dose.

Route of Administration: oral (gavage)

Species/Number: Main Study - 72 mated females
TK Study - 16 mated females

Mean initial weight/age: 2317 g / 5-6 months

Parameters monitored/Intervals:

Clinical - daily

Body weight	-	days 1, 6-18, and 29 of gestation, and days 1, 6, 13, and 20 of lactation
Food consumption	-	not measured
Plasma Concs	-	day 12 (0, 2, 4, 8 and 24 hrs postdose)

Termination:

Dams were sacrificed on day 29 of gestation. Routine pathological examinations of the dams were done, and the number of corpora lutea, fetal viability/loss, and implantations and resorptions were determined. Viable newborns were maintained in an incubator for 24 hrs, at which point they were weighed, examined for malformations and skeletal variations, and necropsied.

Statistics:

Statistical comparisons were made by one-way ANOVA followed by Newman-Keuls test for multiple comparisons, or Fisher's exact test.

Results:

Effects on Dams (Main Study)

Mortality: Three deaths occurred during the study, but only one was likely drug-related; an HD dam died on day 3 apparently because of circulatory collapse.

Clinical Signs:

Restlessness and agitation in HD animals between days 10-18.
Reduced fecal output on several days in 8 LD, 16 MD, and 17 HD.

Body Weight Gain:

Dose-dependent, significant decreases in all 3 groups on day 7, in MD and HD groups from days 8-12, and in HD group on days 13-14. The effect waned with increasing duration of treatment (Fig. C.3.d.1).

Gestation:

One control and one LD dam were not pregnant at the end of the study.
Dams with no living offspring were excluded from statistical analyses.
No miscarriages occurred during the study.

Necropsy:

None of the identified pathologies appeared to be drug-related.

Fig. C.3.d.1.

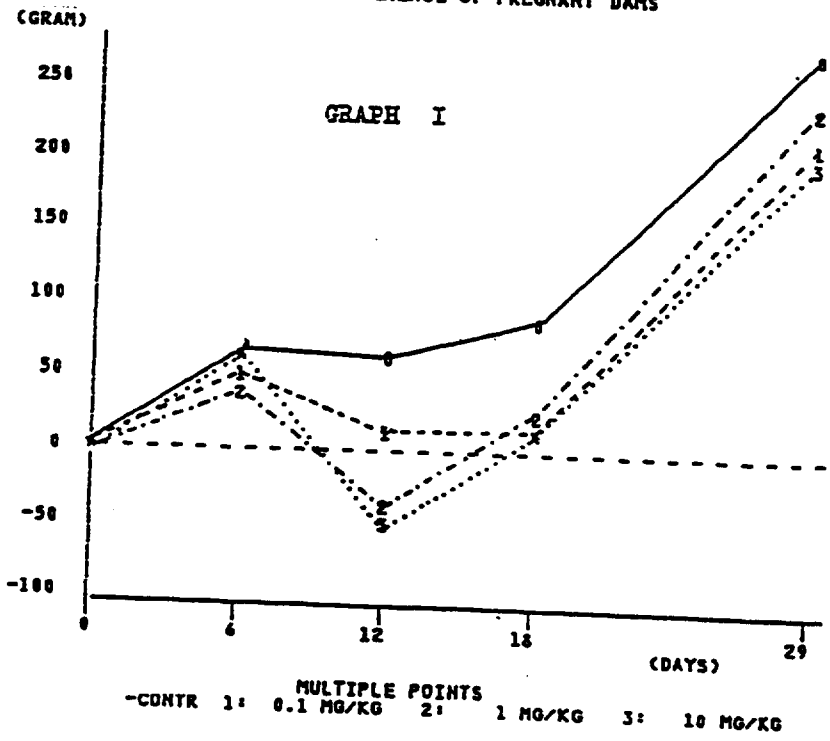
RABBITS

SEGM. 2

BODYWEIGHTS OF PREGNANT DAMS (G)
MEAN VALUES

		N	0	6	12	18	29
CONTROL	MW	17	2284.1	2351.8	2350.6	2370.6	2556.8
	SD		148.7	168.3	180.2	180.5	170.1
0.1 MG/KG	MW	15	2304.7	2349.3	2318.0	2316.0	2515.3
	SD		158.1	155.3	161.6	181.1	198.2
1 MG/KG	MW	18	2310.6	2345.0	2271.1	2336.1	2549.4
	SD		135.3	165.7	154.8	201.2	164.5
10 MG/KG	MW	17	2336.5	2397.6	2287.6	2354.7	2542.4
	SD		138.1	174.8	172.5	152.2	149.8

MEAN BODYWEIGHT DIFFERENCE OF PREGNANT DAMS



MULTIPLE POINTS
-CONTR 1: 0.1 MG/KG 2: 1 MG/KG 3: 10 MG/KG

Autopsy findings in the dams

At the autopsy of the dams after the ovario-hysterectomy (or after death) the following findings were obtained:

Animal no. 006: Approx. bean-sized subcapsular pale area on the liver.
(Histological finding: subcapsular focal, small- to large droplet fatty infiltration).

Animal no. 008: Right uterine horn segmented and empty.

Animal no. 102: Fracture in the region of the 4th lumbar vertebra.

Animal no. 105: Right uterine horn segmented and empty.

Animal no. 111: Agenesia of the accessory lobe of the lung.

Animal no. 118: Foamy contents in the bronchi, multiple haemorrhages in all lobes of the lung.

Animal no. 208: Agenesia of the left uterine horn.

Animal no. 304: Severe lung congestion with oedema. Extensive haemorrhages in the tissue of the mammary gland (Histopathological finding: recent haemorrhages in the subcutis and in the intra- and inter-lobular mammary tissue).

Animal no. 310: Pyometra of right uterine horn.

Further random findings were parovarian cysts and necroses of the fatty tissue in the retroperitoneal adeps renis with the following incidence:

	Contr.	0.1 mg/kg	1 mg/kg	10 mg/kg
parovarian cysts	5	5	2	1
necroses of fatty tissue	1	3	0	3

Effects on Litters

No significant differences were evident among groups in mean litter values of number of corpora lutea, implantations, viable/dead fetuses, and resorptions. Mean fetal birth weights and placental weights also did not differ among groups. There were no drug-related trends in the distribution of "runts" (<65% mean fetal weight; 4 Con, 8 LD, 2 HD) and fetal deaths between 0-24 hrs after birth (5 Con, 6 LD 4 MD) (Tab. C.3.d.1-2).

Tab. C.3.d.1.

SEGM. 2

LITTER DATA
SUM VALUES

	CONTROL	0.1 MG/KG	1 MG/KG	10 MG/KG
TOTAL NUMBER OF ANIMALS	18	18	18	18
MATERNAL MORTALITIES	0	2	0	1
TOTAL RESORPTIONS	0	0	0	0
NATURAL DELIVERIES	0	0	0	0
ANIM. WITH VIABLE FET.	17	15	18	17
CORPORA LUTEA	179	157	183	192
IMPLANTATIONS	133	114	124	127
VIABLE FETUSES	113	99	115	104
MALE IN %	44	49	47	60
FEMALE IN %	56	51	53	40
DEAD FETUSES	0	0	0	0
RESORPTIONS	20	15	9	23
EARLY IN %	60	60	89	70
LATE IN %	40	40	11	30
MALFORMATIONS	1	1	1	2
VARIATIONS	6	2	6	5

Tab. C.3.d.2.

RABBITS

SEGM. 2

LITTER DATA
MEAN VALUES

		CONTROL	0.1 MG/KG	1 MG/KG	10 MG/KG
WEIGHT / FETUS (G)	MW	38.93	35.88	38.65	38.87
	SD	5.13	5.88	4.41	4.75
WEIGHT PLAC./ FETUS (G)	MW	4.92	4.55	4.62	4.63
	SD	0.86	0.72	0.66	0.90
CORPORA LUTEA / DAM	MW	10.5	10.5	10.2	11.3
	SD	2.4	2.1	2.0	1.9
IMPLANTATIONS / DAM	MW	7.8	7.6	6.9	7.5
	SD	2.2	1.4	1.5	1.8
VIABLE FETUSES / DAM	MW	6.6	6.6	6.4	6.1
	SD	2.0	1.7	1.8	2.1
DEAD FETUSES / DAM	MW	0.0	0.0	0.0	0.0
	SD	0.0	0.0	0.0	0.0
RESORPTIONS / DAM	MW	1.2	1.0	0.5	1.4
	SD	1.3	0.9	0.8	1.7
MALFORMATIONS / DAM	MW	0.1	0.1	0.1	0.1
	SD	0.2	0.3	0.2	0.3
VARIATIONS / DAM	MW	0.4	0.1	0.3	0.3
	SD	0.6	0.4	0.8	0.7
VIABLE FET. IN % IMPL.	MW	91.8	90.8	96.8	89.8
	SD	6.5	6.6	6.5	9.9
RESORPTIONS IN % IMPL.	MW	9.8	9.2	3.2	10.2
	SD	6.5	6.6	6.5	9.9
PRE IMPLANTAT. LOSS %	MW	23.4	25.2	31.1	32.5
	SD	4.1	2.3	1.4	2.7
POST IMPLANTAT. LOSS %	MW	9.0	9.2	3.2	10.2
	SD	6.5	6.6	6.5	9.9
MALFORM. IN % VIAB. FET.	MW	0.1	0.1	0.1	0.2
	SD	1.3	1.9	0.8	1.9
VARIAT. IN % VIAB. FET.	MW	1.8	0.3	1.1	0.9
	SD	5.6	1.8	6.6	4.6

CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

Fetal Necropsies

A relatively even distribution was evident in the incidence of malformations and variations among fetuses from different treatment groups (Tab. C.3.d.3). The distribution of anomalies compared favorably to historical data. Deficient ossification of the 5th sternal anlage was noted with a slightly higher frequency in fetuses of the MD group (40% vs. 27.9-29.2% in the other 3 treatment groups).

Tab. C.3.d.3.

SEGM. 2

MALFORMATIONS AND VARIATIONS

COLLECTIVE VALUES

F I N D I N G S	CONTR.	0.1 MG/KG	1 MG/KG	10 MG/KG
MALFORMATIONS				
MULTIPLE MALFORMATIONS	0	1	0	0
SYNOSTOSIS OF STERNABRAE	1	0	0	1
ABSENCE OF GALLBLADDER	0	0	1	0
MISSING OF ONE VERTEBRA	0	0	0	1
VARIATIONS				
FLEXURAE OF FORE PAW(S)	5	1	4	4
13TH RIB	1	0	0	0
MISSING OF 12TH RIB	0	1	0	0
SHORTENED 12TH RIB	0	0	0	1
MISSING OF ACCESSORIUS LOBE OF THE LUNG	1	1	3	0
RUNTS	4	8	0	2

Plasma Concentrations (Satellite Study)

PPX was detectable in all plasma samples. The highest concentrations were noted 2 hr after dosing. Increases in AUC were generally dose proportional. PK parameters ($C_{2\,hr}$, AUC_{1-24}) associated with the lowest test dose were equivalent to or slightly greater than those of humans receiving the projected PPX maintenance dose of 1.5 mg, t.i.d. ($Cmax_{ss}$ = 5.4 - 7.2 ng/ml, AUC_{0-8} = 34.7 - 47.5)

Table 7: Geometric mean value and ranges of plasma concentrations [ng/ml] after oral administration of SND 919 CL 2 Y in pregnant rabbits

hours	dose [mg/kg] 0.1*)	1.0	10.0
0	0.49	12.23	104.38
	0.36 - 0.68	9.78 - 15.30	81.57 - 133.56
2	8.66	92.16	886.99
	6.74 - 11.13	84.10 - 100.98	768.06 - 1024.33
4	6.36	89.93	788.86
	4.42 - 9.15	77.06 - 104.94	632.04 - 984.60
8	4.03	52.26	506.26
	3.05 - 5.32	45.36 - 60.20	422.15 - 607.13
24	0.44	10.40	102.38
	0.30 - 0.65	6.46 - 16.76	79.16 - 132.40

Table 8: AUC (0 - 24 hours) values [ng/ml·h] with geometric means and ranges

animal	Dose [mg/kg] 0.1	1	10
1	(72.81)*)	1120.41	10370.14
2	69.89	1094.90	8047.06
3	75.00	1228.85	11726.36
4	104.70	905.50	10935.35
geometric - mean - range	81.87	1080.90	10170.79

C.3.e. Segment III in Rats: Perinatal and Postnatal Toxicity

Document #(s):

Upjohn TR 7219-94-076

Sponsor Volume: 1.44

Summary:

Pramipexole was administered by gavage at doses of 0, 0.1, 0.5 and 1.5 mg/kg/day to female Wistar rats (24/dose) from day 16 of gestation to day 21 of the rearing phase (lactation). Overt drug-related changes were agitation and increased activity in the MD and HD dams during lactation. Food intake was also decreased at the high dose. No *in utero* toxicities were apparent. The major toxicity observed was an impairment of pup development reflected by a decreased body weight gain during the lactation/rearing phase, and a slight (insignificant) delay in eye-opening in pups of the MD and HD dams. The sponsor suggests that the basis of this effect is CNS activation in the dams leading to an inability of the pups to suckle; no evidence to support this hypothesis was presented. An alternative explanation is the inhibitory effect of PPX on prolactin release impairs milk-production in the dams. Despite the reduced body weight development, fertility of the F1 offspring was not impaired. No remarkable drug-related changes in litter parameters or at necropsy of the pups were evident. Since the development and maintenance of pregnancies of HD rats were comparable to the other groups, in contrast to the Segment I and II studies where PPX dramatically impaired pregnancy, it may be concluded that the deleterious effects of PPX on rat reproduction occur at the early, prolactin-dependent implantation stage of pregnancy (circa days 6-8).

Methods:

Dosages: 0.1, 0.5, 1.5 mg/kg/day (Drug Lot: Batch III; prepared in distilled water) from day 16 of gestation to day 21 of rearing.

Low dose is 5 times the expected human dose (at the time of study initiation). The high dose was selected based on a previous Segment II study, in which signs of maternal and fetal toxicity were apparent.

Route of Administration: oral (gavage)

Species/Number: 96 inseminated females (24/group)

Approximate initial weight/age: 218 g / 10 weeks

Parameters monitored/Intervals:

Clinical	-	daily
Body weight	-	days 1, 7, 11, 16, and 22 of gestation, and daily during lactation

Food consumption	-	weekly
Litter parameters	-	Size, live/still births, and gross abnormalities were recorded. Non-pregnant females were excluded from mean calculations. Litters were reduced to 8 pups (4/sex) at day 4 post-partum. Functional, maturational and behavioral tests were conducted on the pups. At day 21, dams were necropsied, and half the offspring were examined for visceral abnormalities. The remaining weanlings were tested for swimming ability, Preyer reflex, pupillary reflex, water T-maze, and fertility (1 male and 1 female per litter).

Statistics

Statistical comparisons were made by Bartlett's test, one-way ANOVA, Newman-Keuls test for multiple comparisons, and Chi-square and Fisher's exact test.

Results:

Effects on Dams

Mortality: One control dam died from maladministration.

Clinical Signs:

Restlessness and agitation at MD and HD during lactation.

Body Weight Gain:

No significant effects during gestation, but significantly increased in the LD group on day 3 and 4 of lactation (Fig. C.3.e.1).

Food Intake:

Non-significant decrease in HD group (8-15%) during week 3 of gestation and the 3 week lactation period.

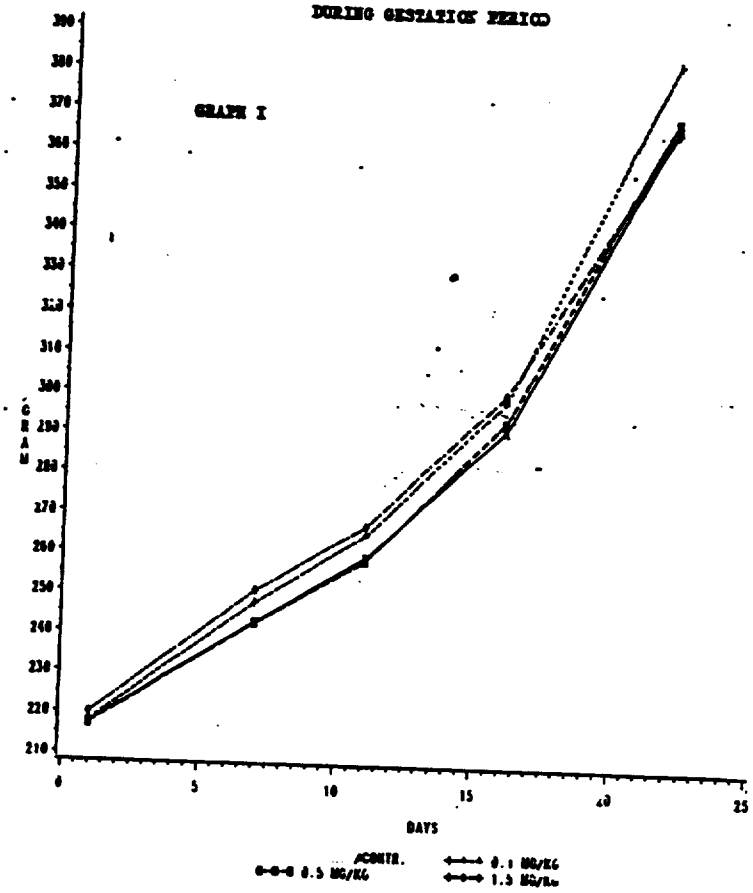
Gestation:

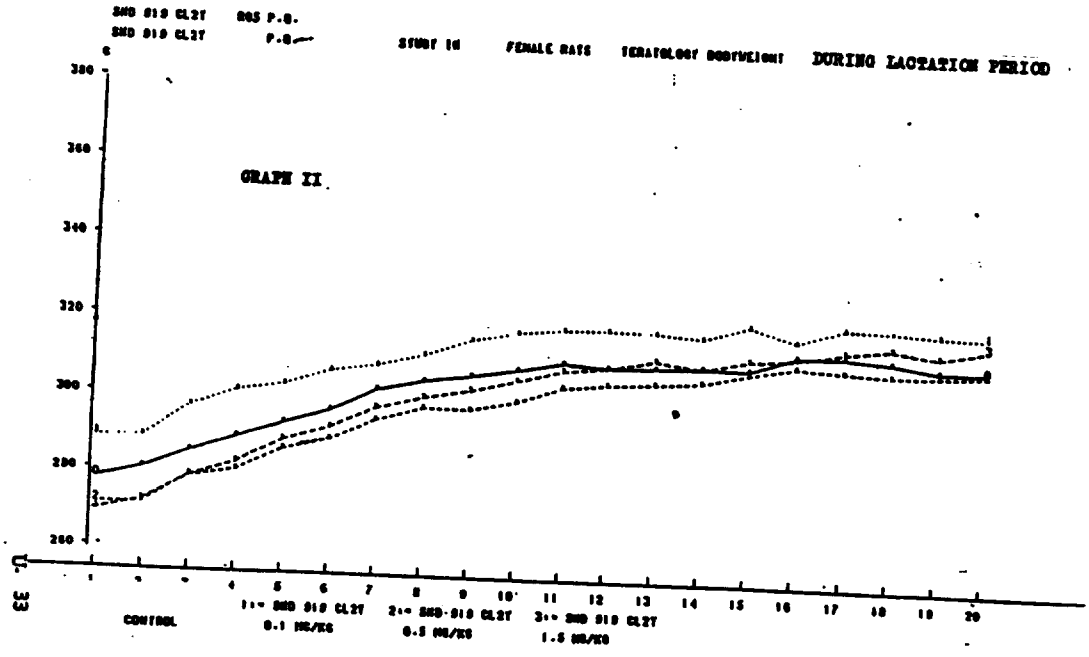
Nine of 96 females were not pregnant (1 CON, 3 LD, 2 MD, 3 HD). All except 1 HD dam delivered on day 23.

Necropsy:

No significant drug-related pathologies were found. One control dam had pulmonary edema, and MD dam had blood and caliculi in the urinary tract.

Fig. C.3e.1.


DURING GESTATION PERIOD
GRAPH I
GRAM
DAYS
CONTR.
0.1 MG/KG
0.5 MG/KG
1.5 MG/KG


SHD 819 CL27 005 P.O.
SHD 819 CL27 P.O.
STUDY 16 FEMALE RATS TERATOLOGY DOSIVLIONI DURING LACTATION PERIOD
GRAPH II
CONTROL
1:= SHD 819 CL27 0.1 MG/KG
2:= SHD 819 CL27 0.5 MG/KG
3:= SHD 819 CL27 1.5 MG/KG

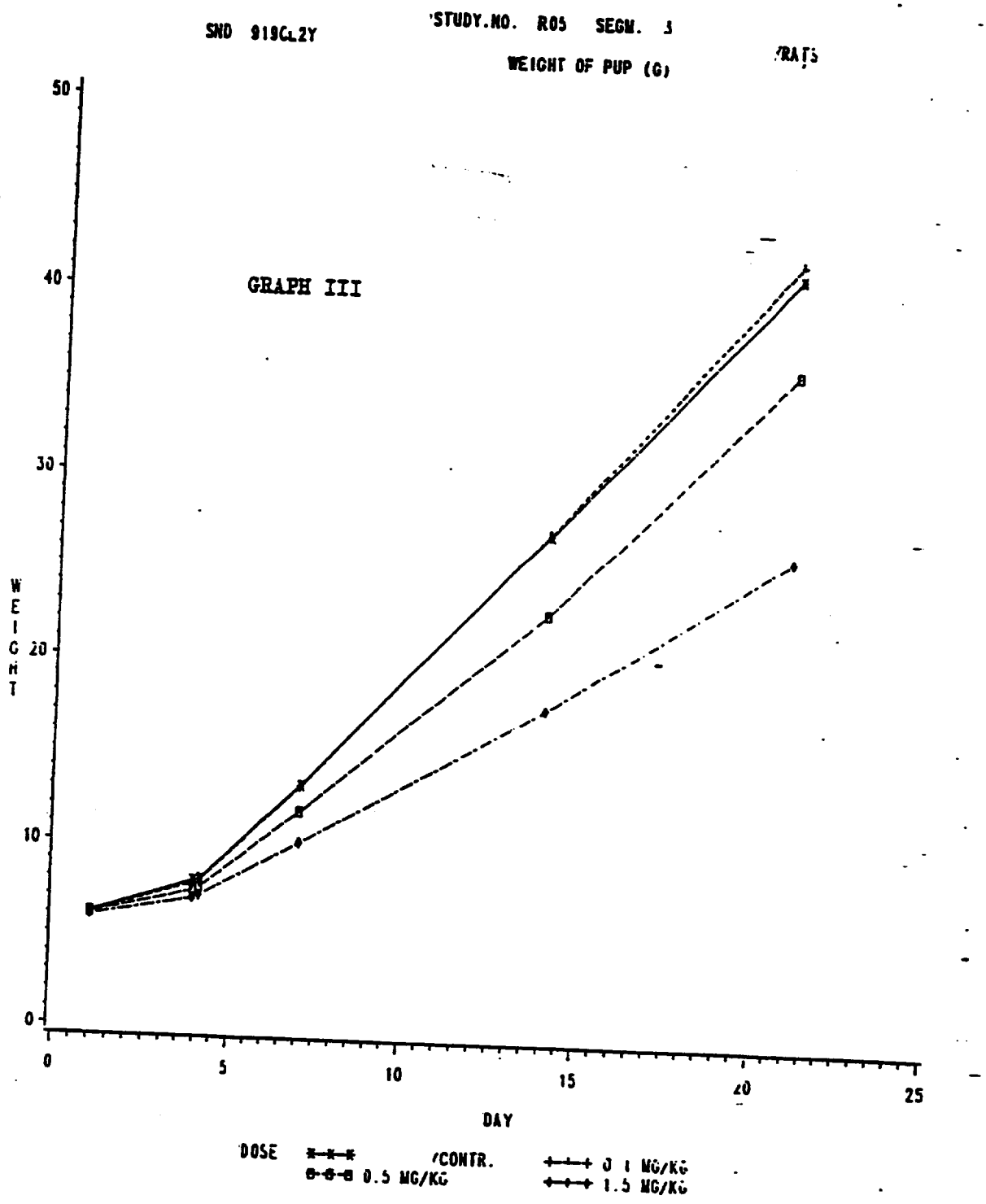
Effects on fetuses and pups

The most notable effects of PPX in the offspring were significant reductions in body weight at days 4 and 21, and body weight gain between days 1-4 and 4-21 in pups from MD and HD dams (Fig. C.3.e.2). Mortality in pups during rearing was due to cannibalism (1 CON, 1 LD, and 1 HD litter) (Tables C.3.e.1-2). With respect to maturational parameters, a slight (insignificant) delay in eye-opening was noted. There were no impairments in swimming, visual, auditory or memory tests (Tab. C.3.e.3). At autopsy, 2 LD and 1 MD weanling had hydronephrosis.

Fertility in Offspring

All females were inseminated within a 10 day mating period except for 1 control, 1 LD, and 1 MD offspring. Three of 80 inseminated females did not become pregnant (1 control, 1 LD, and 1 MD). Mean body weight of the HD group was significantly reduced during gestation, although body weight gain was increased (Tab. C.3.e.4). There were no differences among groups in corpora lutea number, implantations, viable embryos, or resorptions (Tab. C.3.e.5). At autopsy, one dam was diagnosed with hepatocellular necrosis.

Fig. C.3.e.2.


SND 919CL2Y
STUDY.NO. R05 SEGM. 3
WEIGHT OF PUP (G)
RATS
GRAPH III
WEIGHT
50
40
30
20
10
0
0
5
10
15
20
25
DAY
DOSE
CONTR.
0.5 MG/KG
1.5 MG/KG

Tab. C.3.e.1

SKD 919CL2Y

STUDY.NO.: R05 SEGM. 3

RATS

LITTER DATA
SUM VALUES

	/CONTR.	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
TOTAL NUMBER ANIMALS	24	24	24	24
MATERNAL MORTALITY	0	0	1	0
ABORTIONS	0	0	0	0
PREGNANT ANIMALS	23	21	21	21
STILLBIRTHS	1	1	0	1
VIABLE PUPS DAY 1	279	276	278	272
MALE IN %	53.05	46.74	52.52	54.04
FEMALE IN %	46.95	53.26	47.48	45.96
VIABLE PUPS DAY 4	261	273	276	255
VIABLE PUPS DAY 4*	174	165	168	160
VIABLE PUPS DAY 7	173	157	168	158
VIABLE PUPS DAY 14	173	157	167	158
VIABLE PUPS DAY 21	173	157	167	158
MORT. IN PUPS 1 - 4	18	3	2	17
MORT. IN PUPS 4* -21	1	8	1	2
MALFORMATIONS	0	2	1	0
VARIATIONS	0	0	0	0

Tab. C.3.e.2.

SKD 919CL2Y STUDY.NO.: 205 SEGM. 3 RATS

LITTER-DATA
MEAN-VALUES

		/CONTR.	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
GESTATION PERIOD OF DAMS	MW	22.00	22.00	22.00	22.05
	SD	0.00	0.00	0.00	0.22
	N	23.00	21.00	21.00	21.00
WEIGHT/PUP AT (G) DAY 1	MW	6.12	6.12	6.06	5.94
	SD	0.29	0.24	0.23	0.29
WEIGHT/PUP (G) DAY 4	MW	7.95	7.82	** 7.41	*** 7.00
	SD	0.46	0.52	0.49	0.52
WEIGHT/PUP (G) DAY 4=	MW	8.00	7.94	** 7.53	*** 7.11
	SD	0.48	0.46	0.44	0.52
WEIGHT/PUP (G) DAY 21	MW	41.19	41.99	***36.03	***26.03
	SD	3.90	2.37	2.66	6.52
BODYW. INCR. (G) DAY 1-4	MW	1.76	1.63	*** 1.32	*** 1.02
	SD	0.46	0.46	0.40	0.45
BODYW. INCR. (G) DAY 4=-21	MW	33.19	34.07	***28.48	***18.88
	SD	4.04	2.78	2.70	6.17
VIABLE PUPS/ DAM DAY 1	MW	12.13	13.14	13.24	12.95
	SD	2.40	2.89	1.81	2.20
DEAD PUPS / DAM DAY 1	MW	0.04	0.05	0.00	0.05
	SD	0.21	0.22	0.00	0.22
VIABLE PUPS/ DAM DAY 4	MW	11.86	13.00	13.14	12.75
	SD	2.36	2.90	1.85	2.10
VIABLE PUPS/ DAM DAY 4=	MW	7.91	7.86	8.00	8.00
	SD	0.43	0.48	0.00	0.00
VIABLE PUPS/ DAM DAY 21	MW	7.86	7.85	7.95	7.90
	SD	0.47	0.49	0.22	0.31
PUPS LOSS % DAY 1-4	MW	6.31	1.09	0.81	8.52
	SD	20.70	2.77	2.69	22.16
PUPS LOSS % DAY 4=-21	MW	0.57	4.76	0.60	1.25
	SD	2.67	21.82	2.73	3.85
MALFORMATIONS / DAM	MW	0.00	0.10	0.05	0.00
	SD	0.00	0.44	0.22	0.00
VARIATIONS / DAM	MW	0.00	0.00	0.00	0.00
	SD	0.00	0.00	0.00	0.00
MALF. % VIAB. PUPS / DAY 1	MW	0.00	0.68	0.34	0.00
	SD	0.00	3.12	1.56	0.00
VARIAT. % VIAB. PUPS/ DAY 1	MW	0.00	0.00	0.00	0.00
	SD	0.00	0.00	0.00	0.00

** $p < 0.01$
*** $p < 0.001$

CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

SND 919 CL 2 Y

Tab. # C.3.e.3.

RATS

OBSERVATIONS OF F_1-OFFSPRING IN SPONTANEOUS DELIVERY GROUP

SEGM. 3

RESULTS IN PER CENT

STUDY NO. R 05

DOSE	EVALUATED LITTERS	ERECTION OF PINNAE		FUR GROWTH		RUNNING WITH RAISED VENTER		ERUPTION OF MAXILLARY INCISORS		EYE OPENING		
		DAY		DAY		DAY		DAY		DAY		
		4	5	6	7	12	13	12	13	15	16	17
CONTROL	22	8.0	98.9	-	100.0	100.0	100.0	100.0	100.0	20.8	75.1	98.8
0.1 MG/KG	20	8.9	100.0	-	100.0	100.0	100.0	100.0	100.0	17.8	79.0	100.0
0.5 MG/KG	21	22.6	100.0	-	100.0	100.0	100.0	100.0	100.0	6.0	57.5	99.4
1.5 MG/KG	20	17.0	98.7	-	100.0	83.5	99.4	100.0	100.0	8.9	41.1	89.2

Tab. C.3.e.1.

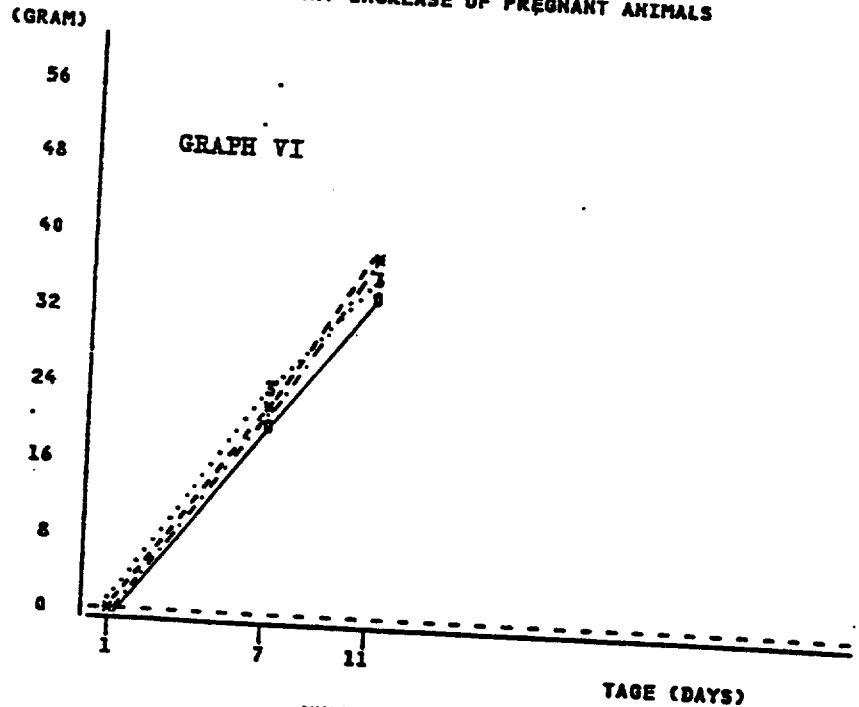
STUDY NO. : R 05 SEGM. 3 SPEC. : RATS

BODY WEIGHT OF PREGNANT ANIMALS (G) (DAYS 1, 7, 11)
MEAN VALUES F_1-GENERATION

		N	1	7	11
CONTROL	MW	20	246.1	266.1	279.4
	SD		18.0	18.9	17.7
0.1 MG/KG	MW	18	239.1	260.5	277.1
	SD		18.6	18.9	19.0
0.5 MG/KG	MW	19	233.6	256.6	271.8
	SD		18.2	19.3	20.5
1.5 MG/KG	MW	20	213.3***	237.6***	250.1***
	SD		19.2	20.1	20.6

*** $p < 0.001$

MEAN BODY WEIGHT INCREASE OF PREGNANT ANIMALS



GRAPH VI

-CONTR 1: 0.1 MG/KG 2: 0.5 MG/KG 3: 1.5 MG/KG

- MULTIPLE POINTS

Tab. C.3.e.5.

LITTER DATA F_1-GENERATION
SUM VALUES
SACRIFICED DAY 14-16)

	CONTROL	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
TOTAL NUMBER OF ANIMALS	21	19	20	20
MATERNAL MORTALITY	0	0	0	0
TOTAL RESORPTIONS	0	0	0	0
NATURAL DELIVERIES	0	0	0	0
ANIM. WITH VIABLE FET.	20	18	19	20
CORPORA LUTEA	313	291	300	313
IMPLANTATIONS	304	277	290	309
VIABLE FETUSES	278	249	264	289
RESORPTIONS	26	28	26	20

LITTER DATA F_1-GENERATION
MEAN VALUES
SACRIFICED DAY 14-16)

		CONTROL	0.1 MG/KG	0.5 MG/KG	1.5 MG/KG
CORPORA LUTEA / DAM	MW	15.6	16.2	15.8	15.6
	SD	2.0	2.3	1.4	1.5
IMPLANTATIONS / DAM	MW	15.2	15.4	15.3	15.4
	SD	2.8	3.3	2.4	1.5
LIFE EMBRYOS / DAM	MW	13.9	13.4	13.9	14.4
	SD	3.8	4.2	2.3	1.5
RESORPTIONS / DAM	MW	1.3	2.0	1.4	1.0
	SD	2.5	2.7	1.7	1.1
LIFE EMBRYOS IN % IMPL.	MW	96.4	90.8	95.4	96.4
	SD	6.9	7.7	4.6	3.0
RESORPTIONS IN % IMPL.	MW	3.6	7.6	4.6	3.6
	SD	6.9	6.5	4.6	3.0
PRE IMPLANTAT. LOSS %	MW	0.6	1.2	0.6	0.2
	SD	3.6	5.6	3.7	1.2

CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

C.4. Genotoxicity

a. Testing for Point Mutagenic Activity of PPX (dihydrochloride) with *Salmonella typhimurium*
b. Testing for Point Mutagenic Activity of PPX (free base) with *Salmonella typhimurium*
c. Cell Transformation Assay in Syrian Hamster Embryo Cells
d. Induction of Chromosome Aberrations in Chinese Hamster Ovary Cells
e. V79 Gene Mutation Assay for HGPRT Mutants
f. *In vivo* Mouse Micronucleus Test

Studies were conducted by:

except for studies *d* (Cytotest) and *e* (NOTOX) (see text for addresses).

All studies complied with GLP.

C.4.a. Testing for Point Mutagenic Activity of PPX dihydrochloride with *Salmonella typhimurium*

Document #(s): Upjohn TR 7219-94-079
Sponsor Volume: 1.44

Summary:

Pramipexole was not mutagenic under the conditions employed in this study. The highest dose tested was appropriate. The strains employed for conferring of his-independence are not sensitive to A-T substitutions. A second study (C.4.b.) was conducted to meet this criterion.

Methods:

Drug concentrations: 10, 100, 500, 1000, 5000 µg/plate (Batch C of PPX dihydrochloride prepared in distilled water)

Positive controls/vehicles:
1-methyl-3-nitro-1-nitrosoguanidine/DMSO (dil. w. 50% DMSO)
2-nitrofluorene/DMSO
4-nitroquinoline-1-oxide/20%DMSO (dil. w. PBS)
9-aminoacridine/water
2-aminoanthracene/DMSO
benzo(a)pyrene/DMSO
emodin/DMSO

Bacterial Tester Strains:

Strain	Genetic characteristics
TA1535	hisG46, ΔuvrB, rfa
TA1537	hisC3076, ΔuvrB, rfa
TA100	hisG46, ΔuvrB, rfa, R fact.
TA98	hisD3052, ΔuvrB, rfa, R fact.

Base-pair (G-C) substitutions or frameshift mutations in the **his** operon confer **his**-independence; **uvrB** gene deletion confers defective excision repair system; **rfa** mutation increases permeability to chemical mutagens; **R factor** increases sensitivity to mutagens.

Metabolizing System: S9 fraction prepared from Arochlor-induced rat (500 mg/kg given five days before tissue harvest)

Test Conditions: Test system components (agar, bacteria, test substance, +/- S9) mixed and poured onto plates (triplicate samples). Plates were incubated for two days at 37° and the number of revertants determined.

Results:

Spontaneous reversion frequencies on control plates were within historical control. Pramipexole did not increase mutation frequency above control values in any tester strain at any dose in the presence or absence of S9. PPX was not toxic to indicator cells. The positive controls produced the expected increases in mutation frequency (Tables C.4.a.1-4).

Tab. C.4.a.1

Table 1: Induction of His$^+$ mutations in S. typhimurium by SMD 919 CL 2 in the absence of a metabolizing system (Experimental part No. MUT 0074/01)

Substance[a]	Concentration (µg/plate)	S9[b]	Number of His$^+$ revertants per plate[c,d]							
			TA1535		TA1537		TA100		TA98	
			n	$\bar{n}$	n	$\bar{n}$	n	$\bar{n}$	n	$\bar{n}$
Control		-	6 15 11	11	5 16 8	10	108 151 127	129	23 20 30	24
SMD 919 CL 2	10	-	8 11 13	11	6 7 5	6	148 154 139	147	22 27 28	26
	100	-	8 11 11	10	4 9 6	6	118 119 157	131	22 18 24	21
	500	-	6 6 4	5	6 7 9	7	116 153 122	130	23 26 20	23
	1000	-	7 8 5	7	4 7 9	7	120 152 144	139	28 17 23	23
	5000	-	5 8 4	6	9 6 4	6	160 140 121	140	30 18 17	22
NPNG	2.5	-	>2000 >2000 >2000		16 20 29	22	>2000 >2000 >2000		19 22 23	21
2-NF	10	-	13 6 8	9	116 131 132	126	>2000 >2000 >2000		>2000 >2000 >2000	

Tab. C.4.a.2.

Table 2: Induction of His$^+$ mutations in S. typhimurium by SMD 919 CL 2 in the absence of a metabolizing system - repeat study (Experimental part No. MUT 0074/05)

Substance[a]	Concentration (µg/plate)	S9[b]	Number of His$^+$ revertants per plate[c,d]							
			TA1535		TA1537		TA100		TA98	
			n	$\bar{n}$	n	$\bar{n}$	n	$\bar{n}$	n	$\bar{n}$
Control		-	27 18 28	24	6 9 7	7	154 C 170	162	27 23 31	27
SMD 919 CL 2	10	-	28 25 24	26	5 8 6	6	171 170 133	158	29 30 19	26
	100	-	30 38 34	34	10 6 8	8	131 166 127	141	19 31 19	23
	500	-	14 14 14	14	4 8 8	7	142 143 167	151	26 18 26	23
	1000	-	18 20 24	21	8 6 11	8	161 160 162	161	27 25 20	24
	5000	-	20 10 24	18	7 7 8	7	139 151 142	144	17 27 17	20
4-NOO	1	-	98 88 58	81	29 29 25	28	>2000 >2000 >2000		549 515 C	532
9-AA	100	-	36 14 26	25	489 280 305	358	156 126 135	139	8 9 11	9

Tab. C.4.a.3

Table 3: Induction of His$^+$ mutations in S. typhimurium by SHO 919 CL 2 in the presence of a metabolizing system (Experimental parts No. MBT 0074/02 and /03)

Substance[a]	Concentration (µg/plate)	S9[b]	Number of His$^+$ revertants per plate[c,d]							
			TA1535		TA1537		TA100		TA98	
			n	$\bar{n}$	n	$\bar{n}$	n	$\bar{n}$	n	$\bar{n}$
Control		+	9 13 12	11	9 7 7	8	167 190 174	177	31 49 44	41
SHO 919 CL 2	10	+	16 8 11	12	14 11 12	12	149 170 186	158	40 42 80	44
	100	+	4 9 17	10	6 8 7	7	177 182 168	176	53 42 36	44
	500	+	12 8 7	9	6 9 11	9	173 172 167	171	50 52 59	54
	1000	+	5 7 14	9	6 6 12	8	173 163 163	166	55 46 60	54
	5000	+	6 17 16	13	8 11 6	8	171 198 176	182	85 88 61	78
2-AA	0.5	+					279 535 468	427		
	2.5	+	375 406 384	388	351 372 368	364			1118 1268 808	1065
	0.5	-					157 151 168	159		
	2.5	-	13 5 9	9	4 20 9	11			41 31 26	33

Tab. C.4.a.4.

Table 4: Induction of His$^+$ mutations in S. typhimurium by SHO 919 CL 2 in the presence of a metabolizing system - repeat study (Experimental part No. MBT 0074/04)

Substance[a]	Concentration (µg/plate)	S9[b]	Number of His$^+$ revertants per plate[c,d]							
			TA1535		TA1537		TA100		TA98	
			n	$\bar{n}$	n	$\bar{n}$	n	$\bar{n}$	n	$\bar{n}$
Control		+	4 14 10	9	3 13 7	8	189 151 153	154	37 35 35	36
SHO 919 CL 2	10	+	14 10 14	13	7 7 9	8	149 148 152	150	50 42 33	42
	100	+	15 7 2	8	6 8 11	8	153 159 149	154	37 41 38	39
	500	+	18 10 16	15	8 11 11	10	132 142 145	140	35 36 41	37
	1000	+	10 20 16	12	6 15 8	9	159 C 173	166	45 44 48	46
	5000	+	13 16 19	16	7 C 9	8	175 162 156	164	58 35 42	45
B(a)P	5	+	14 9 18	14	164 156 120	147	953 C 896	925	592 498 549	546
Emodin	10	+	11 10 8	10	498 309 476	494	274 314 349	312	36 36 40	37

C.4.b. Testing for Point Mutagenic Activity of PPX (free base) with *Salmonella typhimurium*

Document #(s):

Upjohn TR 7219-94-084

Sponsor Volume: 1.44

Summary:

This experiment confirms the previous study that PPX is not mutagenic in *S. typhimurium* strains sensitive to mutations that affect G-C sites. The absence of mutagenicity in the *E. Coli* strains suggests that PPX does not induce mutations by affecting A-T base pairs. The highest dose tested was appropriate, and positive controls produced the expected results.

Methods:

Drug concentrations: 10, 100, 500, 1000, 5000 µg/plate (Batch III of PPX free base prepared in DMSO)

Positive Controls/vehicles: 1-methyl-3-nitro-1-nitrosoguanidine/DMSO
1-ethyl-3-nitro-1-nitrosoguanidine/DMSO
2-nitrofluorene/DMSO
2-aminoanthracene/DMSO

Bacterial Tester Strains:

Strain	Genetic characteristics
TA1535	hisG46, ΔuvrB, rfa
TA1537	hisC3076, ΔuvrB, rfa
TA1538	hisD3052, ΔuvrB, rfa
TA100	hisG46, ΔuvrB, rfa, R fact.
TA98	hisD3052, ΔuvrB, rfa, R fact.

Base-pair (G-C) substitutions or frameshift mutations in the **his** operon confer his-independence; **uvrB** gene deletion confers defective excision repair system; **rfa** mutation increases permeability to chemical mutagens; **R factor** increases sensitivity to mutagens.

In addition, the WP2uvrA strain of E. Coli was used. Point mutations in the trp operon of this strain confer trp-independence. It is sensitive to the base-pair substituting (A-T) activity of alkylating agents.

Metabolizing System: S9 fraction prepared from Arochlor-induced rat (500 mg/kg given five days before tissue harvest)

Test Conditions: Test system components (agar, bacteria, test substance, +/- S9) mixed and poured onto plates (triplicate samples). Plates were incubated for two days at 37° and the number of revertants determined.

Results:

Spontaneous reversion frequencies on control plates were within historical control. PPX did not increase mutation frequency above control values in any tester strain at any dose in the presence or absence of S9. PPX was not toxic to indicator cells. The positive controls produced the expected increases in mutation frequency (Tables C.4.b.1-4).

Tab. C.4.b.1

Table 1. Induction of mutations in the absence of a metabolizing system

Experiment 1 (HUT 0193/01 and /05)

Substance[a]	Conc. (mg/pl.)	S9[b]	Number of revertants per plate[c] TA1535	TA1537	TA1538	TA100	TA98	WP2uvrA
Solvent control (DMSO, 100 µl/pl.)		-	3	29	13	103	19	14
			15	18	13	91	19	27
			5	26	14	104	20	26
			8	24	13	99	19	22
SRD 919 BST	10	-	6	24	11	107	25	20
			5	23	15	93	23	15
			5	23	20	95	28	13
			5	27	15	98	26	16
	200	-	2	24	14	107	15	13
			7	13	11	108	20	13
			3	22	13	96	22	15
			4	26	13	94	19	14
	500	-	3	23	17	83	26	16
			6	23	19	95	15	15
			2	22	13	81	19	16
			4	23	16	86	20	16
	1000	-	4	36	13	86	9	18
			3	36	14	99	28	12
			4	31	19	78	17	15
			4	34	15	88	18	15
	5000	-	5	20	11	81	18	17
			4	40	14	81	19	15
			4	26	9	82	13	14
			4	29	11	75	17	15
NNG [1]	2.5	-	>2000	165	>2000	>2000	>2000	1008
2NF [2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide]	10		>2000	160	>2000	>2000	>2000	798
ENNG [N-ethyl-N'-nitro-N-nitrosoguanidine]	2.5		>2000	168	>2000	>2000	>2000	728
				164				845
Titer of the bacterial suspension (x10⁹/ml)			3.2 (338, 298, 327)[d]	2.2 (249, 196, 215)[d]	2.5 (235, 231, 274)[d]	0.6 (60, 49, 62)[d]	1.9 (205, 198, 162)[d]	1.9 (196, 196, 182)[d]

Tab. C.4.b.2.

Table 2. Induction of mutations in the absence of a metabolizing system

Experiment 2 (HUT 0193/02 and /05)

Substance[a]	Conc. (mg/pl.)	S9[b]	Number of revertants per plate[c] TA1535	TA1537	TA1538	TA100	TA98	WP2uvrA
Solvent control (DMSO, 100 µl/pl.)		-	9	9	15	107	31	23
			19	7	19	129	20	23
			24	9	14	95	30	19
			17	8	16	110	27	22
SRD 919 BST	10	-	8	26	C	126	28	8
			3	22	11	133	31	18
			4	3	29	104	15	17
			5	17	20	121	25	14
	100	-	7	11	15	115	27	16
			14	3	12	116	30	13
			4	10	13	117	27	15
			8	8	13	116	28	15
	500	-	8	7	20	89	14	14
			5	4	19	104	23	10
			6	23	15	137	14	12
			6	11	18	110	17	12
	1000	-	3	18	18	96	35	14
			7	9	16	82	28	15
			2	5	18	105	16	14
			6	11	17	94	26	14
	5000	-	3	3	11	86	11	17
			5	8	20	101	14	11
			7	7	6	107	10	9
			5	6	12	98	12	12
NNG [1]	2	-	1279	145	>2000	>2000	>2000	928
2NF [2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide]	10		1597	143	>2000	>2000	>2000	994
ENNG [N-ethyl-N'-nitro-N-nitrosoguanidine]	2.5		1482	183	>2000	>2000	>2000	968
			1453	157				963
Titer of the bacterial suspension (x10⁹/ml)			2.3 (244, 242, 200)[d]	1.8 (194, 181, 171)[d]	3.0 (294, 302, 297)[d]	0.8 (92, 62, 72)[d]	1.8 (185, 170, 174)[d]	1.9 (199, 178, 206)[d]

Tab. C.4.b.3.

Table 3. Induction of mutations in the presence of a metabolizing system

Experiment 1 (BUT 0193/03 and /05)

Substance[a]	Conc. (µg/pl.)	S9[b]	Number of revertants per plate[c] TA1535	TA1537	TA1538	TA100	TA98	WP2uvrA
Solvent control (DMSO, 100 µl/pl.)		+	6	6	17	86	34	26
			6	14	16	106	29	11
			4	7	24	105	37	17
			5	9	19	99	33	18
SBD 919 BSY	10	+	7	14	30	102	26	16
			5	12	37	100	33	14
			7	16	25	108	18	21
			6	13	31	103	26	18
	100	+	11	7	15	105	30	C
			2	11	26	100	28	15
			5	13	20	94	29	13
			6	10	24	100	28	14
	500	+	7	8	31	124	31	16
			6	12	14	107	42	19
			4	9	14	96	28	14
			6	10	26	109	33	16
	1000	+	2	17	17	107	25	11
			11	9	36	101	23	19
			5	9	26	129	24	9
			6	12	26	126	27	13
	5000	+	7	7	23	121	34	17
			10	4	26	117	34	17
			7	4	18	118	25	14
			8	5	22	119	31	16
2AA (2-4-8)	0.5	+	168	239	554	338	275	304
(1-2)	2.5		207	245	472	358	255	301
(4)	5		218	250	482	396	264	490
			198	245	503	364	265	365
Titer of the bacterial suspension (x10⁹/ml)			2.3 (194, 244, 247)[d]	2.0 (175, 235, 193)[d]	2.9 (282, 318, 244)[d]	0.9 (86, 88, 82)[d]	2.0 (195, 178, 220)[d]	1.9 (196, 196, 182)[d]

Tab. C.4.b.4.

Table 4. Induction of mutations in the presence of a metabolizing system

Experiment 2 (BUT 0193/04 and /05)

Substance[a]	Conc. (µg/pl.)	S9[b]	Number of revertants per plate[c] TA1535	TA1537	TA1538	TA100	TA98	WP2uvrA
Solvent control (DMSO, 100 µl/pl.)		+	14	5	18	122	41	9
			6	3	27	111	38	19
			9	11	22	126	50	26
			10	6	22	126	43	18
SBD 919 BSY	10	+	13	8	24	107	50	16
			11	5	24	123	47	20
			6	8	27	116	50	15
			10	6	25	115	49	17
	100	+	12	9	19	121	46	22
			13	8	26	102	42	23
			7	11	23	119	28	16
			11	9	23	114	39	20
	500	+	5	11	30	110	34	24
			4	6	25	102	31	11
			9	14	23	134	29	18
			6	10	26	115	35	18
	1000	+	5	16	30	107	39	18
			6	7	23	122	45	9
			8	7	24	105	40	18
			6	10	26	111	41	15
	5000	+	7	7	28	108	33	16
			7	4	20	100	27	13
			7	8	22	128	31	12
			7	6	23	112	30	14
2AA (2-4-8)	0.5	+	334	177	354	313	319	351
(1-2)	2.5		367	172	375	346	360	561
(4)	5		341	194	381	332	336	369
			347	181	370	330	338	427
Titer of the bacterial suspension (x10⁹/ml)			2.3 (232, 214, 244)[d]	1.3 (126, 110, 146)[d]	2.0 (200, 198, 194)[d]	0.5 (50, 45, 41)[d]	1.7 (167, 182, 165)[d]	1.9 (199, 178, 206)[d]

C.4.c. Cell Transformation Assay in Syrian Hamster Embryo Cells

Document #(s):

Upjohn TR 7219-94-082

Conducted by:

Sponsor Volume: 1.44

Summary:

In this transformation experiment, no reproducible transforming potential of PPX was detected in Syrian Hamster Embryo cells. The dosage range used in this study (100-400 µg/ml) was limited by cytotoxicity criteria established by the sponsor (minimum desired survival rate of 40-50%). This cytotoxicity level is below that established in the newer guidelines (no more than 20% survival), as is the exposure range (desired upper treatment levels for mammalian cells is 5 mg/ml or 10 mM = 2.9 mg/ml for PPX).

Since this assay is not in the core battery for genotoxicity testing, a repetition of the test at higher doses is not required. In view of the relatively low transformation rate with the positive controls, the utility of this test in predicting genotoxic potential is questionable.

Methods:

Drug Concentrations and Exposures: PPX dihydrochloride (Batch I) prepared in nutrient medium at the following concentrations:

Without S9 activation:

4 hr:	10, 25, 40, 100 µg/ml
48 hr:	10, 25, 40, 100 µg/ml

With S9 activation:

4 hr:	10, 40, 200, 400 µg/ml

Positive Controls/vehicles:

Without S9 activation:

1-methyl-3-nitro-1-nitrosoguanidine/DMSO (0.5 µg/ml medium)

With S9 activation:

Benzo(a)pyrene/DMSO (5 µg/ml medium)

(final concentration of DMSO in medium was 1%)

Test System:

Cultures prepared from 12-14 day Syrian Hamster embryos (decapitated, eviscerated), and propagated in 175 cm^2 (feeder cells) or 25 cm^2 (target cells) flasks. Cultures were exposed to the test substance for the indicated times (4 or 48 hr). Cultures were maintained for up to 10 days after the initial seeding, then fixed and stained. Colonies within each flask were examined for morphological transformations:

- criss-cross growth in marginal zones of colonies
- three-dimensional piling up of cells in center of the colony
- reduced cytoplasm to nuclear ratio

One or two thousand colonies per test condition were scored (100 colonies in 10 or 20 flasks). A response was considered positive if two or more transformed colonies occur in flasks treated with test article. Historical control frequency of spontaneous alterations is 0.05 - 0.1%

Metabolizing System:

S9 fraction prepared from Arochlor-induced rat (500 mg/kg given five days before tissue harvest)

Results:

Determination of cytotoxicity:

Experimental doses for the main study were selected based on the following survival/toxicity data:

Final concentration µg/ml	% relative survival without S9 mix 48 h	with S9 mix 4 h
0 = medium	100.0	100.0
5.0	89.4	96.0
10.0	87.8	95.6
50.0	54.3	84.9
100.0	43.0	71.6
250.0	0.0	59.6
500.0	0.0	38.7
750.0	0.0	2.2
1000.0	0.0	0.0
2900.0	0.0	0.0

According to these data the concentrations applied in the transformation study were chosen.

PPX was toxic at concentrations above 100 µg/ml in the absence of S9, and above 250 µg/ml in the presence of S9. Doses for the transformation experiment were 100 and 400 µg/ml in the absence and presence of S9, respectively.

Transformation Experiment I (Tables C.4.c.1-2):

RESULTS WITHOUT S9 MIX

4 h Treatment Interval

Test groups	number of colonies scored	transf. colonies	% transf. colonies	PE = % survival absolute	relative
untreated cells	1,000	0	0.0	45.7	100.0
MNNG 0.5 µg/ml	1,000	13	1.3	24.9	54.5
test article					
10.0 µg/ml	1,000	1	0.1	45.4	99.3
25.0 µg/ml	1,000	0	0.0	37.8	82.7
40.0 µg/ml	1,000	1	0.1	31.4	68.7
100.0 µg/ml	1,000	0	0.0	22.6	49.5

48 h Treatment Interval

Test groups	number of colonies scored	transf. colonies	% transf. colonies	PE = % survival absolute	relative
untreated cells	1,000	1	0.1	44.0	100.0
MNNG 0.5 µg/ml	1,000	11	1.1	28.0	63.6
test article					
10.0 µg/ml	1,000	0	0.0	43.4	98.6
25.0 µg/ml	1,000	0	0.0	36.6	83.2
40.0 µg/ml	1,000	1	0.1	26.1	59.3
100.0 µg/ml	1,000	2	0.2	20.7	47.0

RESULTS WITH S9 MIX

4 h Treatment Interval

Test groups	number of colonies scored	transf. colonies	% transf. colonies	PE = % survival absolute	relative
untreated cells	1,000	0	0.0	44.9	100.0
B(a)P 5 µg/ml test article	1,000	12	1.2	30.5	67.9
4.0 µg/ml	1,000	0	0.0	45.5	101.3
40.0 µg/ml	1,000	0	0.0	36.9	82.2
200.0 µg/ml	1,000	0	0.0	30.0	66.8
400.0 µg/ml	1,000	0	0.0	21.8	48.6

Similar results were obtained in a repeat experiment in which 2000 colonies per condition were scored, except that no more than 1 transformed colony appeared in PPX-treated cultures at a given concentration.

C.4.d. Induction of Chromosome Aberrations in Cultured Chinese Hamster Ovary Cells

Document #(s):

Upjohn TR 7219-94-081

Conducted by:

Sponsor Volume: 1.44

Summary:

In this clastogenicity study, no reproducible transforming potential of PPX was detected in the Chinese Hamster Ovary cell line. The dosage range used in this study was appropriate, since it approached desired upper treatment levels for cell lines (5 mg/ml or 10 mM = 2.9 mg/ml for PPX) and caused significant cytotoxicity at the highest concentrations. A small, non-reproducible clastogenic effect was observed with activation at the highest test dose (3300 µg/ml).

Methods:

Drug Concentrations and Exposures: PPX dihydrochloride (Batch I) dissolved in F10/HEPES at the following concentrations:

Without S9 activation:	100, 500, 1000, 2000 µg/ml
With S9 activation:	100, 333, 1000, 3330 µg/ml

Positive Controls/vehicles:

Without S9 activation:	Ethylmethanesulfonate (4 or 6 mM) in DMSO
With S9 activation:	Cyclophosphamide (10 or 5 µg/ml) in medium

Test System:

Duplicate monolayer cultures of CHO cells ($1x10^6$) in $75cm^2$ flasks were exposed to test substance for 2 hr. Incubations were continued for 18-19 hrs. Cell division was arrested at metaphase by addition of colchicine during the last two hrs of the incubation. Chromosomal material was condensed and fixed on a glass slide, stained with 5% Giemsa, and examined microscopically for aberrations (gaps, breaks, fragments, dicentrics, exchange figures, numerical variations). 100 Metaphase spreads per culture were examined by light microscopy.

Metabolizing System:

S9 fraction prepared from Arochlor-induced rat (500 mg/kg given five days before tissue harvest)

Statistics: Chi-square analysis, $p<0.05$ (one-tailed test)

Results:

Determination of cytotoxicity:

Experimental doses were selected based on the following cytotoxicity data:

4.1 Cytotoxicity test/dosage selection

TABLE 1 CYTOTOXICITY TEST OF SND 919 C12Y

Test substance concentration (µg/ml)	Cells/6 cm ⌀ culture dish ($x10^5$)b)	
	Directly after exposure (% of control)	After 18-20 h of growth (% of control)
	Without metabolic activation (-S9-mix)	
Control[a)]	4.61 (100%)	11.57 (100%)
1	*	*
3.3	4.77 (103%)	12.39 (107%)
10	*	*
33	4.99 (108%)	10.14 (88%)
100	4.38 (95%)	12.08 (104%)
333	2.97 (64%)	10.85 (94%)
1000	3.48 (75%)	11.48 (99%)
3330	1.80 (39%)	3.35 (29%)
5000	0.92 (20%)	0
	With metabolic activation (+S9-mix)	
Control[a)]	4.41 (100%)	13.25 (100%)
1	*	*
3.3	4.27 (97%)	14.12 (107%)
10	*	*
33	4.57 (104%)	12.05 (91%)
100	4.24 (96%)	*
333	4.35 (99%)	12.20 (92%)
1000	4.57 (104%)	13.40 (101%)
3330	4.48 (102%)	10.17 (77%)
5000	2.71 (61%)	0.50 (4%)

Cytogenetic Test Results:

In the absence of S9, no increase in the number of chromosomal aberrations was observed in PPX-treated cultures (Table C.4.d.2). However, the positive control (EMS) was only "mildly" clastogenic, so the experiment was repeated. A more robust EMS response was obtained, and PPX appeared clastogenic at a concentration of 500 µg/ml (Table C.4.d.3). Since the effect was rather small and no dose-related trends were observed, it is probably not biologically significant.

In the presence of S9, a significant increase in number of chromosomal aberrations was observed in cultures treated with the high concentration of PPX (3300 µg/ml; Tab. C.4.d.4). The effect was relatively small compared to that of cyclophosphamide, and not reproducible (Tab. C.4.d.5).

The frequency of chromosomal aberrations in control cultures were within historical control range for this laboratory (6.6 ± 3.0).

C.4.d.2.

TABLE 4 CHROMOSOME ABERRATIONS[a]: INDIVIDU DATA (WITHOUT METABOLIC ACTIVATION;-S9-mix)

STUDY NUMBER :
PROJECT NUMBER: 0311
STUDY DIRECTOR:

TEST SUBSTANCE IDENTIFICATION: SND 919 C12Y
SOLVENT : F10-HEPES
DOSE RANGE : 100-2000 µg/ml

Concentration (µg/ml)	Culture	No. of cells scored	No. of cells with aberrations gaps included	gaps excluded	g'	g''	b'	b''	f'	f''	exch	dic	d'	misc	Total aberrations (including/excluding gaps)
0	A	100	9	5	4	1				9					14/9
0	B	100	5	5			2			3					5/5
Total	(A + B)	200	14	10											
100	A	100	7	4	2	1		1		3					7/4
100	B	100	5	3	1	1	2			1					5/3
Total	(A + B)	200	12	7											
500	A	100	9	7	2		1			6				sp	10/8
500	B	100	9	5	3	1	1			4					9/5
Total	(A + B)	200	18	12											
1000	A	100	3	2	1					2					3/2
1000	B	100	7	3	2	2	1			2					7/3
Total	(A + B)	200	10	5											
2000	A	100	8	3	5		1			2				poly, endo	8/3
2000	B	100	9	5	4					3	1			sp, endo	9/5
Total	(A + B)	200	17	8											
4 mM EMS	A	100	15	10	5	1	2	1		8				poly	17/11
4 mM EMS	B	100	12	8	3	1	3			5				ma	13/9
Total	(A + B)	200	27*	18											

a) Abbreviations used for various types of aberrations are listed in Appendix 1.
The numerical variations endoreduplication (endo) and polyploidy (poly) were not counted as an aberration.
Significantly different from control group: Chi-Square Test, *P < 0.05, **P < 0.01, or ***P < 0.001

C.4.d.3

TABLE # CHROMOSOME ABERRATIONS[a]: INDIVIDUAL DATA (WITHOUT METABOLIC ACTIVATION; -S9-MIX)

TR No.: 7219-94-081

STUDY NUMBER :
PROJECT NUMBER: 0311
STUDY DIRECTOR:

TEST SUBSTANCE IDENTIFICATION: SND 919 C12Y
SOLVENT : F10-HEPES
DOSE RANGE : 100-2000 µg/ml

Concentration (µg/ml)	Culture	No. of cells scored	No. of cells with aberrations: gaps included	gaps excluded	g'	g''	b'	b''	f'	f''	exch	dic	d'	misc	Total aberrations (including/excluding gaps)
0	A	100	5	3	2	1	1			2					6/3
0	B	100	11	5	9		4			1				2 poly	14/5
Total	(A + B)	200	16	8											
100	A	100	12	9	3		2			6				sp	12/9
100	B	100	7	5	1	1	2			4				3 poly, endo	8/6
Total	(A + B)	200	19	14											
500	A	100	8	8	1		6			1		1		poly	9/8
500	B	100	12	9	3		3			6				2 poly	12/9
Total	(A + B)	200	20	17*											
1000	A	100	8	1	8		1								9/1
1000	B	100	6	2	3	1	2							poly	6/2
Total	(A + B)	200	14	3											
2000	A	100	5	2	3		1					1		3 poly	5/2
2000	B	100	7	2	6		1			1				poly	7/2
Total	(A + B)	200	12	4											
6 mM EMS	A	100	22	16	8	2	10	1		4				sp, poly	26/16
6 mM EMS	B	100	25	20	7		11			11	3			sp	33/26
Total	(A + B)	200	47***	36***											

a) Abbreviations used for various types of aberrations are listed in Appendix 1.
The numerical variations endoreduplication (endo) and polyploidy (poly) were not counted as an aberration.
Significantly different from control group: chi-square test, *$P < 0.05$, **$P < 0.01$, or ***$P < 0.001$

C.4.d.4

TABLE CHROMOSOME ABERRATIONS[a]: INDIVIDUAL DATA (WITH METABOLIC ACTIVATION; +S9-mix)

STUDY NUMBER :
PROJECT NUMBER: 0311
STUDY DIRECTOR:

TEST SUBSTANCE IDENTIFICATION: SND 919 C12Y
SOLVENT : F10-HEPES
DOSE RANGE : 100-3330 µg/ml

Concentration (µg/ml)	Culture	No. of cells scored	No. of cells with aberrations: gaps included	gaps excluded	g'	g''	b'	b''	f'	f''	exch	dic	d'	misc	Total aberrations (including/excluding gaps)
0	A	100	11	7	3	1	1			6				endo	11/7
0	B	100	6	3	3		2			2					7/4
Total	(A + B)	200	17	10											
100	A	100	10	5	4	1				4		1			10/5
100	B	100	11	8	4	1	3			4				ma	13/8
Total	(A + B)	200	21	13											
333	A	100	2	1	1					1					2/1
333	B	100	12	7	5		2			4		1		endo	12/7
Total	(A + B)	200	14	8											
1000	A	100	12	10	3		1			7		2		sp	14/11
1000	B	100	8	6	2		1	2		4					9/7
Total	(A + B)	200	20	16											
3330	A	100	19	15	4		3			13				3ma, poly, endo	23/19
3330	B	100	15	12	5		2			4	2			6ma, 3poly, endo, 2sp	21/16
Total	(A + B)	200	34**	27**											
10 µg/ml CP	A	50	42	35	7	1	13			25	20			2ma, endo, 2 sp	70/62
10 µg/ml CP	B	50	40	38	9	4	10			29	10			sp, 6ma	69/56
Total	(A + B)	100	82***	73***											

a) Abbreviations used for various types of aberrations are listed in Appendix 1.
The numerical variations endoreduplication (endo) and polyploidy (poly) were not counted as an aberration.
Significantly different from control group: Chi-Square Test, * $P<0.05$, ** $P<0.01$, or *** $P<0.001$

C.4.d.5

TABLE 9, CHROMOSOME ABERRATIONS[a]: INDIVIDUAL DATA (WITH METABOLIC ACTIVATION; +S9-mix)

STUDY NUMBER :
PROJECT NUMBER: 0311
STUDY DIRECTOR:

TEST SUBSTANCE IDENTIFICATION: SND 919 Cl2Y
SOLVENT : F10-HEPES
DOSE RANGE : 333-3330 µg/ml

Concentration (µg/ml)	Culture	No. of cells scored	No. of cells with aberrations gaps included	gaps excluded	g'	g''	b'	b''	f'	f''	exch	dic	d'	misc	Total aberrations (including/excluding gaps)
0	A	100	11	9	3	1	3	1		5				poly, 2 endo	13/9
0	B	100	5	4	2		1			3				2 poly, 4 endo	6/4
Total	(A + B)	200	16	13											
333	A	100	9	3	6		2			1					9/3
333	B	100	14	7	6	3	2			5				2 endo, 1 poly	16/7
Total	(A + B)	200	23	10											
1000	A	100	14	11	4	1	5			6				endo, poly, r	17/12
1000	B	100	9	6	4		4			2				2 endo, poly	10/6
Total	(A + B)	200	23	17											
2500	A	100	10	6	5		4			1		1		4 endo, poly	11/6
2500	B	100	11	7	5		4			3				2 poly	12/7
Total	(A + B)	200	21	13											
3330	A	100	13	10	4		6			4				3 endo	14/10
3330	B	100	9	5	5		3			3				poly, endo	11/6
Total	(A + B)	200	22	15											
5 µg/ml CP	A	50	45	44	7	3	21			14	16	2		14 ma, 4 sp	81/71
5 µg/ml CP	B	50	49	49	8		16			41	23			10 ma, 3 sp	101/93
Total	(A + B)	100	94***	93***											

a) Abbreviations used for various types of aberrations are listed in Appendix 1.
The numerical variations endoreduplication (endo) and polyploidy (poly) were not counted as an aberration.
Significantly different from control group: chi-square test, *$p < 0.05$, **$p < 0.01$, or ***$p < 0.001$

C.4.e. V79 Gene Mutation Assay for HGPRT Mutants

Document #(s):

Upjohn TR 7219-94-083

Sponsor Volume: 1.44

Summary:

In this mutagenicity study, PPX did not produce mutations in the HGPRT locus in the Chinese Hamster V79 cell line. The dosage range used in this study was appropriate, since it approached desired upper treatment levels for cell lines (10 mM pramipexole = 2.9 mg/ml for pramipexole). The survival rate at the high concentration of 3000 µg/ml was 35-55%. Positive controls produced the expected mutations.

Methods:

Drug Concentrations and Exposures: PPX dihydrochloride (Batch III) dissolved in DMEM as follows:

Expt. I:	
Without S9 activation:	100, 500, 1000, 2500, 3000 µg/ml
With S9 activation:	100, 1000, 2000, 3000 µg/ml
Expt. II:	
Without S9 activation:	100, 1000, 2500, 3000 µg/ml
With S9 activation:	100, 1000, 2000, 3000 µg/ml

Positive Controls/vehicles:

Without S9 activation:	Ethylmethanesulfonate (500 µg/ml) dissolved in treatment medium
With S9 activation:	DMBA (8 µg/ml) in DMSO (final conc = 1% in medium)

Test System:

The basis of this study is the presence/absence of hypoxanthine-guanine phosphoribosyl transferase in V79 cells. A mutation in the HGPRT locus results in cells which do not convert 6-thioguanine (6-TG) into a toxic metabolite, and thus survive treatment with media containing 6-TG. Mutants arise from base-pair substitutions, frameshifts, deletions, and chromosome rearrangements.

V79 Chinese hamster cells ($5x10^5$) were cultured in 80 cm^2 flasks for mutation

studies (1 flask per point). For survival analysis, 220 cells were plated in 58 cm^2 dishes in triplicate. Cells were exposed to test substance, with and without S9 fraction, for 4 hr. Cells in the survival study were fixed and stained on day 6. Cells in the mutation study were subcultured every 2-3 days. On day 7, cells ($5x10^5$) were plated into 58 cm^2 dishes and medium containing 6-TG was added to cultures for mutant selection. An additional set of 58 cm^2 dishes were seeded with 220 cells to which complete medium was added for determination of plating efficiency. Incubations were continued with media changes for 6-7 days. Cultures were fixed (ethanol/glacial acetic acid, 3:1) and stained (7% Giemsa) on days 13 and 14 after culture initiation for determination of plating efficiency and mutant selection, respectively. Colonies containing more than 50 cells were counted.

Metabolizing System: S9 fraction prepared from Arochlor-induced rat (500 mg/kg given five days before tissue harvest)

Results:

Determination of cytotoxicity:

Significant cytotoxicity occurred with concentrations of 5000 µg/ml in the presence or absence of S9 (Tab. C.4.e.1). Thus, 3000 µg/ml was chosen as the high dose for mutagenicity testing.

Table 1: Results of the preliminary experiment on toxicity

(Experimental parts no. MUT 0127/01 and /02)

Substance	Concentration* (µg/ml)	Number of colonies per plate Individual counts	Mean	Survival %
Without S9 mix:				
Negative control		222, 249, 233	235	100
SND 919 CL2Y	10	227, 234, 231	231	98
	100	238, 207, 216	220	94
	1000	106, 127, 105	113	48
	2500	111, 89, 92	97	41
	5000	25, 23, 17	22	9
With S9 mix:				
Negative control		244, 256, 238	246	100
SND 919 CL2Y	10	235, 240, 229	235	96
	100	252, 228, 239	240	98
	1000	230, 248, 249	242	98
	2500	245, 227, 201	224	91
	5000	81, 86, 53	73	30

Mutagenicity Test Results:

The mutation rate in cultures treated with PPX was approximately equivalent to negative control rates in the presence or absence of S9 in both experiments. The mutation frequency in these cultures were within the normal range of this laboratory. The positive controls EMS and DMBA produced the expected significant increases in mutation rate frequency (Tables C.4.e.2-3). Similar results were obtained in a replicate experiment.

C.4.e.2.

Table [redacted]: Mutagenicity assay; experiment 1; without S9 mix

(Experimental part no. MUT 0127/03)

Toxicity data

Substance	Concentration[a] (µg/ml)	Number of colonies per plate Individual counts	Mean	Survival %
Negative control		215, 218, 201	211	100
SND 919 CL2Y	100	206, 188, 209	201	95
	500	186, 206, 208	200	95
	1000	199, 188, 177	188	89
	2500	131, 123, 160	138	65
	3000	118, 110, 131	120	57
Positive control with EMS	500	183, 176, 190	183	87

Mutation induction

Substance	Conc.[a] (µg/ml)	Plating efficiency Individual plate counts	Mean (A)*	Number of cells seeded per flask (B)	Mutant selection[a] Individual plate counts	Mean (C)	Mutants per 10^6 survivors (D)
Negative control		77, 109, 101	96	238806	0, 0, 3	1.0	4.2
SND 919 CL2Y	100	80, 77, 85	81	199507	0, 0, 0	0	0
	500	103, 117, 104	108	259615	1, 6, 1	2.7	10.4
	1000	61, 77, 85	74	184080	0, 1, 0	0.3	1.6
	2500	120, 117, 103	113	278325	0, 0, 1	0.3	1.1
	3000	126, 112, 110	116	287129	0, 0, 0	0	0
Positive control with EMS	500	72, 79, 68	73	180693	129, 144, 123	132.0	730.5

For footnotes and abbreviations see Table 1.

* Based on number of seeded cells: neg. control, 201; 100 µg/ml, 203; 500 µg/ml, 208; 1000 µg/ml, 201; 2500 µg/ml, 203; 3000 µg/ml, 202; pos. control, 202.

C.4.e.3.

Table 2nd: Mutagenicity assay; experiment 1; with S9 mix

(Experimental part no. MUT 0127/05)

Toxicity data

Substance	Concentration[a] (µg/ml)	Number of colonies per plate Individual counts	Mean	Survival %
Negative control		210, 213, 187	203	100
SND 919 CL2Y	100	202, 176, 184	187	92
	1000	174, 145, 178	166	82
	2000	178, 189, 169	179	88
	3000	125, 153, 131	136	67
Positive control with DMBA	8	74, 65, 64	68	33

Mutation induction

Substance	Conc.[a] (µg/ml)	Plating efficiency Individual plate counts	Mean (A)	Number of cells seeded per flask (B)	Mutant selection[b] Individual plate counts	Mean (C)	Mutants per 10^6 survivors (D)
Negative control		167, 165, 179	170	425000	7, 7, 5	6.3	14.8
SND 919 CL2Y	100	174, 171, 176	174	435000	0, 1, 1	0.7	1.6
	1000	173, 182, 190	182	455000	2, 1, 1	1.3	2.9
	2000	175, 180, 179	178	445000	3, 2, 1	2.0	4.5
	3000	194, 186, 187	189	472500	0, 0, 1	0.3	0.6
Positive control with DMBA	8	92, 94, 123	103	257500	250, 295, 221	255.3	991.5

For footnotes and abbreviations see Table 1.

C.4.f. *In vivo* Mouse Micronucleus Test

Document #(s):

Upjohn TR 7219-94-080

Sponsor Volume: 1.44

Summary:

In this *in vivo* mutagenicity study, a single, high, toxic dose of PPX (1000 mg/kg) did not significantly increase the number of micronucleated polychromatic erythrocytes in the femoral bone marrow of mice at 24-72 hrs after dosing. The positive control cyclophosphamide produced the expected result.

According to 1994 OECD guidelines, this study is deficient with respect to the number of doses employed (one rather than the recommended three), and the number of polychromatic erythrocytes scored for the presence of micronuclei (1000 vs recommended 2000). Since there was no indication that a single high toxic dose of PPX causes even the slightest increase in the occurrence of micronuclei, and a high rate of lethality would be expected at the recommended 2000 mg/kg dose level, a repetition of this study to conform with guidelines will not be required.

Methods:

Dosage/Route: 1000 mg/kg PPX dihydrochloride (Batch C in 10 ml/kg distilled water) by gavage.

Positive Controls/vehicles: Cyclophosphamide

Animals: Chbb:NMRI mice, 27-46 g, 10 weeks old.
35 animals (17 M, 18 F) received drug; 2 M and 3 F died within 1 hr of dosing.

Dosing Regimen:

Group	Dose	Sampling time	Sex	Animal number
0	dist. water	24 h	male female	001 - 005 051 - 055
1	SND 919 CL 2 1000 mg/kg	24 h	male female	101 - 106 151 - 156
2	SND 919 CL 2 1000 mg/kg	48 h	male female	201 - 206 251 - 256
3	SND 919 CL 2 1000 mg/kg	72 h	male female	301 - 305 351 - 356
4	Cyclophosphamide 50 mg/kg	24 h	male female	401 - 405 451 - 455

Note: Failure to comply with OECD guidelines stating that 3 dose levels, or a single dose level of 2000 mg/kg/day should be employed.

Sample Analysis: Femoral marrow smears were fixed on a slide (2 per animal) and stained with Giemsa. At least 1000 polychromatic erythrocytes per animal were scored for the presence of micronuclei. The ratio of polychromatic to normochromatic nuclei was determined by counting 1000 erythrocytes.

Note: OECD guidelines state that 2000 PCEs should be scored.

Results:

A single dose of 1000 mg/kg PPX to male and female mice did not significantly increase the number of micro nucleated polychromatic erythrocytes relative to control levels at 24, 48 or 72 hrs. The ratio of polychromatic to normochromatic erythrocytes also was not affected by PPX. The positive control cyclophosphamide produced the expected increase micronucleated polychromatic erythrocytes.

Table 1: Results of Micronucleus Test with SND 919 CL 2

Dose[a]	Sampling time	Sex	Number of mice	Micronucleated polychromatic erythrocytes (°/oo) Mean ± standard deviation
Vehicle control	24 h	male	5	1.8 ± 0.4
		female	5	1.2 ± 0.8
SND 919 CL 2 1000 mg/kg	24 h	male	5	2.6 ± 1.3
		female	5	2.2 ± 1.3
SND 919 CL 2 1000 mg/kg	48 h	male	5	1.6 ± 0.9
		female	5	2.2 ± 0.8
SND 919 CL 2 1000 mg/kg	72 h	male	5	2.2 ± 0.8
		female	5	1.2 ± 0.4
Cyclophosphamide 50 mg/kg	24 h	male	5	31.4 ± 8.1[b]
		female	5	23.0 ± 5.4[b]

[a] Vehicle control, 10 ml dist. water per kg.
[b] Significantly different from the vehicle control ($\alpha \leq 0.01$).

C.5. Carcinogenicity

C.5.a. Two-Year Mouse Carcinogenicity Study

Conducted by :

Document #(s):

Upjohn TR 7219-94-070

Sponsor Volumes: 1.45-1.48

This study complied with GLP

Summary:

Pramipexole was administered in the diet at doses of 0.3, 2.0, and 10.0 mg/kg/day to Chbb:NMRI mice (50/sex/dose group, 100/sex/control) for two years. Relatively few non-neoplastic and no neoplastic lesions were clearly associated with PPX administration.

The rate of premature decedents was higher in PPX-treated animals than in controls; the effect was significant in males. The highest mortality rate was 46% in MDF and HDF. The primary cause of premature deaths were unscheduled sacrifices due to eczema, a condition observed in both control and treated animals. Body weight gain was significantly reduced by 37-45% in both sexes at the intermediate and high doses at study termination. A relative increase in the incidence of alopecia was also noted in PPX-treated animals. Spontaneous activity was increased in MD and HD females, and HD males.

No statistically significant increases or trends for increases in the incidence of neoplastic lesions in drug-treated animals were apparent according to the sponsor's analysis. A pooled analysis of all mesenchymal/epithelial uterine neoplasms was not presented, but the incidences suggest a possible dose-related positive trend (controls: 10%; LD: 10%; MD: 14%; HD: 16%). Statistically significant **decreases** in the incidence of adrenal cortical adenomas in HD males, and malignant lymphomas in MD and HD females were noted. For all other neoplastic findings, which included systemic neoplasms of the hemolymphoreticular system, and primary neoplasms in the lung, liver, and adrenals in males, and the reproductive tracts of both sexes, the incidences were low, and equivalent in PPX-treated and control animals.

The only histopathological findings that occurred at a higher incidence rate in PPX-treated animals were fibro-osseous proliferative lesions in the femurs of females (all dosage groups). This lesion occurred at a relatively high rate in control females (28%), but approximately doubled in incidence in treated animals (56-62%; similar at the three dosage levels). The more severe lesions were found more frequently in treated animals. This type of lesion is known to occur spontaneously in female mice of other strains including B6C3F1 (Albassam, *et al.*, Vet. Pathol., 28:381, 1991), and has also been observed in mice after

administration of the prostaglandin E analogue misoprostol (Dodd and Port, Vet. Pathol., 24:545, 1987) and estrogens (Gaunt and Pierce, Vet. Pathol., 22:403, 1985). The increased incidence in drug-treated animals may be related to stimulation of estrogen release (Sass and Montali, Lab. Anim. Sci., 30:907, 1980), although no experimental evidence of such a hormonal effect of PPX was presented. Pathological changes that might be expected to accompany a bone abnormality (i.e., blood cell count changes) were not clearly associated with this lesion. Possibly compensatory stimulation of splenic erythropoiesis occurred in both treated and control female mice, and increased hematopoietic activity was noted in the femoral bone marrow of MDF and HDF.

Based on plasma level measurements in satellite groups during weeks 2, 40 and 80 at 4-5 hrs after light onset, exposure to PPX in the high dose group (36-81 ng/ml) was 5-10 fold higher than the $Cmax_{ss}$ in humans following the expected maintenance dose of 1.5 mg, t.i.d.

Thus, administration of PPX in the diet for two years was not significantly carcinogenic in mice. However, conclusive interpretation of these results is hindered by the marked impairment of body weight development at the mid- and high-dose levels. The low exposures at the lowest dose levels cannot be considered adequate for assessing the tumorigenic effects of this compound. The importance of the fibro-osseous proliferative lesion is questionable since similar lesions are known to occur spontaneously in certain strains of mice, and no similar lesion was observed in long-term rat and monkey PPX studies. The "No Effect" dose was considered to be 0.3 mg/kg/day, although a trend for decreased food intake was apparent at this dose.

Methods:

Dosages: 0.3, 2.0, 10.0 mg/kg/day PPX dihydrochloride (Batch II)

The low dose is three times the ED_{50} for anti-Parkinsonian effects in monkeys, and 5-15 times higher than the expected human maintenance dose range of 1.5-4.5 mg/day (70 kg human). The high dose was selected as the highest tolerable dose given the duration of the study and the limitation of excessive CNS stimulation. The reduction in body weight gain by this dose was used as an indicator of drug toxicity.

Route of Administration: Drug-in-diet

Species/Strain/Number: Mouse (Chbb:NMRI)

250 males, 250 females for toxicology
20 males, 20 females for microbiology
159 males, 159 females for toxicokinetics

Toxicology Groups:

Group size and dosage:

Group	Dose mg/kg	Number of animals males	females	Identity number
0 (control A)	0	50	50	0001-0050 0501-0550
1	0.3	50	50	1001-1050 1501-1550
2	2.0	50	50	2001-2050 2501-2550
3	10.0	50	50	3001-3050 3501-3550
4 (control B)	0	50	50	4001-4050 4501-4550

Toxicokinetic Analyses:

Group no.	Animals/sex per sampling	Animals/ plasma pool	Pooled samples/ group & date
5	20 / m	5	4
	20 / f	5	4
6	16 / m	4	4
	16 / f	4	4
7	12 / m	3	4
	12 / f	3	4

Blood was sampled during weeks 2, 40 and 80 at 10.00 to 11.00 AM (4-5 hrs after light onset.

Mean initial weights/age:

males: 29.3g / 37 days
females: 24.5g / 37 days

Parameters monitored/Intervals:

Clinical	-	daily
Body weight	-	weekly (wks 1-26), monthly (wks 27-104)
Food consumption	-	weekly
Water consumption	-	weekly (weeks 14, 26, 39, 52, 65, 78, 91, 104)
Effective dose	-	calculated weekly (wks 1-26); monthly thereafter
Hematology	-	done only prior to sacrifice
Plasma Conc	-	in satellite groups as described above
Histopathology	-	on the following tissues:

Adrenal glands	Rectum
Aorta	Salivary glands
Brain	Seminal vesicle
Caecum	Skeletal muscle
Cervical lymph node	Skin
Colon	Spinal cord
Duodenum	Spleen
Femur/stifle joint (incl. bone marrow)	Sternum[1)]
Heart	Stomach
Ileum	Testes with epididymides[2)]
Jejunum	Thymus
Kidneys	Thyroid gland
Larynx[1)]	Tongue
Liver/gallbladder	Trachea
Lungs	Urinary bladder
Mammary gland area	Uterus with cervix
Mesenteric lymph node	Vagina
Oesophagus	Both pinnae with ear tattoo[1)]
Ovaries	
Pancreas	
Parathyroid glands	All gross lesions incl. tumours/suspected tumours and regional lymph nodes
Periph. (sciatic) nerve	
Pituitary gland	
Prostate gland	

Both eyes with optic nerve and Harderian glands were fixed in Heidenhein's Susa solution.

1)= conserved but not prepared histologically.
2)= fixed in Bouin's solution.

Stains:	Hematoxylin/Eosin	-	all organs/tissues, tumors/lesions
	Masson's Trichrome	-	heart, kidney, liver, gall bladder lung, aorta, tumors/lesions

Statistics

Routine group comparisons were made by the Bartlett test, one-way ANOVA and Newman-Keuls test. The Exact Log-rank test was used for group comparisons of categorical tumor-bearing animal data, and for between-group comparisons of the number of premature decedents.

Plasma concentration data were evaluated after logarithmic transformation by regression analysis and ANOVA to determine the effects dose, time point and sex.

Statistical evaluation of neoplastic lesions was according to Peto et al. (1980) using the trend test with respect to dose. Probability levels for significant findings were 0.05 for rare neoplasms and 0.01 for common neoplasms.

Results:

Mortality: 87 males and 101 females died or were sacrificed moribund prior to the end of the study.

Group	Contr. A		Contr. B		1		2		3	
Sex	m	f	m	f	m	f	m	f	m	f
Died	7	4	3	5	8	10	9	8	15	5
Sacr.	6	9	7	15	13	13	13	14	6	18
Total	13	13	10	20	21	23	22	22	21	23
%	26	26	20	40	42	46	44	44	42	46

The increased mortality in treated males was statistically significant ($p = 0.0298$ by a one-tailed positive trend test; $p = 0.0112$ by heterogeneity test). The major factor contributing to the higher mortality rate was sacrifice due to debilitating eczema.

Skin lesions, in particular eczematous changes and frank dermal ulceration, were a significant reason for sacrificing animals during study. As is evident from the following table, the incidence of these lesions in premature decedents was somewhat higher in the treated groups:

Controls		Group 1		Group 2		Group 3	
m	f	m	f	m	f	m	f
Absolute values:							
5	3	6	0	8	2	5	5
As a percentage of total animals in group:							
5	3	12	0	16	4	10	10

Causes of death are listed in Table C.5.a.1

Table C.5.a. Causes of Death or Sacrifice:

Controls (A&B)

Males	23 deaths	Females	33 deaths
neoplasia	- 10	neoplasia	- 22
dermatitis/eczema	- 4	eczema	- 1
edema	- 3	hemometra	- 1
botryomycosis	- 2	wound	- 1
undetermined	- 4	atrial thrombosis	- 1
		posterior paralysis	- 1
		amyloidosis	- 1
		undetermined	- 5

Low-Dose

Males	21 deaths	Females	23 deaths
neoplasia	- 9	neoplasia	- 13
eczema	- 3	amyloidosis	- 3
edema	- 1	hemometra	- 1
botryomycosis	- 1	glomerulosclerosis	- 1
ulceration	- 1	skull fracture	- 1
glomerulosclerosis	- 1	undetermined	- 4
undetermined	- 5		

Mid-Dose

Males	22 deaths	Females	22 deaths
neoplasia	- 4	neoplasia	- 9
dermatitis/eczema	- 8	amyloidosis	- 1
edema	- 3	eczema	- 2
purulent prostatitis	- 1	hemorrhage	- 2
brain hemorrhage	- 1	hemorrhagic cyst	- 1
undetermined	- 5	pyometra	- 1
		peritonitis	- 1
		abscess	- 1
		circulatory failure	- 1
		undetermined	- 3

High-Dose

Males	21 deaths	Females	23 deaths
neoplasia	- 4	neoplasia	- 12
eczema	- 3	dermatitis/eczema	- 2
edema	- 3	wound	- 1
abd. wall perforation	- 1	botryomycosis	- 1
pyelonephritis	- 1	skin erosion	- 1
skin erosion	- 1	circulatory failure	- 1
mucosal hemorrhage	- 1	caudal paralysis	- 1
undetermined	- 7	pyometra	- 1
		undetermined	- 3

Clinical Signs:

Observation	Group Contr. A+B	1	2	3
Incr. spont. activity	0	0	0	96
Alopecia	12	14	18	42

Males

Observation	Group Contr. A+B	1	2	3
Incr. spont. activity	0	0	98	98
Alopecia	19	20	52	52
Skin lesion	6	6	18	20

Females

Body Weight Gain (Fig. C.5.a.1):

M & HDM	-	sig. decrease - all time points
LDF	-	sig. increase - wks 1-3, 5-6, 9, 15, 17, 19-70, 78, 86-98
M & HDF	-	sig. decrease - from wk 3 to end of study

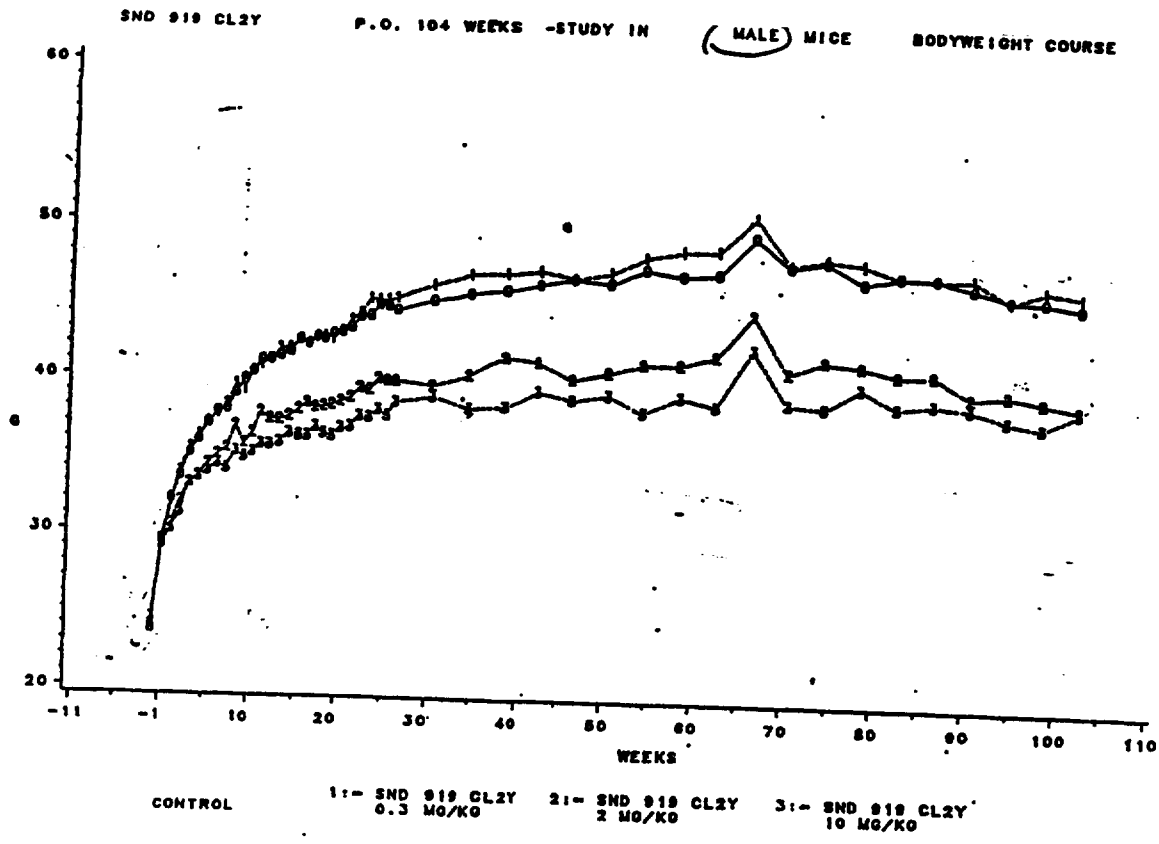
Food Intake:

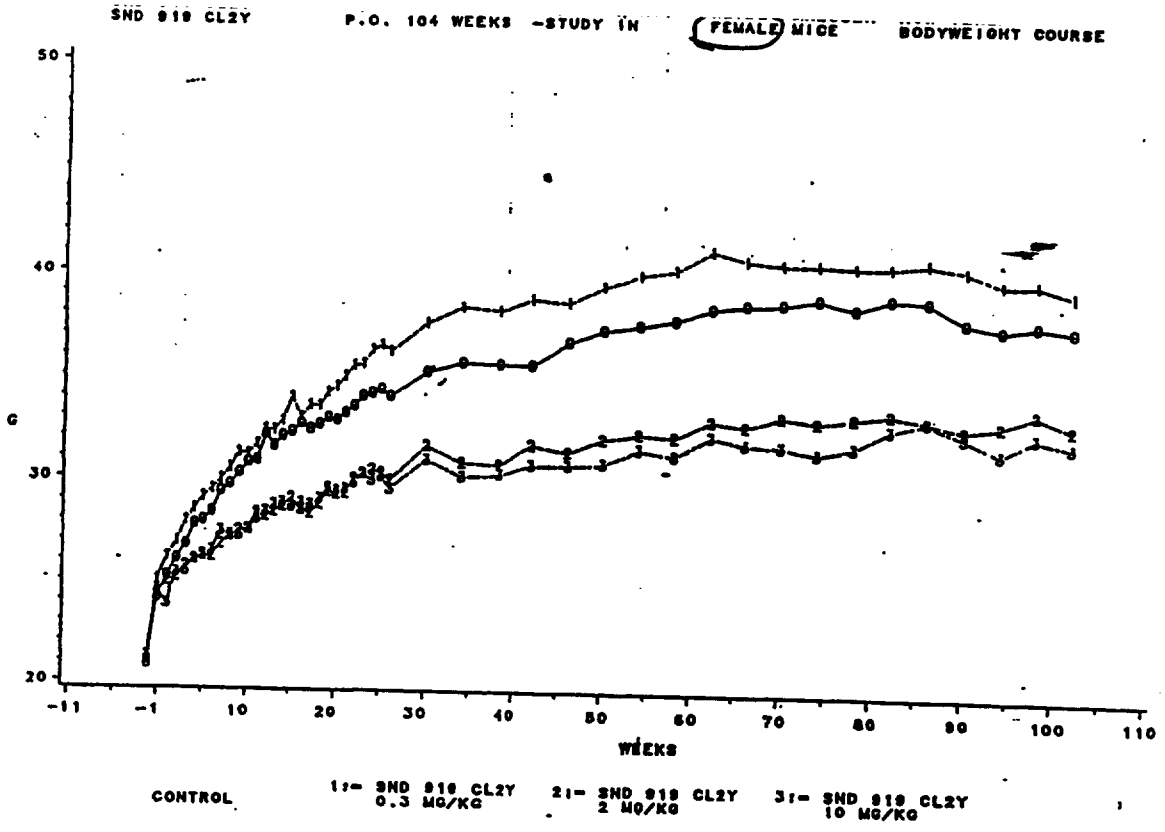
LDM	-	tendency for decrease; effect was significant at several time points
M & HDM	-	tendency for increase; effect was significant at several time points
LDF	-	tendency for decrease at wks 25-78
M & HDF	-	tendency for increase; effect was significant at several time points

Water Intake:

LDM	-	no effect
M & HDM	-	tendency for increase; effect was significant at several time points
LDF	-	no effect
M & HDF	-	tendency for increase; effect was significant at several time points

Fig. C.5.a.1.


SND 919 CL2Y
P.O. 104 WEEKS -STUDY IN
MALE MICE
BODYWEIGHT COURSE
G
WEEKS
CONTROL
1:- SND 919 CL2Y 0.3 MG/KG
2:- SND 919 CL2Y 2 MG/KG
3:- SND 919 CL2Y 10 MG/KG


SND 919 CL2Y
P.O. 104 WEEKS -STUDY IN
FEMALE MICE
BODYWEIGHT COURSE
G
WEEKS
CONTROL
1:- SND 919 CL2Y 0.3 MG/KG
2:- SND 919 CL2Y 2 MG/KG
3:- SND 919 CL2Y 10 MG/KG

Alopecia:

	Male	Female
CON	12%	19%
LD	14%	20%
MD	18%	52%
HD	42%	52%

Effective dose: Weekly recordings indicated that effective drug intake was usually within 20% of intended intake. Most variations were in the direction of "greater than intended" intakes.

	Group 1	2	3
Intended dose (mg/kg)	0.3	2.0	10.0
Males			
Effective dose (mg/kg)			
Mean	0.31	2.11	10.19
Range			
Percentage of intended dose			
Mean	102	105	102
Range			
Females			
Effective dose (mg/kg)			
Mean	0.31	2.11	10.07
Range			
Percentage of intended dose			
Mean	103	105	101
Range			

Hematology:

A number of animals had abnormal WBC counts at sacrifice. This included several controls as well as PPX-treated animals, and there was no clear dose-relationship. (The sponsor has not indicated their criteria for the noted hematological findings in individual animals).

WBC

Individual variations in animals with abnormal blood counts at termination (Tab. C.5.a.2):

Tab. I. Control animals sacrificed at the end of the study

animal no.	leucocytosis	relative lymphocytosis	relative granulocytosis	blasts	anaemia
0018	+++	+++			
0020	+	+++			+
0040	+				
0045	+	++			+
0501	+	+++			
0536	+	++			
4008	+	++			
4025	+	++			
4041	+				
4044	+	++			
4045	++	++			
4049	+	++			
4519	++	++			
4548	+	++			

Tab. II Treated animals sacrificed at the end of the study

animal no.	leucocytosis	relative lymphocytosis	relative granulocytosis	blasts	anaemia
1014	+	+			
1043	+	+++			+
2006	+				
2027	+++	+++	++		
2031	+	++			
3037	+	+			
3517	leucopenia				
3519	+++	+++			
3535	+	+			

In addition, the following hematological changes were noted in animals with "normal" WBC counts:

anemia, slight	-	2 0M, 3 0F 3 LDF 2 MDM, 1 MDF 3 HDF
" , moderate	-	1 0M 1 LDF
" , marked	-	1 0F
erythrocytosis	-	1 0M, 1 0F 1 LDF 1 HDM

WBC

Individual variations in animals with abnormal blood counts sacrificed moribund (Tab. C.5.a.3)

Tab. III Control animals sacrificed moribund

animal no.	leucocytosis	relative lymphocytosis	relative granulocytosis	blasts	anaemia	
0029	+		++			sarcoma, body ca
0510	++				+	lymphoma, thymic
0527	+				++	" non-thym
0540	++		++			leiomyosarc
4026	+					botryomycosis
4036	+					"
4527	+				+	paralysis

Tab. IV. Treated animals sacrificed moribund

animal no.	leucocytosis	relative lymphocytosis	relative granulocytosis	blasts	anaemia	Cause of Death
1037	+		+		*	histio. sarc
1039	+		++			?
1040	+		+			histio. sarc
1041	+					eczema
1046	+		+			histio. sarc
1506	+		++ 1)			thymic lymphoma
1517	+++	+++			+	non-thy "
1537	+				+	squam CA (skin)
2011	+					
2022	+++	+++	+		+++	sarcoma
2039	+					thymic lymphoma
2047	+					eczema
2505	+		1)	+		"
2507	+		++ 1)		+	peritonitis
2512	+	++			++	histo. sarc
		+				?
3048	+					
3502	+++		1)		+	eczema
3518	++		1) +			botryomycosis
3522	+		++		+++	stromal cell CA (uto
3532	+				++	sarcoma
3538	++	+++			++	eczema
						thymic lymphon

1) shift to the left * polycythemia

The following hematological changes were noted in animals with "normal" WBC counts:

anemia, slight	-	1 0M, 3 0F 1 LDM, 5 LDF 3 MDM, 5 MDF 3 HDM, 6 HDF
" , moderate	-	6 0F 1 LDF 2 MDF 3 HDF
" , marked	-	1 HDF (this animal was also stated to have polycythemia???)

Group variations:

Statistically significant mean changes were noted on various parameters, but few clearly dose/drug-related effects were evident.

At termination:

increased Hct	-	HDM
decreased lymphocytes(%)	-	MDM, HDM
increased lymphocytes(%)	-	LDF

Moribund sacrifices:

decreased RBC, Hb	-	trend (N.S.) in males
decreased Hct	-	HDM
increased leucocytes	-	MDM (2° to 1 abnormally high value)
increased lymphocytes(%)	-	MDM

(The page containing mean values of RBC parameters for females sacrificed moribund was omitted.)

Plasma Concentrations:

The concentration of PPX was above the LOQ (0.1 ng/ml) in all samples at 4-5 hrs after light onset. Increases in plasma concentrations were approximately dose-proportional except for females during week 2 and both sexes during week 40 where the increases were greater than dose proportional (Fig. C.5.a.2; Tab. C.5.a.4). ANOVA indicated that significantly higher concentrations were present in females, although specific occurrences of this finding were not indicated (Tab. C.5.a.5). There was no evidence of drug accumulation.

Tab. C.5.a.4.

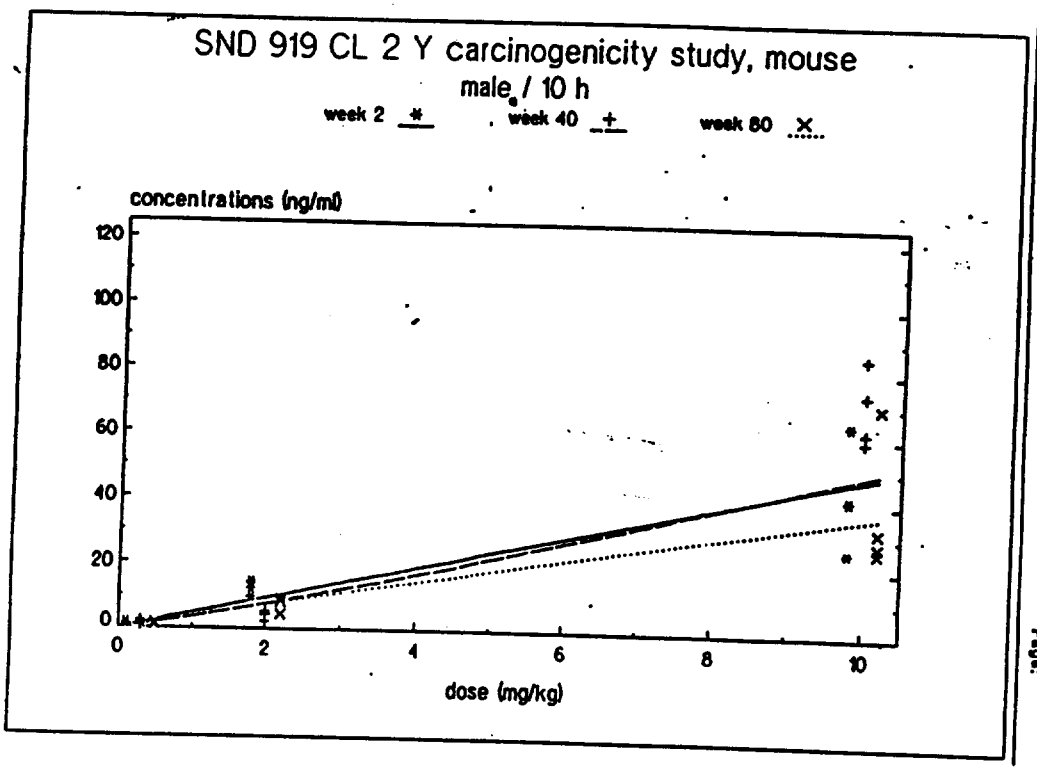
Sex	Dose [mg/kg]	Week 2	Week 40	Week 80
male	0.3	1.28 (0.98-1.67)	1.19* (0.70-2.02)	1.21 (0.93-1.56)
male	2.0	12.48 (10.44-14.93)	3.96 (2.66-5.90)	7.48 (5.39-10.38)
male	10	41.27 (28.44-59.88)	69.69 (59.11-82.16)	36.02 (22.87-56.72)
female	0.3	0.99 (0.91-1.08)	0.92* (0.52-1.60)	1.77 (1.47-2.12)
female	2	10.55 (7.42-15.00)	9.09 (4.08-20.25)	9.54 (8.40-10.83)
female	10	79.81 (66.89-95.22)	80.80 (54.33-120.18)	53.14 (37.60-75.12)

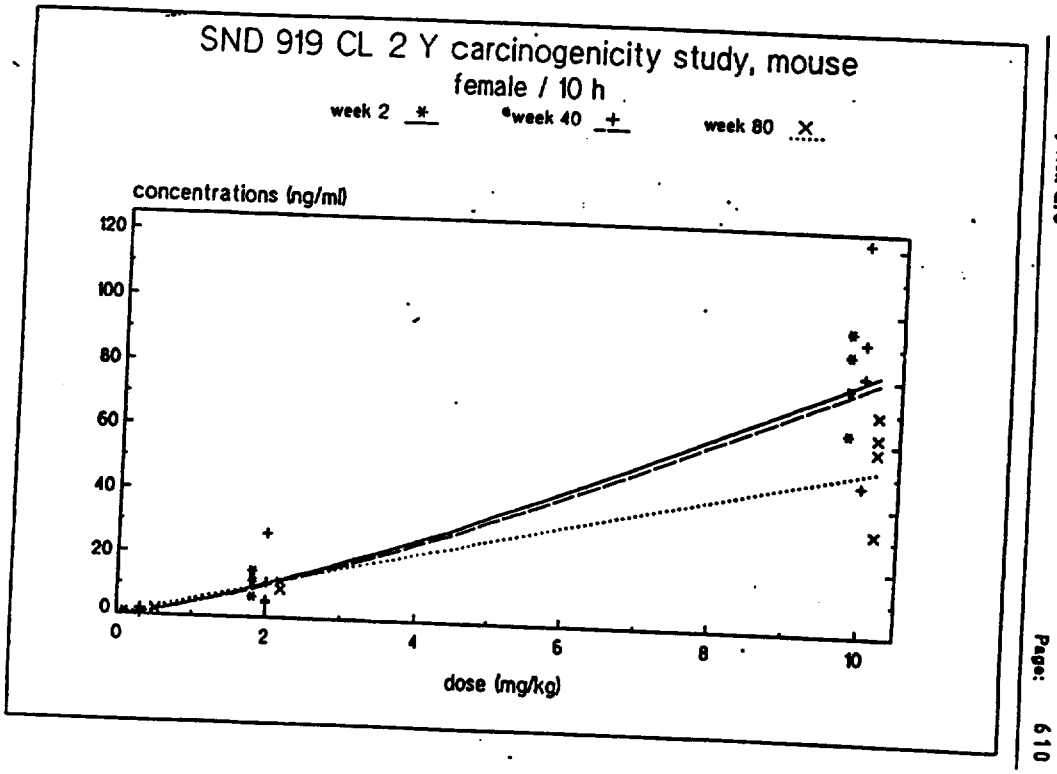
SND 919 C12 Y / carcinogenicity study / mouse
analysis of variance of the log-transformed plasma concentrations

Tab. C.5.a.5

variability	df	mean squares	p value
between mean values of			
- weeks	2	0.07801	0.068
- sexes within weeks	3	0.09219	0.026
common regression	1	32.80579	< 0.001
between slopes of			
- weeks	2	0.13793	0.010
- sexes within weeks	3	0.05935	0.104
about regression lines	6	0.09966	0.004
between pooled samples.	52	0.02753	
total	69		

Fig. C.5.a.2


SND 919 CL 2 Y carcinogenicity study, mouse
male / 10 h
week 2 *
week 40 +
week 80 X
concentrations (ng/ml)
120
100
80
60
40
20
0
0
2
4
6
8
10
dose (mg/kg)
Report/Study No.: G70
Page: 609


SND 919 CL 2 Y carcinogenicity study, mouse
female / 10 h
week 2 *
week 40 +
week 80 X
concentrations (ng/ml)
120
100
80
60
40
20
0
0
2
4
6
8
10
dose (mg/kg)
Report/Study No.: G70
Page: 610

Pathology:

Non-Neoplastic Lesions

Statistically significant drug effects were:

	Group Incidence Rate (%)				
Lesion	0	4	1	2	3
Fibro-osseous proliferative lesion (femur) - increase (F)	36	20	62*	60*	56*
Fat marrow (femur epiphysis) - decrease (F)	48	56	42	20*	21*
seminiferous tubule atrophy - decrease	36	36	18	18*	14*

The most notable finding was the fibro-osseous proliferative lesion in the femurs of female mice, which was not described in detail by the sponsor, nor was any potential significance suggested. The lesion occurred spontaneously in control animals, but its incidence was significantly increased by PPX treatment; the incidence rates were similar in all dosage groups. A possibly related finding was decreased femoral fat content in MDF and HDF, suggestive of increased hematopoietic activity.

Albassam et al. (Vet. Pathol., 28:381, 1991) have reported upon the spontaneous occurrence of an apparently similar osseous lesion in the femurs and sternums of female B6C3F1 mice (but not male B6C3F1 or female CF1 mice). The lesion was characterized by the lining of epiphyseal plates by large osteoblasts and had large vascularized centers. Similar drug-induced lesions have been produced by estrogens (Silberberg and Silberberg, Gerontology, 16:201, 1970; Gaunt and Pierce, Vet. Pathol., 22:403, 1985), and the sponsor speculates that a dopaminergic-induced imbalance in estrogen:progesterone levels may account for this lesion. No experimental support for this mechanism (i.e., estrogen level measurements) was provided. The prostaglandin E analogue misoprostol also produces an osseous lesion in female mice (Dodd and Port, Vet. Pathol. 24:545, 1987), and the finding appears in the labeling of that product.

Neoplastic lesions

According to the sponsor's analysis, the only statistically significant differences in the incidence of neoplasia between treated and control animals were **decreased** occurrences of the following tumors:

	Group/Incidence rate (%)				
Neoplasm	0	4	1	2	3
malignant lymphomas - decrease (F)	46	42	32	22*	16*
adrenal cortical adenomas - decrease (M)	32	16	16	12	6*

There was also a non-significant trend for decreased occurrence of hepatocellular adenomas in treated males.

Inspection of the Tumor Distribution Summary (Tab. C.5.a.6) and statistical analysis tables (Tab. C.5.a.7) reveals some notable findings or tendencies. The incidence of uterine stromal polyps tended to increase at the higher doses (controls: 2%; LD: 2%; MD: 6%; HD: 6%; p= 0.0778 by the Trend Test), as did the incidence of all mesenchymal/epithelial uterine neoplasms (control: 10%; LD: 10%; MD: 14%; HD: 18%; not statistically analyzed). The Test of Heterogeneity indicated a statistically significant increase in the incidence of histiocytic sarcomas in PPX-treated male mice (p = 0.0018), but the tumors were found only in 4 LD animals and are thus not clearly drug-related.

There were no significant differences between PPX-treated and control animals with respect to the number of primary neoplasms, the number of mice with primary neoplasms, mice with more than one neoplasm, mice with metastases, the number of benign and malignant neoplasms per group and sex (Tab. C.5.a.8).

Tab. C.5.a.6

TR No.: 7219-94-070

Name of finished product	TABULATED STUDY REPORT	
Name of active ingredient Pramipexole (SND 919 CL 2 Y)	ref. to III.E.210 2/6 Page Number	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 28.06.93 Number: G70 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <x> no < >		Frequency according to dose and sex (n)									
		(0) Contr. A		(4) Contr.B		(1)		(2)		(3)	
		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated											
Organ	Identification of the tumour										
BRAIN	OLIGODENDROGLIOMA	1	-	-	-	-	-	-	-	-	-
	NEOPLASM (NOS)	-	-	-	-	-	-	-	-	-	1
LUNGS	ADENOMA	22	9	11	8	12	13	8	6	13	6
	CARCINOMA	1	2	-	-	-	2	-	1	-	-
LIVER	ADENOMA/HEPATOC.	5	-	7	1	2	-	-	-	2	-
	HEMANGIOSARCOMA	3	1	4	-	2	1	1	-	1	-
	CARCINOMA/HEPATOC.	-	-	-	-	1	-	1	-	-	-
TONGUE	CARCINOMA/SQUAMOUS	1	-	-	-	-	-	-	-	-	-
DUODENUM	SARCOMA/OSSIFYING	-	-	-	-	-	-	1	-	-	-
TESTES	LEYDIG CELL TUMOR	4	-	3	-	2	-	-	-	5	-
PROSTATE	ADENOMA	1	-	-	-	-	-	-	-	-	-
SEMINAL VESICLES	LEIOMYOMA	1	-	-	-	-	-	-	-	-	-
OVARIES	LUTEOMA	-	-	-	-	-	-	-	-	-	1
	ADENOMA/TUBULAR	-	1	-	2	-	1	-	2	-	-
	TUMOR/GRANULOSA CELL	-	1	-	4	-	2	-	5	-	3
	LIPOMA	-	1	-	-	-	-	-	-	-	-

* P < 0.05 ** P < 0.01

TR No.: 7219-94-070 · Tab. C.5.a.b. (cont)

Name of finished product	TABULATED STUDY REPORT	
Name of active ingredient Pramipexole (SND 919 CL 2 Y)	ref. to III.E.210 3/6 Page Number	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 28.06.93 Number: G70 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <x> no < >		Frequency according to dose and sex (n)									
		(0) Contr. A		(4) Contr.B		(1)		(2)		(3)	
		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated											
Organ	Identification of the tumour										
UTERUS	POLYP/STROMAL	-	2	-	-	-	1	-	3	-	3
	LEIOMYOMA	-	4	-	1	-	2	-	2	-	2
	FIBROMA	-	-	-	-	-	-	-	-	-	1
	GRANULAR CELL TUMOR (m)	-	-	-	-	-	-	-	-	-	1
	LEIOMYOSARCOMA (m)	-	-	-	-	-	1	-	-	-	1
	ADENOCARCINOMA (m)	-	-	-	-	-	1	-	-	-	-
	SARCOMA/STROMAL CELL (m)	-	2	-	1	-	-	-	2	-	1
VAGINA	FIBROMA	-	1	-	-	-	-	-	-	-	-
URINARY											
BLADDER	CARCINOMA/TRANSIT. CELL	-	-	-	-	-	-	-	-	-	1
PITUITARY											
GLAND	ADENOMA/P. DISTALIS	-	-	-	1	1	2	-	3	-	-
THYROID	ADENOMA/FOLLICULAR	-	-	-	1	-	1	-	-	-	-
	CARCINOMA/FOLLICULAR	-	-	-	-	-	-	1	-	-	-
PARA-											
THYROID											
GLANDS	ADENOMA	-	2	-	-	-	-	-	-	-	-

* P < 0.05 ** P < 0.01

TR No.: 7219-94-070 . Tab. C.5.a.6 (cont.)

Name of finished product	TABULATED STUDY REPORT	
Name of active ingredient Pramipexole (SND 919 CL 2 Y)	ref. to III.E.210 4/6 Page Number	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 28.06.93 Number: G70 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <x> no < >		Frequency according to dose and sex (n)									
		(0) Contr. A		(4) Contr.B		(1)		(2)		(3)	
		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated											
Organ	Identification of the tumour										
ADRENAL											
CORTEX	ADENOMA/A-CELL	-	-	-	-	1	-	-	-	-	1
	ADENOMA/B-CELL	6	-	3	-	3	-	6	-	3	1
	ADENOMA/B-CELL/EXTD.** (males)	8	-	5	-	3	-	2	-	-	-
	ADENOMA/Z. FASCICUL.	3	-	-	1	1	-	-	-	-	-
ADRENAL											
MEDULLA	MEDULL. TUMOR/BENIGN	1	-	-	-	-	-	-	-	-	-
	MEDULL. TUMOR/MALIGN.	-	-	-	1	-	-	-	-	-	-
MESENT.											
LYMPH NODE	HEMANGIOMA	-	-	-	1	-	-	-	-	-	-
SYSTEMIC											
NEOPLASMS	THYMIC LYMPHOMA* (females)	3	18	4	16	4	13	4	8	4	7
	NONSPECIF. LYMPHOMA	1	-	1	1	1	-	-	-	-	-
	NON-THYMIC LYMPHOMA	3	5	4	3	6	3	3	3	4	1
	MAST CELL TUMOR	1	-	-	-	-	-	2	-	-	1
	BONE MARROW LYMPHOMA	-	-	-	1	-	-	-	-	-	-
	HISTIOCYTIC SARCOMA	-	1	-	4	4	2	-	2	-	1
	MYELOID LEUKEMIA	-	1	-	-	-	-	-	-	-	-

* P < 0.05, ** P < 0.01 (=negative trend)

TR No.: 7219-94-070 Tab. C.5.a.6. (cont.)

Name of finished product	TABULATED STUDY REPORT	
Name of active ingredient Pramipexole (SND 919 CL 2 Y)	ref. to III.E.210 5/6 Page Number	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 28.06.93 Number: G70 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <x> no < >		Frequency according to dose and sex (n)									
		(0) Contr. A		(4) Contr.B		(1)		(2)		(3)	
		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated											
Organ	Identification of the tumour										
HARDERIAN											
GLANDS	ADENOMA	2	1	2	2	2	3	-	-	-	-
	ADENOCARCINOMA	-	-	-	-	-	1	-	-	-	-
SPLEEN	HEMANGIOSARCOMA	-	-	-	-	-	-	1	-	-	-
SKIN	LIPOMA	-	-	1	-	-	-	-	-	-	-
	HEMANGIOMA	-	-	-	-	-	1	-	-	-	-
	HEMANGIOSARCOMA	1	-	-	-	-	1	-	-	-	-
	CARCINOMA/BASAL CELL	-	-	-	-	-	1	-	-	-	-
	CARCINOMA/SQUAMOUS	-	-	-	-	-	1	-	-	-	-
	SARCOMA/OSSIFYING	-	1	-	-	-	-	-	-	-	-
	LEIOMYOSARCOMA	-	1	-	-	-	1	-	1	-	1
	SCHWANNOMA	-	-	-	1	-	-	-	-	-	-
	SARCOMA/UNDIFFERENT.	-	-	-	-	-	-	-	1	-	-
BODY											
CAVITIES	LIPOMA	-	-	-	-	-	-	1	-	-	-
	SARCOMA/OSSIFYING	1	-	-	-	-	-	-	-	1	-
	SARCOMA/UNDIFFERENT.	-	-	-	1	-	-	-	-	-	1

* P < 0.05 ** P < 0.01

Tab. C.5.a.7.

PATHOLOGY REPORT — PAGE : TR1
STATISTICAL EVALUATION — PROJECT: G 70

TEST ARTICLE : SND 919 CL 2 Y — PATHOL. NO.: 91009
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING — DATE : 11-MAY-93
SPONSOR : — PATHDATA SYSTEM Vb3.6

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
COMBINED PREVALENCE AND DEATH RATE METHOD (PETO ET AL., 1980)

DOSE GROUPS : G0,G1,G2,G3,G4 — SEX: MALE
STATUS AT NECROPSY: K0 INCL. +
TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE	
BRAIN	OLIGODENDROGLIOMA	2.204-	0.2776	
LUNGS	ADENOMA	5.941+	0.4052#	
LUNGS	CARCINOMA	2.197-	0.2776	
TONGUE	CARCINOMA/SQUAMOUS	2.128-	0.2810	
LIVER	ADENOMA/HEPATOC.	13.911-	0.1611#	
LIVER	HEMANGIOSARCOMA	11.670-	0.1660#	
LIVER	CARCINOMA/HEPATOC.	2.172-	0.3409	
TESTES	LEYDIG CELL TUMOR	18.343+	0.0901#	-?? h... Con + HD
PROSTATE	ADENOMA	2.203-	0.2776	
SEMINAL VESICLES	LEIOMYOMA	2.176-	0.2776	
PITUITARY GLAND	ADENOMA/P.DISTALIS	2.553-	0.2611	
THYROID (BOTH LOBES)	CARCINOMA/FOLLICULAR	0.190-	0.4797	
ADRENAL CORTEX	ADENOMA/B-CELL	2.901-	0.4286#	
ADRENAL CORTEX	ADENOMA/Z.FASCICUL.	8.888-	0.1151#	
ADRENAL CORTEX	ADENOMA/B-CELL/EXTD.	35.788-	0.0094#	-highest in con.
ADRENAL CORTEX	ADENOMA/A-CELL	1.876-	0.3050	
ADRENAL MEDULLA	MEDULL.TUMOR/BENIGN	2.190-	0.2776	
SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA	6.288-	0.1635	
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA	1.540+	0.4626#	
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	7.369+	0.3228#	
SYSTEMIC NEOPLASMS	HISTIOCYTIC SARCOMA	7.470-	0.1539	
SYSTEMIC NEOPLASMS	MAST CELL TUMOR	2.517-	0.3483	
SPLEEN	HEMANGIOSARCOMA	0.176-	0.4813	
HARDERIAN GLANDS	ADENOMA	12.472-	0.0808	
SKIN	HEMANGIOSARCOMA	2.405-	0.2611	
SKIN	LIPOMA	2.149-	0.2776	
BODY CAVITIES	SARCOMA/OSSIFYING	5.671+	0.1379	

Explanation of Symbols

p = one-tailed p-value
- = negative trend
+ = positive trend
# = number of animals with tumors > 5% in at least one sex/dose group

Tab. C.5.a.7. (cont.)

PATHOLOGY REPORT
STATISTICAL EVALUATION

TEST ARTICLE : SND 919 CL 2 Y
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR :

PATHOL. NO.: 91009
DATE : 11-MAY-93
PATHDATA SYSTEM Vb3.6

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
COMBINED PREVALENCE AND DEATH RATE METHOD (PETO ET AL., 1980)

DOSE GROUPS : G0,G1,G2,G3,G4
STATUS AT NECROPSY: K0 INCL. +
SEX: MALE
TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
BODY CAVITIES	LIPOMA	0.000+	0.5000#
	POOLED ORGANS/FINDINGS		
SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA		
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA		
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	0.736+	0.4876#
	POOLED ORGANS/FINDINGS		
ADRENAL CORTEX	ADENOMA/B-CELL		
ADRENAL CORTEX	ADENOMA/Z.FASCICUL.		
ADRENAL CORTEX	ADENOMA/B-CELL/EXTD.		
ADRENAL CORTEX	ADENOMA/A-CELL	45.815-	0.0158#

DOSE GROUPS : G0,G1,G2,G3,G4
STATUS AT NECROPSY: K0 INCL. +
SEX: FEMALE
TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
BRAIN	NEOPLASM (NOS)	7.706+	0.0192
LUNGS	ADENOMA	19.597-	0.1788#

Tab. C.5.a.7. (cont.)

PATHOLOGY REPORT
STATISTICAL EVALUATION

TEST ARTICLE : SND 919 CL 2 Y
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR :

PATHOL. NO.: 91009
DATE : 11-MAY-93
PATHDATA SYSTEM Vb3.6

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
COMBINED PREVALENCE AND DEATH RATE METHOD (PETO ET AL., 1980)

DOSE GROUPS : G0,G1,G2,G3,G4
STATUS AT NECROPSY: K0 INCL. +
TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

SEX: FEMALE

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
LUNGS	CARCINOMA	9.616-	0.1170
LIVER	ADENOMA/HEPATOC.	2.242-	0.2743
LIVER	HEMANGIOSARCOMA	4.326-	0.1977
URINARY BLADDER	CARCINOMA/TRANSIT.C.	7.731+	0.0192
OVARIES	ADENOMA/TUBULAR	8.839-	0.1587
OVARIES	TUMOR/GRANULOSA CELL	4.570+	0.3707#
OVARIES	LIPOMA	2.190-	0.2743
OVARIES	LUTEOMA	7.810+	0.0170
UTERUS	SARCOMA/STROMAL CELL	0.012+	0.4996
UTERUS	LEIOMYOMA	1.019-	0.4653#
UTERUS	ADENOCARCINOMA	1.942-	0.3015
UTERUS	LEIOMYOSARCOMA	5.775+	0.1357
UTERUS	FIBROMA	7.758+	0.0188
UTERUS	GRANULAR CELL TUMOR	7.758+	0.0188
UTERUS	POLYP/STROMAL	15.578+	0.0778#
VAGINA	FIBROMA	2.282-	0.2709
PITUITARY GLAND	ADENOMA/P.DISTALIS	7.384-	0.2090#
THYROID (BOTH LOBES)	ADENOMA/FOLLICULAR	4.642-	0.1977
PARATHYROID GLANDS	ADENOMA	4.745-	0.1894
ADRENAL CORTEX	ADENOMA/B-CELL	7.758+	0.0188
ADRENAL CORTEX	ADENOMA/Z.FASCICUL.	2.242-	0.2743
ADRENAL CORTEX	ADENOMA/A-CELL	7.627+	0.0222
ADRENAL MEDULLA	MEDULL.TUMOR/MALIGN.	2.242-	0.2743
SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA	2.306-	0.2676
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA	17.653-	0.1075#
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	52.989-	0.0250#
SYSTEMIC NEOPLASMS	BONE MARROW LYMPHOMA	2.242-	0.2743

M+F
C = 9/200
LD = 3/100
MD = 6/100
HD = 9/100

Tab. C.5.a.7. (cont.)

TEST ARTICLE : SND 919 CL 2 Y
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR :
PATHOL. NO.: 91009
DATE : 11-MAY-93
PATHDATA SYSTEM Vb3.6

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
COMBINED PREVALENCE AND DEATH RATE METHOD (PETO ET AL., 1980)

DOSE GROUPS : G0,G1,G2,G3,G4 SEX: FEMALE
STATUS AT NECROPSY: K0 INCL. +
TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
SYSTEMIC NEOPLASMS	HISTIOCYTIC SARCOMA	8.252-	0.2420#
SYSTEMIC NEOPLASMS	MAST CELL TUMOR	7.758+	0.0188
SYSTEMIC NEOPLASMS	MYELOID LEUKEMIA	2.360-	0.2676
MESENT. LYMPH NODE	HEMANGIOMA	2.464-	0.2483
HARDERIAN GLANDS	ADENOCARCINOMA	1.976-	0.2981
HARDERIAN GLANDS	ADENOMA	12.725-	0.0778#
SKIN	HEMANGIOSARCOMA	2.038-	0.2946
SKIN	SARCOMA/OSSIFYING	2.362-	0.2644
SKIN	LEIOMYOSARCOMA	3.160+	0.3372
SKIN	CARCINOMA/BASAL CELL	2.075-	0.2912
SKIN	HEMANGIOMA	1.942-	0.3015
SKIN	CARCINOMA/SQUAMOUS	2.014-	0.2946
SKIN	SCHWANNOMA	2.333-	0.2676
SKIN	SARCOMA/UNDIFFERENT.	0.274-	0.4705
BODY CAVITIES	SARCOMA/UNDIFFERENT.	5.318+	0.1587

	POOLED ORGANS/FINDINGS		
SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA		
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA		
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA		
SYSTEMIC NEOPLASMS	BONE MARROW LYMPHOMA		
		75.982-	0.0059#

	POOLED ORGANS/FINDINGS	TREND	P-VALUE
ADRENAL CORTEX	ADENOMA/B-CELL		
ADRENAL CORTEX	ADENOMA/Z.FASCICUL.		
ADRENAL CORTEX	ADENOMA/A-CELL		
		13.142+	0.0212

Tab. C.5.a.7. (cont.)

PATHOLOGY REPORT

TEST ARTICLE : SND 919 CL 2 Y
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR :

PATHOL. NO.: 91009
DATE : 11-MAY-93
PATHDATA SYSTEM Vb3.6

TABLE FOR HETEROGENEITY ON NEOPLASTIC LESIONS

SEX: MALES

ORGAN/TISSUE	TYPE OF NEOPLASM	P-VALUE
LUNGS	ADENOMA	0.4296
LIVER	ADENOMA/HEPATOC.	0.0663
LIVER	HEMANGIOSARCOMA	0.6462
TESTES	LEYDIG CELL TUMOR	0.1536
ADRENAL CORTEX	ADENOMA/B-CELL	0.5593
ADRENAL CORTEX	ADENOMA/B-CELL/EXTD.	0.0720
ADRENAL CORTEX	ADENOMA/Z.FASCICUL.	0.5123
ADRENAL CORTEX	ADENOMAS/TOTAL	0.1450
HARDERIAN GLANDS	ADENOMA	0.3355
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	0.8941
SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA	-
SYSTEMIC NEOPLASMS	NONTHYMIC LYMPHOMA	0.5578
SYSTEMIC NEOPLASMS	MALIGN.LYMPHOMA/TOTAL	0.5740
SYSTEMIC NEOPLASMS	HISTOCYTIC SARCOMA	0.0018

SEX: FEMALES

LUNGS	ADENOMA	0.1048
OVARIES	TUMOR/GRANULOSA CELL	0.5743
UTERUS	POLYP/STROMAL	0.3589
UTERUS	LEIOMYOMA	0.9954
PITUITARY GLAND	ADENOMA/P.DISTALIS	0.1239
HARDERIAN GLANDS	ADENOMA	0.1154
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	0.0715
SYSTEMIC NEOPLASMS	NONSPEC.LYMPHOMA	-
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA	0.6700
SYSTEMIC NEOPLASMS	BONE MARROW LYMPHOMA	-
SYSTEMIC NEOPLASMS	MALIGN.LYMPHOMA/TOTAL	0.0204
SYSTEMIC NEOPLASMS	HISTIOCYTIC SARCOMA	0.9139

NOTE: STATISTICAL CALCULATION WAS PERFORMED ONLY IF THE NUMBER OF NEOPLASMS EXCEEDED 5% PER DOSE GROUP AND SEX.

END OF REPORT SECTION

Tab. C.5.a.8.

PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 24/ 781
PROJECT: G 70

TEST ARTICLE : SND 919 CL 2 Y
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR :

PATHOL. NO.: 91009
DATA : 11-MAY-93
PATHDATA SYSTEM Vb3.6

EVALUATION OF NEOPLASTIC LESIONS
STATUS AT NECROPSY: MO, INCL. +

NUMBER OF ANIMALS WITH NEOPLASMS:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
NO.EXAM:	50	50	50	50	50	50	50	50	50	50
NO.AFF.:	40	35	30	33	32	37	23	27	24	30
% :	80.0	70.0	60.0	66.0	64.0	74.0	46.0	54.0	48.0	60.0

DOSE GR:	TOTAL	
SEX :	M	F
NO.EXAM:	250	250
NO.AFF.:	149	162
% :	59.6	64.8

NUMBER OF ANIMALS WITH MORE THAN ONE PRIMARY NEOPLASM:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
NO.EXAM:	50	50	50	50	50	50	50	50	50	50
NO.AFF.:	24	12	14	15	11	15	7	10	9	5
% :	48.0	24.0	28.0	30.0	22.0	30.0	14.0	20.0	18.0	10.0

DOSE GR:	TOTAL	
SEX :	M	F
NO.EXAM:	250	250
NO.AFF.:	65	57
% :	26.0	22.8

Tab. C.5.a. 8. (cont.)

NUMBER OF ANIMALS WITH METASTASES:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
NO.EXAM:	50	50	50	50	50	50	50	50	50	50
NO.AFF.:	0	0	0	1	0	1	0	0	0	1
% :	0.0	0.0	0.0	2.0	0.0	2.0	0.0	0.0	0.0	2.0

DOSE GR:	TOTAL	
SEX :	M	F
NO.EXAM:	250	250
NO.AFF.:	0	3
% :	0.0	1.2

NUMBER OF PRIMARY NEOPLASMS/GROUP/SEX:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
PRIM.T.:	76	55	46	52	46	56	32	39	35	35

DOSE GR:	TOTAL	
SEX :	M	F
PRIM.T.:	235	237

NO.OF BENIGN, UNCLASSIFIED, MALIGN. NEOPLASMS/GROUP/SEX:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
BENIGN :	61	23	33	23	28	28	18	21	25	19
UNCLASS:	0	0	0	0	0	0	0	0	0	0
MALIGN.:	15	32	13	29	18	28	14	18	10	16

DOSE GR:	TOTAL	
SEX :	M	F
BENIGN :	165	114
UNCLASS:	0	0
MALIGN.:	70	123

C.5.b. Two-Year Rat Carcinogenicity Study

Conducted by :

Document #(s):

Upjohn TR 7219-94-068

Sponsor Volumes: 1.49-1.54

This study complied with GLP

Summary:

Pramipexole was administered in the diet at doses of 0.3, 2.0, and 8.0 mg/kg/day to Wistar rats (50/sex/dose group, 100/sex/control) for two years. Toxicokinetic analyses were conducted in satellite groups at weeks 2, 50, and 100.

Mortality occurred in all treatment groups at various times during the study; there were no clear drug-related effects. The highest percentage of mortality was 40% in LDF. Body weight gain was significantly reduced at most time points in all three treatment groups. In MDF and HDF, body weight gain was reduced by 22 and 28%, respectively, at the end of the study. Other clinical observations included increased spontaneous activity in HDF, decreased food intake in males and LDF, and increased food intake in MDF and HDF.

The only neoplastic lesion that occurred at a higher incidence rate in PPX-treated rats were Leydig cell adenomas in MD (2.0 mg/kg/day) and HD (8.0 mg/kg/day) males. Leydig cell hyperplasia also occurred in MD and HD rats. Drug-related **decreases** in the incidence mammary gland neoplasia (MDF, HDF), benign adrenal medullary neoplasms (LDF, MDF, HDF), and pituitary adenomas (MD, HD of both sexes) were observed. Adrenal medullary hyperplasia was also reduced in MDF and HDF. Non-neoplastic changes in females were enlarged corpora lutea (HD rats), uterine lesions and hemorrhage (MD and HD), alterations in mammary gland patterns from female-like to male/female-like (MD and HD), and diffuse hepatocellular fatty changes (MD and HD). Retinal degeneration occurred in MD and HD groups of both sexes.

Toxicokinetic analyses indicated that in the low dose group, plasma exposure levels 2 hrs after light onset were lower the steady-state Cmax in humans receiving the projected maintenance dose of 1.5 mg PPX, t.i.d., 2-5 fold higher than the human $Cmax_{ss}$ after the intermediate dose, and 10-30 fold higher after the highest dose.

The proposed mechanism for the neoplastic and non-neoplastic lesions in reproductive and endocrine tissues is PPX-induced inhibition of prolactin secretion as demonstrated at week 60 and 69 (ca. 10-fold decrease in females, 100-fold decrease in males). In males, reductions in serum prolactin purportedly lead to a down-regulation of LH receptors. This triggers a compensatory increase in LH production and release leading to Leydig cell

hyperplasia and adenomas. The sponsor cites a study by Rao et al. (1984) which demonstrates that the dopamine agonist bromocriptine elevates LH; however, no evidence for a similar action of PPX on serum LH or LH receptor number was provided. Nonetheless, the finding is suggested to be of questionable relevance to humans given the high background incidence of this tumor in rats (as demonstrated in this experiment), and since several widely-used compounds also produce Leydig cell tumors in rats but are not known to do so in humans (cimetidine, hydralazine, vidarabine, israpidine). Additional evidence that Leydig cell adenomas may be species-specific is that a similar tumor was not observed in the mouse. The reduction in serum prolactin is also suggested to underlie the decreased incidence of pituitary adenomas, since prolactin normally stimulates anterior pituitary cell proliferation. The decreased incidence of benign adrenal medullary neoplasia is suggested to result from a dopamine receptor-mediated inhibition of chromaffin cell catecholamine release which decreases the proliferative potency of the chromaffin cells.

The corpora lutea enlargement, uterine changes, and changes in the glandular pattern of the mammary glands in PPX-treated female rats were also observed in the one year rat study. The sponsor has presented an argument to discount the potential human relevance of this finding based on the divergent effects of prolactin in rats and humans. In the rat, prolactin is luteolytic, and in its absence non-functional corpora lutea persist (and enlarge). In addition, prolactin stimulates progesterone secretion in the rat, and a reduction in the prolactin-progesterone stimulus results in unopposed actions of estrogen. Aging rats are susceptible to a chronic estrogenic state which leads to the uterine changes. However, this does not occur in aging women due to ovarian involution. Once again these proposed pathways in rats should be considered speculative in the case of PPX since studies of PPX-induced hormonal changes were not presented to support these arguments. The role of PPX inhibition of prolactin secretion in the mammary gland tissue pattern change was described in the one-year rat study.

Retinal degeneration in both male and female rats from the mid- and high-dose groups was the most notable non-neoplastic finding of this study. Follow-up studies to address this issue have been conducted by the sponsor, submitted to the IND, and reviewed. These studies will be independently reviewed by an FDA consultant (Dr. Tim O'Neill). The only noteworthy aspect of the current NDA submission that needs to be addressed as a part of this review is related to dosage level/exposure. The sponsor minimizes the relevance of the retinal degeneration findings in the discussion since the doses at which the effects were observed were "between 20 and 80 times the intended therapeutic dose in man." Based on an expected $Cmax_{ss}$ in humans of 7-8 ng/ml, the exposure level in MD rats (14-27 ng/ml) is only 2-3 times higher than this level.

Hepatocellular fatty changes (steatosis) were observed in PPX-treated females. These were characterized as either diffuse or restricted to zones 1 and 2. Increased incidences of diffuse changes were dose-dependent and statistically significant in the MD and HD groups. Fatty changes restricted to zones 1 and 2 occurred at a lower rate (Con=7%; LD=24%, MD=22%, LD=18%). The potential mechanism or significance of these findings were not discussed. However, in the 52-week rat study, PPX caused a dramatic dose-dependent reduction in serum cholesterol and triglycerides suggesting a possible interference with hepatic transport or mobilization by PPX. Since both the biochemical and histological changes were observed only in females, a hormonal-based mechanism may be responsible. A direct relationship between the biochemical and histological changes could not be established in

either study. In the 52-week study, steatosis (peripheral fatty changes) occurred in all treatment groups, but the biochemical changes were more clearly dose-dependent. Clinical chemistry was not analyzed in the two-year study. Finally, there was no clear relationship between steatosis and more severe liver histopathologies; the highest incidence of necrosis (multicellular) was in MD females.

In summary, the only potential tumorigenic effect of PPX identified in this study was the induction of Leydig cell adenomas in males, possibly through an indirect hormonal mechanism that is not clinically relevant. The marked impairment of body weight development in MDF and LDF interferes with the interpretation of this study, and no conclusions regarding the carcinogenicity of PPX in female rats can be drawn. The "No Effect" dose was considered to be 0.3 mg/kg/day, although a decrease in body weight gain was apparent at this dose.

Methods:

Dosages: 0.3, 2.0, 8.0 mg/kg/day PPX (Lot: Batch II)

Low dose is 3-4 fold higher than the ED_{50} for anti-Parkinsonian effects in monkeys. It is 5-15 times higher than the expected human maintenance dose range of 1.5-4.5 mg/day (70 kg human). The high dose was selected as the highest tolerable dose given the duration of the study and the limitation of excessive CNS stimulation.

Route of Administration: Drug-in-diet

Species/Strain/Number: Rat/Wistar (Chbb:THOM)

250 males, 250 females for toxicology

Group size and dosage:

Group	Dose mg/kg	Number of animals males	females	Identity number
0 (control A)	0	50		0001-0050
			50	0501-0550
1	0.3	50		1001-1050
			50	1501-1550
2	2.0	50		2001-2050
			50	2501-2550
3	8.0	50		3001-3050
			50	3501-3550
4 (control B)	0	50		4001-4050
			50	4501-4550

Three satellite groups (5,6 and 7) were used for toxicokinetic analyses. Blood was sampled from 5 rats/sex in each group on days 2 and 7 of weeks 2, 50 and 100.

Mean initial weights/age:

males:	144.8g / 39 days
females:	131.6g / 39 days

Parameters monitored/Intervals:

Clinical	-	daily
Body weight	-	weekly (wks 1-26), monthly (wks 27-104)
Food consumption	-	weekly
Water consumption	-	weekly (weeks 13, 26, 39, 52, 65, 78, 91, 104)
Effective dose	-	calculated weekly (wks 1-26); monthly thereafter
Hematology	-	done only prior to sacrifice
Prolactin measurements	-	by RIA in wks 60 and 69
Plasma Conc	-	in satellite groups as described above
Histopathology	-	on the following tissues:

The following organs were placed in 7.5% buffered formaldehyde solution for histological preparation:

Adrenal glands	Prostate gland
Aorta	Rectum
Brain	Salivary glands
Caecum	Seminal vesicle
Cervical lymph node	Skeletal muscle
Colon	Skin
Duodenum	Spinal cord
Eyes/Harderian glands[3)]	Spleen
Femur/stifle joint (incl. bone marrow)	Sternum[1)]
	Stomach
Heart	Testes with epididymides[2)]
Ileum	Thymus gland
Jejunum	Thyroid gland
Kidneys	Tongue
Larynx[1)]	Trachea
Liver	Urinary bladder
Lungs	Uterus with cervix
Mammary gland	Vagina
Mesenteric lymph node	
Oesophagus	Both pinnae with ear tattoo[1)]
Ovaries	
Pancreas	
Parathyroid glands	All gross lesions incl. tumours/suspected tumours and regional lymph nodes
Periph. (sciatic) nerve	
Pituitary gland	

1)= conserved but not prepared histologically.

2)= fixed in Bouin's solution.

3)= fixed in Heidenhein's Susa solution.

Tissues were fixed in 7.5% formalin (except eyes and Harderian glands were fixed in Susa's solution, and the testes with epididymides in Bouin's solution), embedded in Paraplast, and stained with H/E. Aorta, heart, kidneys, liver, lungs, and gross lesion were also stained with Masson-Goldner's trichrome technique. Sectioning was as follows:

Adrenal glands (6), aorta (1), bone and bone marrow [femur] (1), brain [cerebrum, cerebellum] (2), cervix (1), epididymides (2), esophagus (1), eyes (2), Harderian glands (2), heart (1), kidneys (2), large intestine [cecum, colon, rectum] (3), liver (1), lungs (1), lymph nodes [cervical, mesenteric] (2), mammary gland area (1), optic nerves (2), ovaries (2), pancreas (1), parathyroids (6), pituitary gland (3), prostate (1), salivary glands [sublingual, submandibular] (2), sciatic nerve (2), seminal vesicle (1), skeletal muscle (1), skin (1), small intestine [duodenum, jejunum, ileum] (3), spinal cord [cervical, thoracic, lumbar] (3), spleen (1), stomach (1), testes (2), thymus (1), thyroid gland (2), tongue (1), trachea (1), urinary bladder (1), uterus (3), vagina (1), and all gross lesions.

Statistics

Analyses of routine samples were by Bartlett's test, or one-way ANOVA and Newman-Keuls test.

Tumor-bearing animals were categorized according to Peto et al. (1980) (1: incidental; 2: probably incidental; 3: probably fatal; 4: fatal), and analyzed using the positive and negative trend tests with respect to dose, and test for heterogeneity. Only p-values <0.05 for rare neoplasms, and <0.01 for common neoplasms were considered statistically significant.

The Exact Log Rank test was also used for group comparisons only when the number of tumor-bearing animals in a group was greater than 2, and for between-group comparisons of the number of premature decedents.

Results:

Mortality: 40 males and 69 females died over the course of the study. Causes of death are in Table C.5.b.1.

Group	Contr. A		Contr. B		1		2		3	
Sex	m	f	m	f	m	f	m	f	m	f
Died	4	4	0	2	3	6	1	9	3	7
Sacr.	4	9	9	8	4	14	5	6	7	4
Total	8	13	9	10	7	20	6	15	10	11
%	16	26	18	20	14	40	12	30	20	22

No clear time- or dose-relationship was evident to implicate PPX as a causative factor.

Table. C.5.b.1. Causes of Death or Sacrifice:

Controls (A&B)

Males	17 deaths
neoplasia	- 11
pneumonia	- 2
dermatitis	- 1
renal failure	- 1
cong. heart failure	- 1
undetermined	- 1

Females	23 deaths
neoplasia	- 16
cong. heart failure	- 1
pyometra/pyometritis	- 3
pneumonia	- 1
multicell. necrosis	- 1
pyelonephritis	- 1

Low-Dose

Males	7 deaths
neoplasia	- 3
myodegeneration	- 1
pyelitis/cystitis	- 1
pneumonia	- 1
undetermined	- 1

Females	20 deaths
neoplasia	- 11
pyometra/pyometritis	- 5
ovarian abscesses	- 2
cong. heart failure	- 1
liver abscesses	- 1

Mid-Dose

Males	6 deaths
neoplasia	- 2
myocarditis	- 1
undetermined	- 3

Females	15 deaths
neoplasia	- 6
pyometra/pyometritis	- 5
pyelonephritis	- 2
pneumonia	- 1
multicellular necrosis	- 1

High-Dose

Males	10 deaths
neoplasia	- 8
pneumonia	- 2

Females	11 deaths
neoplasia	- 2
pyometra/pyometritis	- 9

Clinical: increased activity - HDF

Body Weight Gain (Fig. c.5.b.1):

LDM	-	sig. decrease - weeks 1-12, 15, 19, 21-23, 25-82
M & HDM	-	sig. decrease - all time points except HDM at wks 90-106
LDF	-	sig. decrease - all time points except wks 14, 15, 90
M & HDF	-	sig. decrease - all time points

Food Intake (Fig. C.5.b.2):

Males	-	tendency for decrease; no sig. effect at end of study
LDF	-	tendency for decrease; no sig. effect at end of study
M & HDF	-	tendency for increase

Water Intake: No remarkable trends

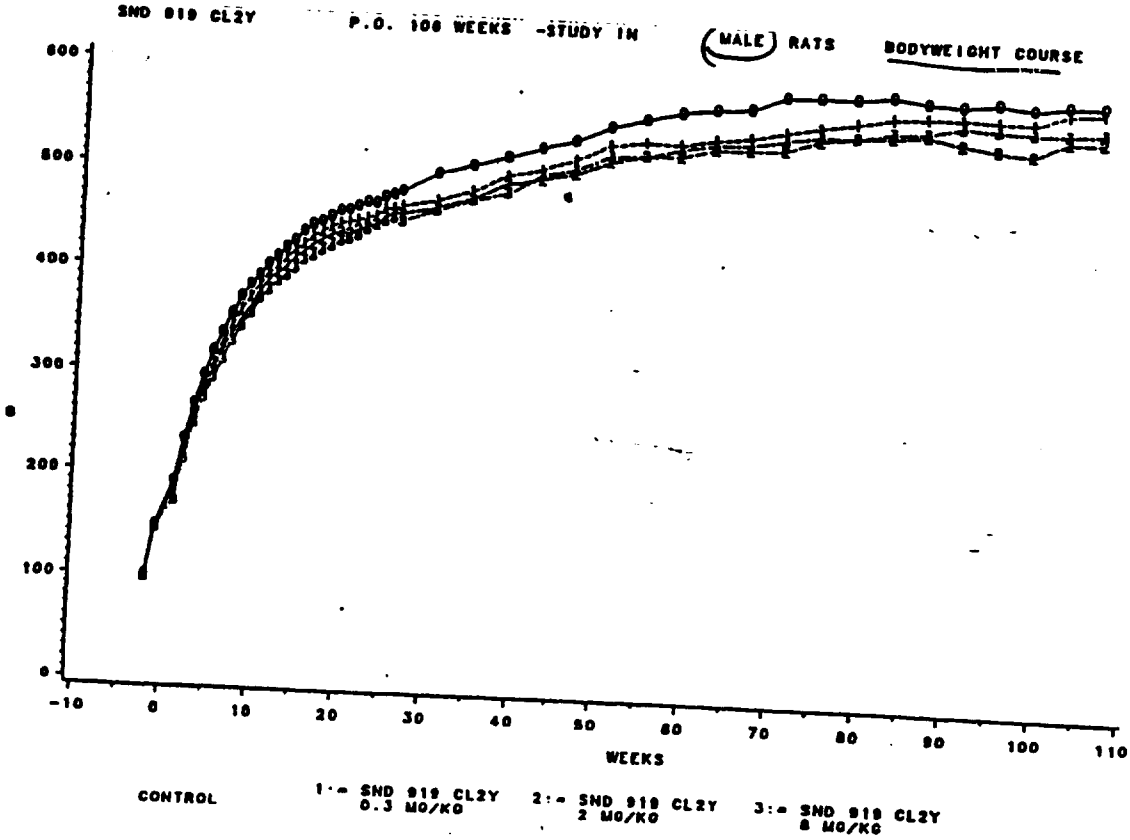
Effective dose: The large ranges in means, particularly in females, are primarily the result of larger than intended intakes in the latter portion of the study (i.e., after week 74).

SND 919 CL2Y : 104 - WEEK - STUDY IN RATS

EFFECTIVE DOSE

SEX		INTENDED DOSE					
		0.30 MG/KG		2.0 MG/KG		8.0 MG/KG	
		MEAN	%	MEAN	%	MEAN	%
FEMALE	MIN	0.24	79.7	1.76	88.1	6.83	85.4
	MAX	0.38	127.6	2.62	131.1	10.27	128.3
MALE	MIN	0.26	87.9	1.66	83.2	6.45	80.6
	MAX	0.34	114.3	2.38	118.8	9.70	121.2

Fig. C.5.b.1.


SND 919 CL2Y
P.O. 108 WEEKS -STUDY IN
MALE RATS
BODYWEIGHT COURSE
600
500
400
300
200
100
0
-10
0
10
20
30
40
50
60
70
80
90
100
110
WEEKS
CONTROL
1:= SND 919 CL2Y 0.3 MG/KG
2:= SND 919 CL2Y 2 MG/KG
3:= SND 919 CL2Y 8 MG/KG

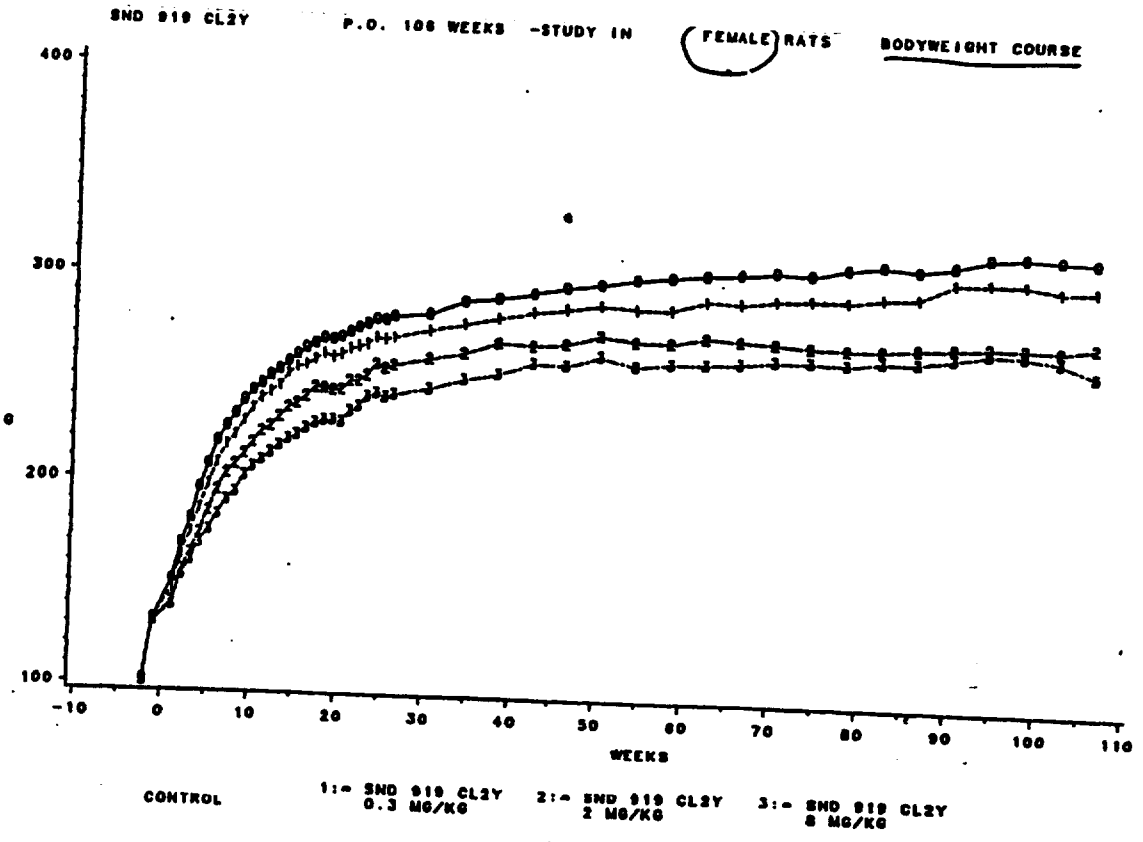
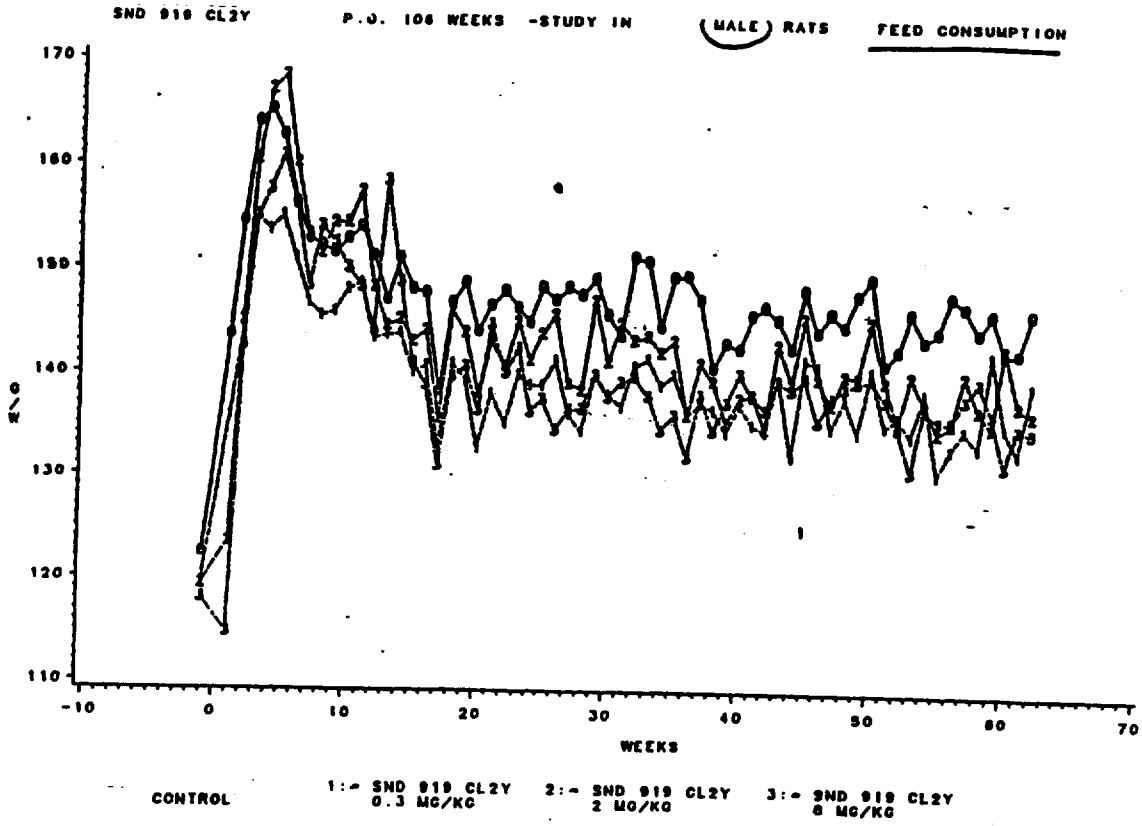

SND 919 CL2Y
P.O. 108 WEEKS -STUDY IN
FEMALE RATS
BODYWEIGHT COURSE
400
300
200
100
-10
0
10
20
30
40
50
60
70
80
90
100
110
WEEKS
CONTROL
1:= SND 919 CL2Y 0.3 MG/KG
2:= SND 919 CL2Y 2 MG/KG
3:= SND 919 CL2Y 8 MG/KG

Fig. C.5.b.2.


SND 919 CL2Y P.O. 106 WEEKS -STUDY IN (MALE) RATS FEED CONSUMPTION
G/W
WEEKS
CONTROL
1:- SND 919 CL2Y 0.3 MG/KG
2:- SND 919 CL2Y 2 MG/KG
3:- SND 919 CL2Y 8 MG/KG

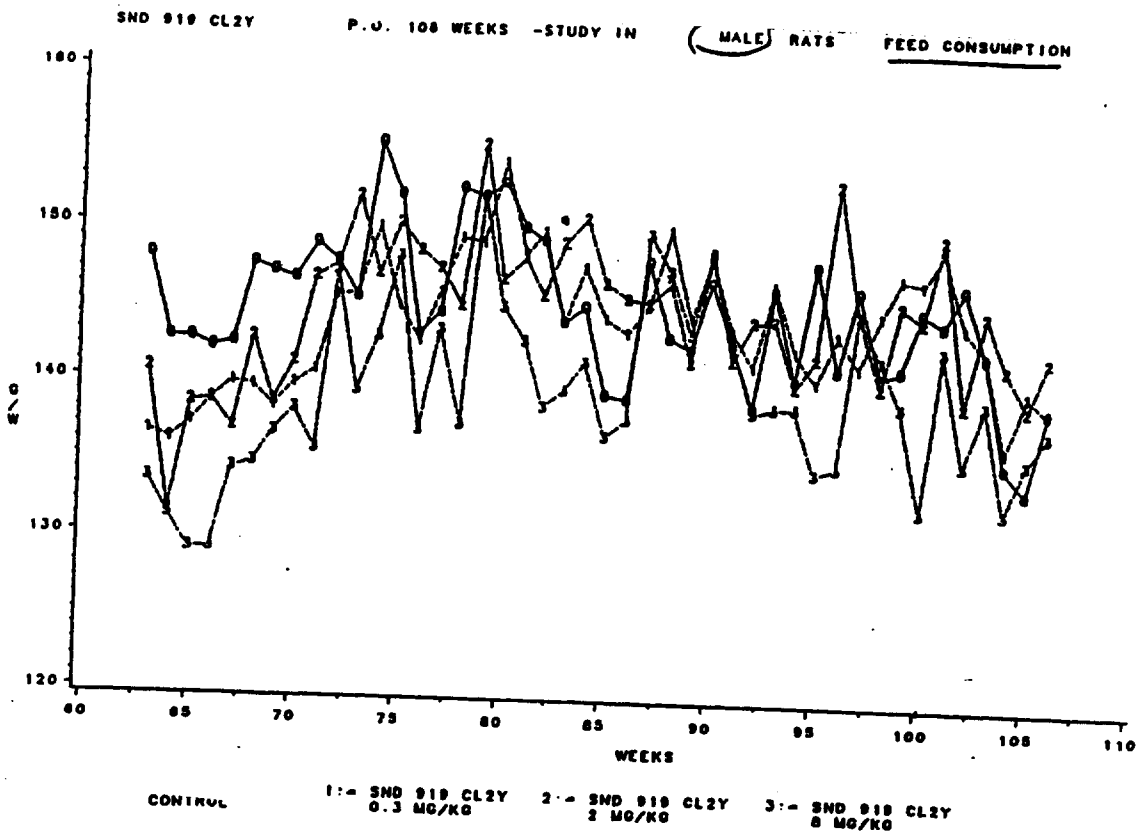
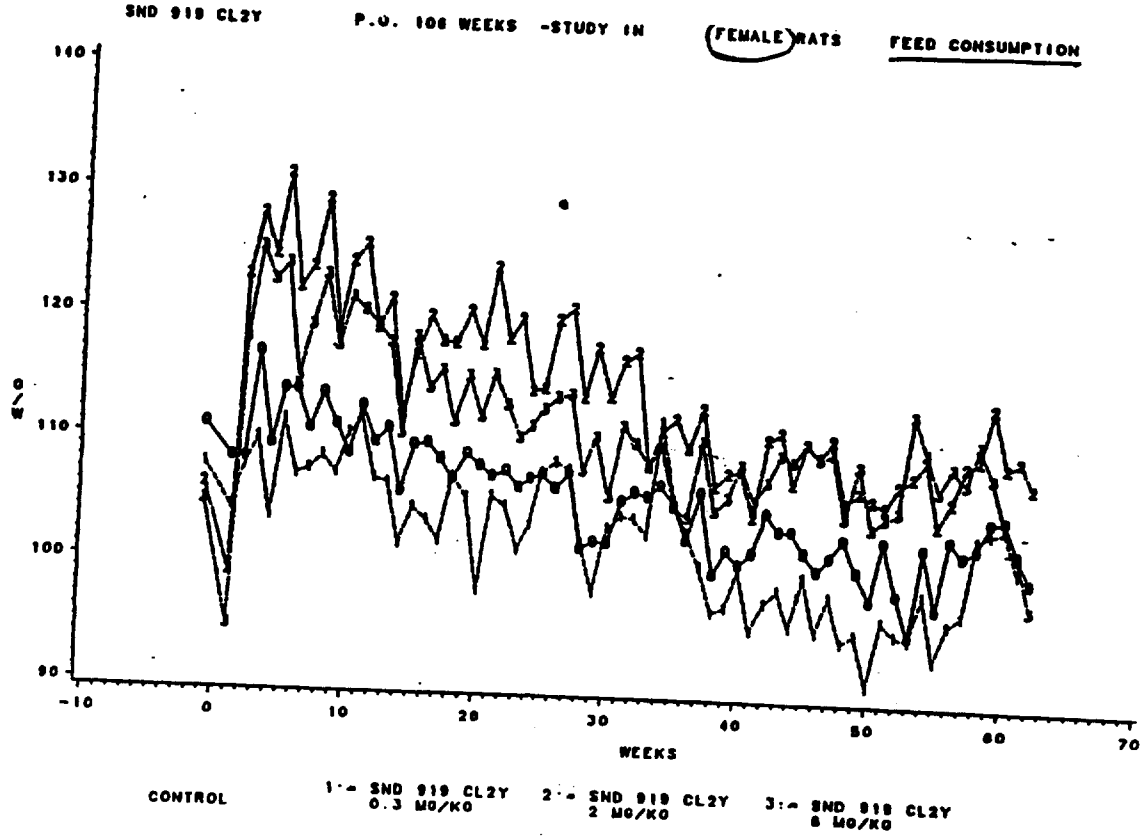
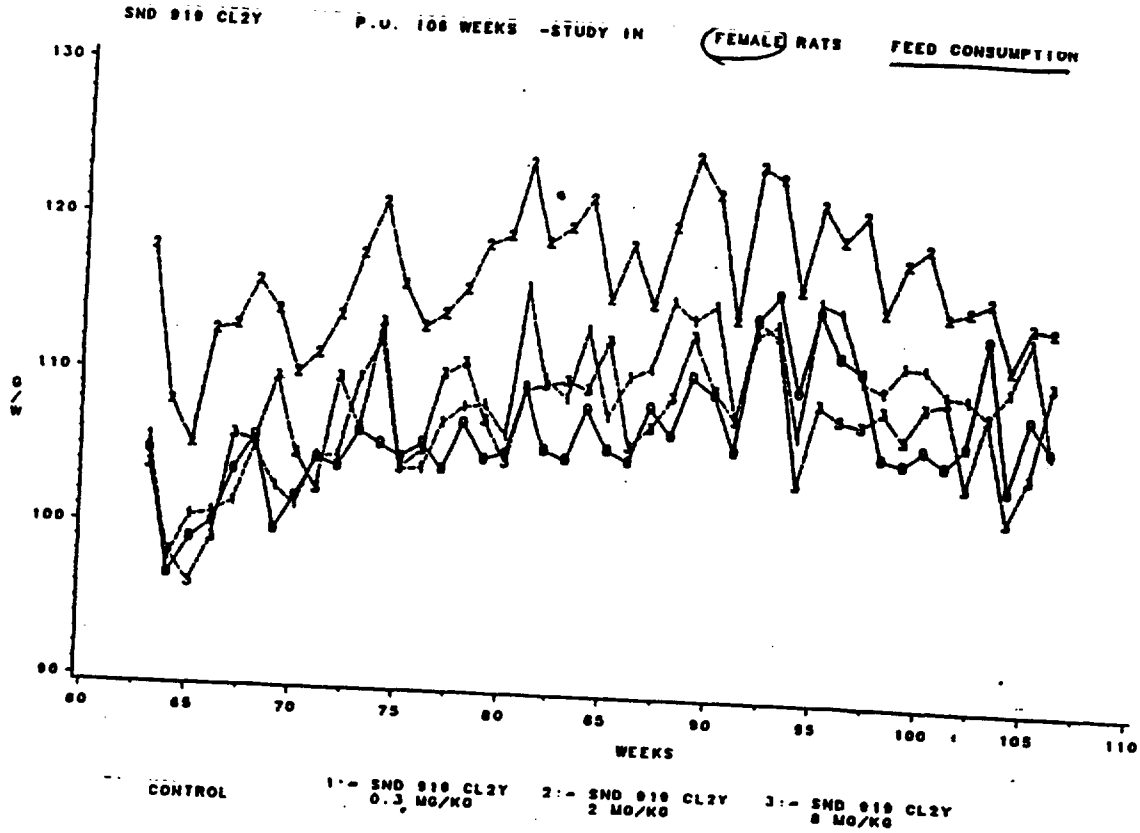

SND 919 CL2Y P.O. 106 WEEKS -STUDY IN (MALE) RATS FEED CONSUMPTION
G/W
WEEKS
CONTROL
1:- SND 919 CL2Y 0.3 MG/KG
2:- SND 919 CL2Y 2 MG/KG
3:- SND 919 CL2Y 8 MG/KG

Fig. C.5.b.2. (cont.)





Hematology:

Group variations (at termination):

Statistically significant mean changes were noted on various parameters, but few clearly dose/drug-related effects were evident.

increased RBC	-	MDF, HDF
increased Hct	-	MDF, HDF
increased MCH	-	HDM
decreased MCH	-	HDF
increased MCHC	-	HDM
decreased MCHC	-	L, M & HDF
decreased eosinophils	-	L, M & HDF
decreased monocytes	-	M & HDF

Individual variations (at termination):

increased WBCs	-	1 Con M, 1 Con F 1 LDM, 1 LDF 1 MDM 1 HDM
anemia, slight	-	5 Con M, 7 Con F 2 LDF 2 MDM 2 HDF
" , marked	-	1 MDF
polycythemia	-	1 Con M 1 MDM 1 HDM

Individual variations (in moribund sacrifices) (Tab. C.5.b.2):

Contol Animals

animal no.	leucocytosis	relative lymphocytosis	relative granulocytosis	blasts	anaemia
0514	•		•		•
0515	•		•		•••
0549	•		••		
4009	•		••		•••
4034	•••	•••			•
4047	•		monocytosis		
4535	•				•

animal no.	leucocytosis	relative lymphocytosis	relative granulocytosis	blasts	anaemia
LD 1503	•		•		
1519	••				•••
1525	•		•		
1534	•		•		•
1536	•••	••			•
1537	••		••		••
1543	•		•		
MD 2005	••		••		•
2020	•		••		
2034	•		•		
2502	•		•		••
2507	•		•		••
HD 3009	•		eosinophilia		
3023	•		••		
3024	•				•
3040	•				•
3505	••		••		•
3521	•				•
3536	•		•		•

In a further 11 animals without changes in the total white blood cell count, a slight (nos. 0520, 1036, and 3050), moderate (nos. 1011, 1510, 1548, 2048, 2530, and 3523), or marked (nos. 0013 and 4517) anaemia was established.

Prolactin Measurements (Tab. C.5.b.3):

An inverse dose-relationship was observed at both time points in both sexes except for MDM at week 60, which had higher levels than control males.

Tab. C.5.b.3.

Influence of SND 919 CL 2 Y on Prolactin Levels (ng/ml) (week 60)

Dose (mg/kg)		Male	Female
0	mean	108.03	166.44
(control)	s.d.	48.64	117.19
	n	4	4
0.3	mean	30.68	141.33
	s.d.	12.36	158.43
	n	7 **	6
2.0	mean	134.60	34.35
	s.d.	54.37	27.04
	n	10	9 *
8.0	mean	< 0.39	15.87
	s.d.	-	9.53
	n	9 **	9 **

Influence of SND 919 CL 2 Y on Prolactin Levels (ng/ml) (week 69)

Dose (mg/kg)		Male	Female
	mean	66.98	251.64
Control	s.d.	28.38	103.41
	n	4	4
0.3	mean	37.56	136.86
	s.d.	28.77	76.26
	n	7 *	8
2.0	mean	<18.59	86.38
	s.d.	-	46.07
	n	9 *	9 *
8.0	mean	< 0.66	27.76
	s.d.	-	24.75
	n	7 **	10 **

Plasma Concentrations (Tab. C.5.b.4):

Increases in plasma concentrations were approximately dose-proportional. Levels at the 8.00 time-point (time of day) were higher than the 14.00 hr time-point. Measurements taken on different days within the same week did not appear to differ. There was a tendency for drug accumulation in males, but not females; this was particularly evident at week 100. There was no clear sex difference with the exception of the HD groups at week 100, where levels in males appeared to be higher.

(Note: There appears to be a discrepancy between the graphical and tabular data presentation. This likely occurred because 8 hr was used as a time point reference under two different scenarios - according to time of day (8.00 hr), and according to the number of hours after light onset (14.00 hr) (i.e., blood was collected at 8.00 hr (AM) - two hrs after light onset, and 8 hr after light onset - 14.00 hr). Analysis of the individual data indicates that the tabular presentation on pages 5/24/241-2 is the accurate presentation).

Table 5.E.9. Rat Mean Plasma Pramipexole Concentrations (ng/mL) in the 2-Year Carcinogenicity Study[a]

Sex	Dose (mg/kg)	Two Hours After Start of Light Phase					
		Week/Day					
		2/2	2/7	50/2	50/7	100/2	100/7
Female	0.3	2.39 (1.76-3.25)	1.96 (1.32-2.91)	1.86 (1.36-2.55)	1.66 (1.43-1.93)	4.52 (3.53-5.78)	3.64 (2.28-5.80)
	2.0	14.86 (12.86-17.56)	16.08 (10.20-25.35)	19.30 (14.74-25.27)	19.54 (14.69-26.00)	22.66 (16.82-30.53)	18.80 (10.97-32.20)
	8.0	77.53 (67.29-89.33)	103.11 (94.58-112.41)	80.25 (59.88-107.55)	75.43 (62.18-91.51)	65.81 (53.25-81.33)	70.79 (23.70-211.4)
Male	0.3	1.71 (1.23-2.36)	1.60 (1.24-2.06)	2.12 (1.60-2.80)	2.13 (1.78-2.55)	3.18 (1.80-5.62)	2.85 (1.45-5.60)
	2.0	15.03 (12.86-17.56)	13.13 (10.57-16.31)	20.18 (16.45-24.76)	18.51 (14.65-23.38)	27.14 (22.43-32.85)	22.97 (15.86-33.27)
	8.0	77.20 (51.04-116.77)	79.44 (61.66-102.34)	93.21 (83.23-104.38)	70.11 (30.60-160.68)	140.66 (104.44-189.43)	133.95 (108.46-165.44)

Table 5.E.9. Rat Mean Plasma Pramipexole Concentrations (ng/mL) in the 2-Year Carcinogenicity Study[a]

Sex	Dose (mg/kg)	Eight Hours After Start of Light Phase					
		Week/Day					
		2/2	2/7	50/2	50/7	100/2	100/7
Female	0.3	0.88 (0.44-1.75)	0.60 (0.19-1.92)	1.43 (1.31-1.56)	0.64 (0.29-1.39)	4.97 (2.81-8.79)	2.63 (1.70-4.06)
	2.0	3.73 (2.00-6.95)	7.09 (4.75-10.60)	6.73 (4.78-9.49)	5.93 (3.08-11.43)	28.10 (15.31-44.51)	19.50 (9.53-40.66)
	8.0	14.34 (8.05-25.56)	32.67 (21.24-50.25)	21.72 (9.85-47.93)	25.00 (17.59-35.53)	83.12 (44.55-155.07)	24.58 (9.25-65.34)
Male	0.3	0.34 (0.18-0.64)	0.75 (0.40-1.39)	0.96 (0.50-1.86)	1.03 (0.35-3.03)	1.51 (0.68-3.36)	1.38 (0.56-3.43)
	2.0	5.42 (3.03-9.70)	3.20 (1.96-5.21)	9.59 (6.25-14.73)	7.02 (6.17-7.98)	16.28 (8.47-31.27)	8.47 (4.94-14.52)
	8.0	24.59 (9.65-62.65)	25.23 (19.44-32.74)	57.09 (40.89-79.71)	47.30 (32.74-68.33)	65.52 (36.96-116.15)	47.17 (34.40-64.67)

Pathology:

Non-neoplastic lesions

Aside from the retinal degeneration findings which are discussed in other portions of this review, the most significant findings were primarily in reproductive tissues, putatively due to the prolactin-inhibiting effects of PPX. Macroscopic lesions in treated females included enlarged or discolored ovaries, and uterine dilatation with hemorrhagic or watery contents. Microscopic alterations in these tissues were enlarged corpora lutea, and chronic suppurative lesions in the uterus. These lesions are suggested to result from a estrogen:progesterone imbalance in the absence of prolactin, which normally stimulates progesterone secretion. In addition, the glandular pattern of mammary gland tissue changes from a female-type tubuloalveolar pattern to a more male-like lobuloalveolar pattern in the absence of prolactin. The Leydig cell hyperplasia is also suggested to be linked to prolactin inhibition. In the absence of prolactin, LH receptors will down-regulate leading to compensatory increases in serum LH, and supposedly hypertrophy of Leydig cells (this is a speculative mechanism; a question that arises is how the Leydig cells respond to LH if the receptors are reduced in density). The reduced incidence of adrenal medullary hyperplasia is suggested to result from PPX-inhibition of catecholamine release from adrenal chromaffin cells.

Changes in the incidences of microscopic lesions were summarized as follows:

		Group/Incidence Rate (%)				
	Lesion	0	4	1	2	3
INCREASE	retinal degeneration (M)	0	0	0	51*	90*
	" (F)	2	0	0	21*	77*
	Leydig cell hyperplasia	70	78	80	92*	92*
	corpora lutea - enlarged	16	10	8	10	74*
	uterus, pyometra	4	10	14	24*	28*
	" , dilatation	18	47	34	58*	90*
	" , hemorrhage	2	10	18	24*	24*
	mammary gland - lobuloalveolar pattern (F)	0	0	0	0	34*
	mammary gland - mixed lobulo-alveolar/tubuloalveolar pattern (F)	0	0	2	26	46
	hepatocellular fatty change (F)	6	4	4	34*	52*
	vagina, blood	0	4	4	2	10

D E C R	adrenal medullary hyperplasia (F)	47	57	55	30*	29*
	mammary gland - cystic change (F)	42	18	38	6*	0*
	pulmonary alveolar macrophages (F)	44	40	44	40	22*

Neoplastic Lesions:

According to the sponsor's analysis, the only tumor that occurred with a higher frequency in PPX-treated animals than in controls was the Leydig cell adenoma. However, this tumor occurred with a high background incidence. The mechanism for increased incidence in PPX-treated animals is similar to that described for the Leydig cell hyperplasia.

	Group/Incidence rate (%)				
Neoplasm	0	4	1	2	3
Leydig cell adenoma - increase	26	18	34	44*	44*
mammary gland (all types) - decrease	14	8	12	0*	0*
pituitary adenoma - decrease (M)	8	20.4	12	0*	2*
" - " (F)	40	64	60	20.4 *	4.1*
benign adrenal medullary neoplasm - decrease (F)	38.8	65.3	32.7 *	8.7*	6.1*
thyroid C-cell carcinoma - decrease (F)	2	8	6	2	0
total # neoplasms - decrease (F)				*	*

The incidence of squamous papillomas in the cervix approached statistical significance by the Heterogeneity test ($p = 0.0548$), but the highest incidence of these tumors occurred at the lowest dose.

Summary of Distribution of Neoplasms (Tab. C.5.b.6):

Name of company		TABULATED STUDY REPORT		
Name of finished product		ref. to III.E.210		
Name of active ingredient: Pramipexole (SND 919 CL 2 Y)		3/9 Page Number		
ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data				
Ref. to document.: Volume: Page: to Addendum No.: Report date: 05.05.94 Number: G75 Study period (years): 1989 - 1991				
Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <x> no < >		Frequency according to dose and sex (n)		

		(0) Contr. A		(4) Contr.B		(1)		(2)		(3)	
		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated		50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour										
BRAIN	GRANULAR CELL TUMOUR	1	1	-	-	-	2	1	-	-	-
	OLIGODENDROGLIOMA	-	1	-	-	1	-	-	-	-	-
LUNGS	BRON./ALV. CARCINOMA	-	1	-	1	1	-	-	-	-	-
TONGUE	HEMANGIOMA	-	-	-	-	1	-	-	-	-	-
	GRANULAR CELL TUMOUR	-	-	-	1	-	-	-	-	-	-
	SARCOMA, NOS	-	-	-	-	-	-	-	-	1	-
JEJUNUM	LEIOMYOMA	-	-	-	-	-	-	-	1	-	-
	ADENOCARCINOMA	-	-	-	-	-	1	-	-	-	-
	LEIOMYOSARCOMA	-	-	-	1	-	-	-	-	-	-
ILEUM	LEIOMYOSARCOMA	-	-	-	-	-	1	-	-	-	-
STOMACH	ADENOCARCINOMA	1	-	-	-	-	-	-	-	-	-
CAECUM	ADENOCARCINOMA	-	-	-	-	-	-	1	-	-	-
LIVER	HEPATOC. ADENOMA	3	-	4	1	3	1	4	1	1	-
	CHOLANGIOMA	-	-	-	2	-	1	-	1	-	1
	HEPATOC. CARCINOMA	3	-	2	-	5	-	1	-	2	-
	CHOLANGIOCARCINOMA	-	-	1	-	-	-	-	-	-	-
PANCREAS	ISLET-CELL ADENOMA	3	-	-	-	-	-	1	-	-	-
	ACINAR CARCINOMA	-	-	-	-	-	1	-	-	-	-

* P < 0.05 ** P < 0.01

Tab. C.5.b.6 (cont.)

TR No. 7219-94-068

Name of company	TABULATED STUDY REPORT	
Name of finished product		
Name of active ingredient Pramipexole (SND 919 CL 2 Y)	ref. to III.E.210	
	4/9 Page Number	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 05.05.94 Number: G75 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <x> no < >		Frequency according to dose and sex (n)									
		(0) Contr. A		(4) Contr.B		(1)		(2)		(3)	
		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated		50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour										
KIDNEYS	TUBULAR ADENOMA	-	1	-	-	-	-	-	-	1	-
	NEPHROBLASTOMA	1	-	-	-	-	-	-	-	-	-
	LIPOSARCOMA	-	1	1	-	-	-	-	-	-	-
URINARY											-
BLADDER	TRANSIT. PAPILLOMA	-	2	-	1	-	-	-	1	1	1
	SQUAMOUS PAPILLOMA	-	-	-	-	-	-	-	-	-	1
	TRANSIT. CARCINOMA	-	-	-	-	-	-	1	-	1	-
	SQUAMOUS CARCINOMA	1	-	-	-	-	-	-	-	-	-
TESTES	LEYDIG CELL ADENOMA**	13	-	9	-	17	-	22	-	22	-
OVARIES	GRANULOSA CELL TUMOR (B)	-	5	-	1	-	1	-	1	-	1
	THECA CELL TUMOUR	-	-	-	1	-	2	-	1	-	-
	LUTEOMA	-	-	-	4	-	-	-	1	-	-
	CARCINOMA, NOS	-	-	-	-	-	-	-	1	-	-
UTERUS	ADENOMA	-	-	-	1	-	-	-	-	-	-
	LEIOMYOMA	-	-	-	-	-	-	-	-	-	1
	HEMANGIOMA	-	-	-	-	-	-	-	2	-	1
	GRANULAR CELL TUMOUR	-	-	-	1	-	1	-	-	-	-
	ADENOCARCINOMA	-	2	-	2	-	2	-	2	-	1
	HEMANGIOSARCOMA	-	-	-	1	-	-	-	3	-	1

* P < 0.05 ** P < 0.01 (positive trend)

Tab. C.5.b.6. (cont)

TR No. 7219-94-068

Name of company Name of finished product Name of active ingredient Pramipexole (SND 919 CL 2 Y)	TABULATED STUDY REPORT ref. to III.E.210 5/9 Page Number	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 05.05.94 Number: G75 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <x> no < >		Frequency according to dose and sex (n)									
		(0) Contr. A		(4) Contr.B		(1)		(2)		(3)	
		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated		50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour										
UTERUS	LEIOMYOSARCOMA	-	-	-	-	-	1	-	-	-	1
CERVIX	SQUAMOUS PAPILLOMA	-	1	-	1	-	5	-	3	-	1
	STROMAL SARCOMA	-	3	-	1	-	3	-	4	-	1
	SQUAMOUS CARCINOMA	-	-	-	1	-	-	-	-	-	-
PITUITARY GLAND											
	ADENOMA m: **; f: ***	4	20	10	32	6	30	-	10	1	2
THYROID GLAND											
	FOLLICULAR ADENOMA	-	-	1	-	-	-	-	-	-	1
	C CELL ADENOMA	3	5	2	7	2	4	5	1	3	9
	GANGLIONEUROMA	1	-	-	-	-	-	-	-	-	-
	FOLLICULAR CARCINOMA	-	-	-	1	-	1	1	-	-	-
	C CELL CARCINOMA f: *	2	1	2	4	3	3	3	1	1	-
PARA-THYROID GLANDS											
	ADENOMA	-	1	2	2	2	3	1	-	1	-
ADRENAL CORTEX											
	ADENOMA	1	4	1	-	1	-	-	2	-	1
	CARCINOMA	1	-	-	-	-	-	-	1	-	1

* P < 0.05 ** P < 0.01 *** P < 0.001 (negative trend)

TR No. 7219-94-068

Name of company Name of finished product Name of active ingredient Pramipexole (SND 919 CL 2 Y)	TABULATED STUDY REPORT ref. to III.E.210 6/9 Page Number	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 05.05.94 Number: G75 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <x> no < >		Frequency according to dose and sex (n)									
		(0) Contr. A		(4) Contr.B		(1)		(2)		(3)	
		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated		50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour										
ADRENAL MEDULLA											
	MEDULLARY TUMOUR (B) f: ***	10	19	13	32	7	16	9	4	6	3
	MEDULLARY TUMOUR (M)	2	-	2	1	1	-	-	-	1	-
THYMUS	THYMOMA	-	-	-	-	-	1	-	-	-	-
MESENT. LYMPH NODE											
	HEMANGIOMA	-	-	5	1	2	-	3	1	4	-
HEMOLYMPH. SYSTEM											
	HISTIOCYTIC SARCOMA	-	1	1	1	-	1	-	1	-	-
	MALIGNANT LYMPHOMA	3	1	8	4	6	3	1	1	4	3
SPLEEN	HEMANGIOSARCOMA	1	1	-	1	-	1	1	-	2	-
SUBLINGUAL GLAND											
	ACINAR CARCINOMA	-	-	-	-	-	1	-	-	-	-
MAMMARY GLAND AREA											
	FIBROADENOMA	-	5	-	2	-	2	-	-	-	-
	ADENOMA f: **	-	1	-	-	-	-	-	-	-	-
	PAPILL. CYSTADENOMA	-	-	-	-	-	1	-	-	-	-
	CARCINOMA	-	1	-	2	-	3	-	-	-	-
BONE	GRANULAR CELL TUMOUR	-	1	-	-	-	-	-	-	-	-
	SCHWANNOMA (M)	-	-	-	-	-	-	-	-	1	-

* P < 0.05 ** P < 0.01 *** P < 0.001 (negative trend)

Tab. C.5.b.6 (cont.)

TR No. 7219-94-068

Name of company Name of finished product Name of active ingredient Pramipexole (SND 919 CL 2 Y)	TABULATED STUDY REPORT ref. to III.E.210 7/9 Page Number	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 05.05.94 Number: G75 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <x> no < >		Frequency according to dose and sex (n)									
		(0) Contr. A		(4) Contr.B		(1)		(2)		(3)	
		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated		50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour										
BONE MARROW	HEMANGIOSARCOMA	-	-	1	-	-	-	-	-	-	-
SUBMANDIB. GLAND	SARCOMA, NOS	-	-	2	-	-	-	-	-	-	-
SKIN	KERATOACANTHOMA	2	-	2	-	1	-	-	-	-	-
	TRICHOFOLLICULOMA	-	-	1	-	-	-	-	-	-	-
	SEBACEOUS ADENOMA	-	-	1	-	-	-	-	-	-	-
	TRICHOLEMMOMA	-	-	-	-	-	-	1	-	-	-
	LIPOMA	-	-	1	-	-	-	-	-	-	-
	FIBROMA	1	-	1	-	1	-	-	-	-	-
	SQUAMOUS CARCINOMA	-	-	-	-	-	1	-	-	2	-
	BASAL CELL CARCINOMA	-	-	1	-	2	-	-	-	-	2
	SEB/SQUAM. CARCINOMA	1	-	-	-	-	1	-	-	-	-
	SCHWANNOMA (M)	-	-	-	-	-	-	-	-	2	-
	HEMANGIOSARCOMA	-	-	1	-	-	-	1	-	1	-
	MAST CELL TUMOUR	-	-	-	-	-	-	-	-	1	-
	SARCOMA, NOS	-	-	1	-	-	-	-	-	1	-
	FIBROSARCOMA	-	-	-	-	-	1	-	-	-	-

* P < 0.05 ** P < 0.01

TR No. 7219-94-068

Name of company Name of finished product Name of active ingradient Pramipexole (SND 919 CL 2 Y)	TABULATED STUDY REPORT ref. to III.E.210 8/9 Page Number	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 05.05.94 Number: G75 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <x> no < >		Frequency according to dose and sex (n)									
		(0) Contr. A		(4) Contr.B		(1)		(2)		(3)	
		m	f	m	f	m	f	m	f	m	f
Number of animals evaluated		50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour										
ADIPOSE TISSUE	LIPOMA	1	-	2	1	-	-	1	-	-	-
EARS	HEMANGIOMA	-	-	-	-	1	-	-	-	-	-
TAIL	SCHWANNOMA	-	-	-	-	-	-	-	-	1	-

* P < 0.05 ** P < 0.01

Results of Trend Test (Tab. C.5.b.7):

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
P VALUES FOR POSITIVE AND NEGATIVE TRENDS

DOSE GROUPS : 0, 1, 2, 3, 4
STATUS AT NECROPSY: KO INCL. +
SEX: MALE

ORGAN/TISSUE	TYPE OF NEOPLASM	POSITIVE TREND	NEGATIVE TREND
LIVER	HEPATOC. ADENOMA	-	0.1236
LIVER	HEPATOC. CARCINOMA	-	0.2608
PANCREAS	ISLET-CELL ADENOMA	-	0.1567
TESTES	LEYDIG CELL ADENOMA	0.0057	-
PITUITARY	ADENOMA	-	0.0066
THYROID GLAND	C CELL ADENOMA	0.3635	-
THYROID GLAND	C CELL CARCINOMA	-	0.2286
ADRENAL MEDULLA	MEDULLARY TUMOR (B)	-	0.1110
ADRENAL MEDULLA	MEDULLARY TUMOR (M)	-	0.2998
MESENT. LYMPH NODE	HEMANGIOMA	0.1590	-
SYSTEMIC NEOPLASMS	MALIGNANT LYMPHOMA	-	0.2715

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
P VALUES FOR POSITIVE AND NEGATIVE TRENDS

DOSE GROUPS : 0, 1, 2, 3, 4
STATUS AT NECROPSY: KO INCL. +
SEX: FEMALE

ORGAN/TISSUE	TYPE OF NEOPLASM	POSITIVE TREND	NEGATIVE TREND
OVARIES	GRANULOSA CELL TUMOR	-	0.1607
OVARIES	LUTEOMA	-	0.1026
CERVIX	SQUAMOUS PAPILLOMA	-	0.2051
CERVIX	STROMAL SARCOMA	-	0.2054
PITUITARY	ADENOMA	-	< 0.0001
THYROID GLAND	C CELL ADENOMA	0.0858	-
THYROID GLAND	C CELL CARCINOMA	-	0.0382
PARATHYROID GLANDS	ADENOMA	-	0.0558
ADRENAL CORTEX	ADENOMA	-	0.3407
ADRENAL MEDULLA	MEDULLARY TUMOR (B)	-	< 0.0001
SYSTEMIC NEOPLASMS	MALIGNANT LYMPHOMA	0.4648	-
MAMMARY GLAND AREA	FIBROADENOMA	-	0.0234
MAMMARY GLAND AREA	CARCINOMA	-	0.0566
MAMMARY GLAND AREA	(COMBINED NEOPLASMS)	-	0.0032
UTERUS	HEMANGIOSARCOMA	0.3030	-

Test for Heterogeneity (Tab. C.5.b.8):

TABLE FOR HETEROGENEITY ON NEOPLASTIC LESIONS

		SEX: MALE
ORGAN/TISSUE	TYPE OF NEOPLASM	P- VALUE
LIVER	HEPATOC. ADENOMA	0.5938
LIVER..	HEPATOC. CARCINOMA	0.3381
PANCREAS	ISLET-CELL ADENOMA	0.4029
TESTES	LEYDIG CELL ADENOMA	0.0100
PITUITARY	ADENOMA	0.0071
THYROID GLAND	C CELL ADENOMA	0.5848
THYROID GLAND	C CELL CARCINOMA	0.7685
ADRENAL MEDULLA	MEDULLARY TUMOR (B)	0.3218
ADRENAL MEDULLA	MEDULLARY TUMOR (M)	0.4930
MESENT. LYMPH NODE	HEMANGIOMA	0.7732
SYSTEMIC NEOPLASMS	MALIGNANT LYMPHOMA	0.2421

TABLE FOR HETEROGENEITY ON NEOPLASTIC LESIONS

		SEX: FEMALE
ORGAN/TISSUE	TYPE OF NEOPLASM	P- VALUE
OVARIES	GRANULOSA CELL TUMOR	0.5104
OVARIES	LUTEOMA	0.3011
UTERUS	HEMANGIOSARCOMA	0.1430
CERVIX	SQUAMOUS PAPILLOMA	0.0548
CERVIX	STROMAL SARCOMA	0.4969
PITUITARY	ADENOMA	< 0.0001
THYROID GLAND	C CELL ADENOMA	0.0723
THYROID GLAND	C CELL CARCINOMA	0.2787
PARATHYROID GLANDS	ADENOMA	0.0755
ADRENAL CORTEX	ADENOMA	0.4655
ADRENAL MEDULLA	MEDULLARY TUMOR (B)	< 0.0001
SYSTEMIC NEOPLASMS	MALIGNANT LYMPHOMA	0.7136
MAMMARY GLAND AREA	FIBROADENOMA	0.0632
MAMMARY GLAND AREA	CARCINOMA	0.0887

C.6. Local Tolerance and Allergenic Studies

Sponsor Volumes: 1.49-1.54

Summary:

PPX was relatively free of locally irritating or allergenic effects. In rabbits, PPX caused mild ocular effects only after repeated treatment for 4 weeks, and mild irritation of abraded skin after repeated applications. PPX was considered a mild sensitizing agent in guinea pigs. PPX did not induce hemolysis in human blood.

Study Results:

C.6.a. Rabbit Eye Irritation (single dose)- 0.1g PPX (formulation not specified) into one eye did not produce local ocular irritation.

C.6.b. Rabbit Eye Irritation (multiple doses) - 0.05, 0.1, 0.25, and 0.5% PPX in 0.1 ml (8 times daily for 3 days) did not produce local ocular irritation (high dose of 0.5% = 0.5 mg/dose).

C.6.c. Rabbit Eye Irritation (4-week study) - 0.00625, 0.05, and 0.5% in 50 µl applied 6 times daily to the conjunctival sac caused a mild to moderate increase in conjunctival secretion and mild reddening. The effect was not concentration-related.

C.6.d. Dermal Irritation in Rabbits (single dose) - Topical application of 0.5g/0.5 ml PPX to shaved skin area did not produce irritation, erythema or edema.

C.6.e. Dermal Irritation in Rabbits (multiple doses) - 0.1g/0.1 ml PPX was applied topically to a shaved intact or a shaved abraded skin area once daily for 5 days. No irritation occurred on the intact area. Mild irritation with erythema and eschar occurred on the abraded area.

C.6.f. Dermal Irritation in Rabbits (4-week patch application) - Application of a patch containing 10.75 mg PPX free base for 4 weeks to shaved areas caused slight irritation. Irritation was also observed in placebo-treated animals, and thus may have resulted from mechanical trauma due ti repeated patch removal and replacement.

C.6.g. Paravenous Injectable Tolerability in Rats - 0.2 ml of an 0.1% PPX solution was injected medially and laterally to the jugular vein. Slight hemorrhages and edema in the area were observed between 1-24 hr after treatment.

C.6.h. Acute Intravenous Tolerance in Rabbits - 0.2 ml of an 0.1% PPX solution was injected into the rabbit ear vein. Slight erythemas were observed in 3 of 4 animals, and bluish-red discoloration in 2 of 4 animals within the first few days of administration. Saline injection also caused 2 cases of erythemas.

C.6.i. Acute Intra-arterial Local Tolerance in Rabbits - 0.5 ml of an 0.1% PPX solution was injected into the rabbit ear central artery. Slight erythemas were observed in 4 of 4 animals, and bluish-red discoloration in 3 of 4 animals. Similar effects were observed in saline-treated controls (2 of 4 cases of erythemas, 3 of 4 cases of discolorations).

C.6.j. Skin Sensitization in Guinea Pigs - Animals were sensitized by six intradermal injections of 1% PPX free base (0.1 ml) into the dorsal skin. On days 8-10, 12.5 mg PPX was applied to the same area. On day 22, the animals were challenged by application of 12.5 mg PPX to an area of the left flank. A contact dermatitis response was noted in 5 of 20 animals. On day 36, animals were rechallenged with 6.25 mg PPX. Four of 20 animals had an allergic contact dermatitis, but only one of these animals had the reaction previously. Thus, PPX was considered a mild sensitizing reagent.

C.6.k. Skin Sensitization in Guinea Pigs to Patch Exposure - Animals were sensitized to the PPX patch exposure (contains 11.5-12.9 mg PPX free base) by either nine applications over 3 weeks or 15 applications over 5 weeks (6 hrs per application. Animals were challenged on day 29 and rechallenged on day 43. No allergic contact dermatitis and no primary skin irritations occurred.

C.6.l. Test for Hemolytic Effect - An 0.1% solution of PPX (HCl) did not induce hemolysis in preparations of citrated human blood.

D. PHARMACOKINETIC/ADME STUDIES

Conducted by :

1. Rats
   a. Biochemical investigations with [^{14}C]-SND 919 CL2Y in rats (absorption, distribution, excretion, metabolism).
   b. Whole body autoradiographic studies with SND 919 CL2Y in rats.
   c. Studies on the placental transfer and on the crossing of the blood-brain barrier of [^{14}C]-SND 919 CL2Y in the rat.
   d. Pramipexole: Steady-state concentrations in brain, liquor, and plasma of male rats after oral administration of 0.5 mg/kg (once per day) over 8 days.
   e. Excretion of [^{14}C]-SND 919 CL2Y into rat milk after a single oral dose of 0.5 mg/kg.

2. Rabbit
   a. Pharmacokinetics and metabolism [of pramipexole] in the rabbit after intravenous and oral administration of a single dose of 1 mg/kg.

3. Monkeys
   a. Plasma concentrations and renal excretion in Rhesus monkeys after administration of three single intragastric doses (0.1, 0.5 and 1.0 mg/kg) and one intravenous dose (0.5 mg/kg).

4. Humans
   a. Pharmacokinetics and metabolism of [^{14}C]-pramipexole after single intravenous and oral doses in healthy volunteers.
   b. A single dose tolerance and pharmacokinetic study of intravenous pramipexole in healthy male volunteers.

5. Multiple Species
   a. Balanced excretion studies and metabolic profile following oral administration of [14C]-SND 919 CL2Y to the mouse, rat, rabbit, dog, monkey and pig.
   b. Studies on the metabolism of pramipexole including experiments to detect a potential metabolic inversion at the optical active center of the molecule.

D.1. Rat Pharmacokinetics

D.1.a. Biochemical investigations with [^{14}C]-SND 919 CL2Y in rats (absorption, distribution, excretion, metabolism).

Document #(s):

Upjohn TR 7256-94-035

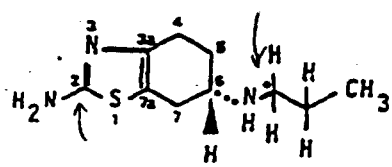
Sponsor Volume: 1.56

Summary:

Radiolabeled PPX was administered to Wistar rats at doses of 0.25 mg/kg i.v. or 0.01-79.1 mg/kg, p.o. Plasma levels and excretion balances were determined. PPX was absorbed rapidly and nearly completely following oral administration. Elimination of radiolabel is relatively slow, and not complete by 96-120 hr. The parent compound is eliminated primarily by renal excretion, whereas the fecally excreted portion is primarily polar metabolites of biliary origin. Plasma protein binding was relatively low in rat and other species (dog, pig, monkey, man).

Methods:

Substance administered: [^{14}C]-pramipexole labeled at the 2-position of the thiazole ring, or C1 of the propyl group



x 2 HCl

* = ^{14}C labelling
(Active substance carrying the ^{14}C label in the 2 position of the thiazole ring was used in some preliminary experiments.)

Dosing Regimen:

Study	Dose (mg/kg)	Route of Administration	No. of Animals N	Batch No.*
Exhalation of $^{14}CO_2$	0.24	IV	2	1
" "	0.6	IV	3	2
" "	0.5	IV	2	3
Blood levels	0.4	Oral	10	1
Plasma levels	2.5	IV	5	-
Excretion	0.25	IV	11	1
Excretion	0.01	Oral	4	1
"	0.1	Oral	4	
"	1.4	Oral	4	
"	10.8	Oral	4	
"	79.1	Oral	4	
Excretion (bile)	0.28	IV	4	3

Parameters measured: exhalation, excretion balance (urine, feces), blood levels, plasma protein binding (different species), biliary excretion, metabolite profiles (urine, feces)

Results:

Exhalation study: With the propyl-C radiolabelled material, 4.6% of an i.v. dose was exhaled as CO_2 during 0-24 hrs postdose. With the thiazole ring-labeled material, less than 1% was eliminated by this route. Thus, the ring-labeled material was used for subsequent studies.

Excretion balance: Average elimination (% dose) during 0-96 hr collection:

		Urine	Feces
intravenous	0.25 mg/kg	52.9	36.5
oral	0.01 "	51.9	28.7
	0.1 "	64.8	38.3
	1.4 "	48.2	41.2
	10.8 "	52.1	29.3
	79.1 "	43.6	25.8

No effect of dose or sex

Biliary Excretion: 20-48% of iv dose in 0-24 hr (ca. equivalent to fecal excretion).

PK parameters:

Blood [^{14}C]-Activity after **Oral** dosing (0.4 mg/kg)

		AUC (ng.ml/hr)	MRT (hr)	Cl (ml/min)
Single dose	Male	469	9.8	3.9
	Female	581	19.0	3.4
After 3 doses	Male	537	16.0	3.4
	Female	577	14.6	3.5

Parent Compound after **IV** dosing (2.5 mg/kg)

	AUC (ng.ml/hr)	MRT (hr)	Cl (ml/min)	$t_{1/2}(\alpha)$ (min)	$t_{1/2}$ (β) (hr)	Vd (l)
2m/3f	840	1.5	13	4.0	1.2	1.2

Plasma Protein Binding: Relatively low (8-12%) in all species tested (rat, dog, pig, monkey, man)

Metabolite Profiles:

Urine: 0-24 hr collection.
Chromatographic profiles are similar irrespective of route, dose and sex.
Parent accounts for 50-80% of radioactivity; metabolites are 5-30%.

Bile: 0-6 or 0-12 hr collection.
Parent accounts for ≤5% of radioactivity.
9-11 metabolites are present; 65-70% are polar.

Feces: 0-24 hr collection.
Parent accounts for ≤5% of radioactivity.
76-79% polar metabolites.

D.1.b. Whole body autoradiographic studies with SND 919 CL2Y in rats.

Document #(s):

Upjohn TR 7256-95-018

Sponsor Volume: 1.59

Summary:

After i.v. administration of 1.3 mg/kg [^{14}C]-pramipexole, radioactivity was rapidly distributed. Aside from the gut, the highest tissue concentrations were found in the lacrimal, salivary, and adrenal glands, kidney, pancreas, bone, liver and lung. The significant levels of radioactivity in the small intestine after i.v. administration is indicative of biliary excretion of PPX or its metabolites. Brain levels of radioactivity peaked at 2 hrs, and were detectable up to 6 hrs. At 24 hrs, radioactivity was still detected in liver, kidney, and adrenals.

Two hrs after p.o. administration of 1.3 mg/kg, a similar pattern of distribution was observed, although levels of radioactivity were lower. At 24 hrs, radioactivity was still present in the lacrimal, salivary, adrenal glands, kidney, and liver.

Methods:

Substance administered: [^{14}C]-pramipexole labeled at the of the propyl group; Batch I, 7400 MBq/g (200 μCi/mg)

Dosages/Routes: 1.3 mg/kg (ca. 1.57 MBq/animal) administered i.v. (tail vein) or p.o.

Animals: Male Chbb:THOM Wistar rats, 150-170 g.

Sacrifice times: i.v.: 10 min, 2, 4, 6, 24 hr
p.o.: 30 min, 2, 4, 6, 24 hr

Tissue Preparation: Animals were sacrificed, frozen and sectioned for autoradiography by standard techniques. Autoradiogram exposure time was 7 days. Tissue uptake of radioactivity was determined with a microscope photometer; field sections were 100 μm in diameter. Intensities of light penetration, which decrease with uptake of radioactivity, was scored on a scale of 0-7.

Results:

The following table summarizes the experimental results.

Tab. 1: Photometric analysis of the whole body autoradiograms after i.v. and p.o. administration of SND 919 CL 2 Y
0 = maximum transmission = no radioactivity
7 = minimum transmission = maximum radioactivity

Organ	i.v.					p.o.				
	30'	2 h	4 h	6 h	24 h	30'	2 h	4 h	6 h	24 h
Pancreas	6	4	2	0	0	2	2	0	0	0
Blood	2	1	1	0	0	1	0-1	0	0	0
Brown nuchal fat	4	2	1	0	0	1	2	0	0	0
Contents of large intestine	0	1	7	upto 7	upto 7	0	2	7	upto 7	upto 7
Mucosa of large intestine	4	2	-	0	0	1	0	0	0	0
Contents of small intestine	upto 7	7	upto 7	upto 6	0	upto 7	7	upto 7	upto 7	upto 6
Mucosa of small intestine	5	3	3	0	0	0	0	0	0	0
Fat	1	0	0	0	0	0	0	0	0	0
Brain	3	4	3	1-2	0	0-1	2	1	0-1	0
Urine	7	6	2	1	0	4	4	2	0	0
Skin	3	2	2	1	0	1	2	1	0	0
Heart	4	2	1	0	0	1	1	0	0	0
Testes	2	3	2	2	0	0	2	0	0	0
Bone	5	4	-	0	0	1	-	0	0	0
Liver	5	4-5	5	3	2	3	4	3	3	2
Lung	5	2	1	0	0	1	2	0	0	0
Gastric contents	upto 7	7	7	upto 6	0	7	7	7	7	upto 6
Gastric mucosa	4-7	2	2	2	0	-	0	1	2	0
Spleen	5	4	2	1	0	1	3	0	0	0
Muscle	4-5	2	1	0	0	1	2	0	0	0
Adrenal medulla	7	4	3	1	1	2	3	1	1	0-1
Kidney	6	4	3	1-2	1	2	3	2	1	1
Rib	5	3	1	0	0	1	3	0	0	0
Spinal marrow	3	3	1	0	0	0-1	2	1	0	0
Thyroid	2	1	1	0	0	0-1	2	1	0	0
Salivary glands	6-7	5-6	3-4	2	0	3	4-5	3	2	1
Thymus	4	3	2	0	0	1	3	0	0	0
Lacrimal gland	5	4	3	2	0	2	3	2	1	1
Vertebra	5	4	1	0	0	1	3	0	0	0
Dental germ	-	3	1	0	0	1	2	0	0	0
Intervertebral disks	3	1	0	0	0	0	1	0	0	0

D.1.c. Studies on the placental transfer and on the crossing of the blood-brain barrier of [^{14}C]-SND 919 CL2Y in the rat.

Document #(s):

Upjohn TR 7256-94-103

Sponsor Volume: 1.59

Summary:

[^{14}C]-PPX (1.0 mg/kg) was administered to pregnant Wistar rats by the i.v. or oral routes, and its capacity to penetrate the blood:brain barrier or blood:placental barrier was determined. By either route, PPX and/or its metabolites rapidly crossed both the blood:placental and blood:brain barriers. Concentrations of label tended to be higher in the placenta than in maternal blood or in the fetus. Highest fetal tissue concentrations of radiolabel were detected in the liver. In both dams and fetuses, brain levels are higher than plasma levels for up to 6 hrs postdose.

Methods:

Substance administered: [^{14}C]-pramipexole labeled at the 2-position of the thiazole ring; Batch 7, 7800 MBq/g (210 μCi/mg). Cold substance was Batch II.

Dosages/Routes: 1.0 mg/kg (ca. 1.57 MBq/animal) administered i.v. (tail vein) or p.o.

Animals: 44 pregnant Chbb:THOM Wistar rats

Design: Radioactivity distribution was assessed by tissue analysis with liquid scintillation spectroscopy, and by whole body autoradiography (WBAR). In the tissue analysis studies, animals (n=2 per condition) were administered drug by i.v. or p.o. routes on day 14 or 19 of gestation and sacrificed at for time points (i.v.: 1, 3, 6 or 24 hr; p.o.: 30 min, 3, 6 or 24 hr). For the WBAR study, rats (n=1) were sacrificed at 10 min, 6 or 24 hrs after i.v., and 1, 6 or 24 hrs after p.o. treatments on day 14 or 19 of gestation.

Analysis: WBAR studies were conducted according to standard procedures. Tissue analyses were conducted on the following tissues:

14th day of pregnancy:	blood	-	dam
	plasma	-	dam
	heart	-	dam
	liver	-	dam
	muscle	-	dam
	brain	-	dam
	uterus		
	placenta		(3-4 placentas were pooled as one sample and measured)
	amniotic fluid		
	fetus		(4 fetuses were measured individually per animal)
19th day of pregnancy:	blood	-	dam
	plasma	-	dam
	heart	-	dam
	liver	-	dam
	muscle	-	dam
	brain	-	dam
	uterus		
	placenta		(4 placentas were measured individually per animal)
	amniotic fluid		
	fetus		(4 fetuses were measured individually per animal)
	blood	-	fetus
	liver	-	fetus (livers of 3-4 fetuses)
	fetal tissue		(muscle and bones of the hind limbs)
	fetal brain		

Results:

WBAR Studies:

After intravenous treatment, radioactivity distributed rapidly, and crossed the placental barrier within 10 min. Label was detected in the fetus up to 6 hr postdose. Levels appeared to be higher in the placenta than in the fetus. Low levels were detectable within the placenta and fetus at 24 hrs.

A similar pattern of distribution was observed at 6 and 24 hrs after oral administration.

Isolated Tissue Analyses:

Intravenous studies: Levels of radioactivity appeared to be higher in the placenta than in the fetus on both day 14 and day 19. Maternal blood and liver concentrations were higher than in corresponding fetal tissues. Within the fetus, highest concentrations of radiolabel were detected in liver. Low levels of radioactivity were present in amniotic fluid. Up to six hrs postdose, brain concentrations of radiolabel were higher than blood concentrations in both the dams and fetuses. The calculated half-life of tissue elimination in fetuses is slightly longer than in the dams.

Spectroscopic radioactivity determinations in isolated tissues are summarized in the Tables D.1.c.1-4.

Table ●: Comparison of the concentration values (ng equivalent/g blood or ng equivalents/g organ) in the blood of the dams, in the placentas and in the total fetus after i.v. administration of [^{14}C]-SND 919 CL 2 Y (days 14 and 19 of pregnancy, mean values each of 2 animals)

D.1.c.1

	day 14			day 19		
measuring time	blood dam	placenta	fetus	blood dam	placenta	fetus
10 min	326.16	623.36	406.82	430.20	707.70	287.70
3 h	114.88	255.81	102.99	147.43	433.09	179.64
6 h	74.29	106.37	80.92	81.27	138.92	69.43
24 h	37.71	35.52	23.71	40.28	52.97	29.16

Table ●: Comparison of the concentration values (ng equivalents/g blood) in the maternal blood and in the fetal blood after i.v. administration of [^{14}C]-SND 919 CL 2 Y (day 19 of pregnancy, mean values each of 2 animals)

D.1.c.2.

measuring time	day 19		
	blood dam	blood fetus	ratio blood dam : blood fetus
10 min	430.20	184.76	2.3 : 1
3 h	147.43	103.84	1.4 : 1
6 h	81.27	49.87	1.6 : 1
24 h	40.28	34.37	1.2 : 1

Table [illegible]: Comparison of the concentration values (ng equivalents/g organ) in the livers of the dams and the livers of the fetuses and quotient of the concentrations in the livers and concentration in the blood after i.v. administration of [^{14}C]-SND 919 CL 2 Y
(day 19 of pregnancy, mean values each of 2 animals)

D.1.c.3

measuring time	liver dam	liver fetus	liver dam / blood dam	liver fetus / blood fetus
10 min	3477.98	448.29	8.1	2.4
3 h	1481.78	278.85	10.1	2.7
6 h	787.19	105.39	9.7	2.1
24 h	380.99	82.33	9.4	2.4

Table [illegible]: Ratios of the radioactivity concentrations in the brains and the blood of dams and fetuses after i.v. administration of [^{14}C]-SND 919 CL 2 Y

D.1.C.4.

	time			
day 14 of pregnancy	0.166 h	3 h	6 h	24 h
brain dam / blood dam	1.5	4.5	2.7	0.8
day 19 of pregnancy				
brain dam / blood dam	1.5	2.9	3.1	1.1
brain fetus / blood fetus	1.6	1.9	1.9	1.0

Oral studies: As with the i.v. route, maternal blood and liver concentrations are higher than in corresponding fetal tissues, and the fetal liver contains higher concentrations than other fetal tissues. Also, higher brain levels relative to blood levels of radioactivity were detected in both dams and fetuses.

Data from the oral administration studies are summarized in Tables D.1.c.5-8:

Table [illegible]: Comparison of the concentration values (ng equivalent/g blood or ng equivalents/g organ) in the blood of the dams, in the placentas and in the total fetus after oral administration of [^{14}C]-SND 919 CL 2 Y
(days 14 and 19 of pregnancy, mean values each of 2 animals)

D.1.c.5.

	day 14			day 19		
measuring time	blood dam	placenta	fetus	blood dam	placenta	fetus
1 h	139.58	229.15	145.79	131.39	255.65	114.61
3 h	91.82	192.68	102.81	166.69	354.22	201.78
6 h	98.46	147.70	65.94	148.69	274.94	146.78
24 h	37.91	54.71	33.17	39.61	64.29	38.43

Table [illegible]: Comparison of the concentration values (ng equivalents/g blood) in the blood of the dams and in the blood of the fetuses after oral administration of [^{14}C]-SND 919 CL 2 Y
(day 19 of pregnancy, mean values each of 2 animals)

D.1.c.6.

measuring time	day 19		
	blood dam	blood fetus	ratio blood dam : blood fetus
1 h	131.39	69.33	1.8 : 1
3 h	166.69	114.66	1.4 : 1
6 h	148.69	111.65	1.3 : 1
24 h	39.61	44.49	1 : 1

Table [redacted]: Comparison of the concentration values (ng equivalents/g organ) in the livers of the dams and in the fetal livers, and the quotients of the concentrations in the livers and the concentrations in the blood after oral administration of [^{14}C]-SND 919 CL 2 Y
(day 19 of pregnancy, mean values each of 2 animals)

D.1.c.7.

measuring time	liver dam	liver fetus	liver dam / blood dam	liver fetus / blood fetus
1 h	1773.72	183.52	13.5	2.6
3 h	1648.20	280.52	9.5	2.4
6 h	1305.84	197.75	8.8	1.7
24 h	369.57	74.05	9.3	1.6

Table [redacted]: Ratios of the radioactivity concentrations in the brains and the blood of dams and fetuses after oral administration of [^{14}C]-SND 919 CL 2 Y

D.1.c.8

	time			
day 14 of pregnancy	1 h	3 h	6 h	24 h
brain dam / blood dam	1.8	3.3	2.4	1.7
day 19 of pregnancy				
brain dam / blood dam	1.8	3.5	2.9	1.5
brain fetus / blood fetus	2	1.6	1.1	0.9

D.1.d. Pramipexole: Steady-state concentrations in brain, liquor, and plasma of male rats after oral administration of 0.5 mg/kg (once per day) over 8 days.

Document #(s):

Upjohn TR 7256-95-031

Sponsor Volume: 1.60

Summary:

This study was conducted to determine the steady-state pharmacokinetics of PPX in rats following once daily oral administration of 0.5 mg/kg/day for 8 days. Highest levels of PPX were observed in brain tissue, and occur at later time points than in the plasma or CSF. The half-life of PPX in the three compartments was similar.

Methods:

Dosing Regimen: Oral administration of 0.5 mg/kg PPX (Batch II) once daily for 8 days.

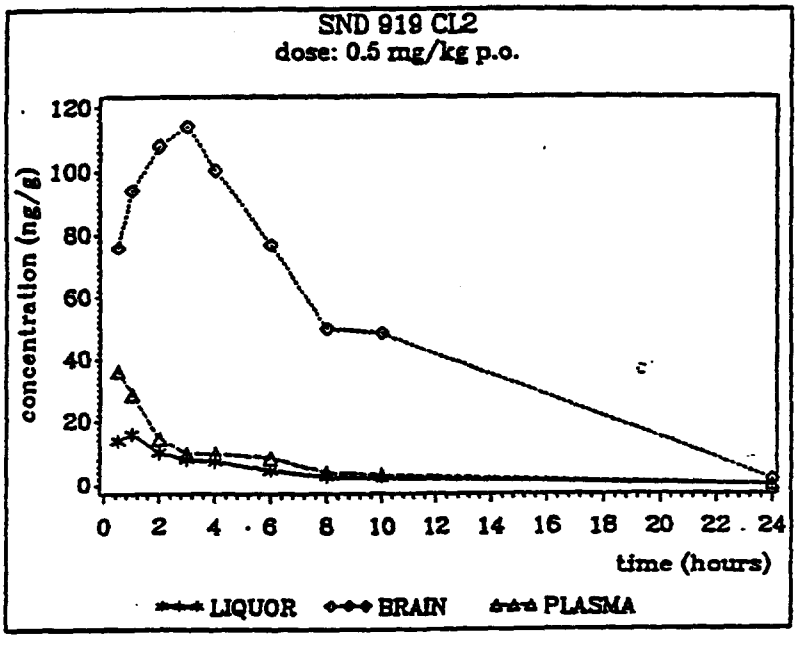
Animals: 35 male Chbb:THOM rats (32 drug, 3 controls), 180 - 200g.

Sample collection: Rats (n=3-4/time point) were anesthetized for collection of brain "liquor", then sacrificed for collection of brain and plasma samples.

Pramipexole measurements: by HPLC-EC after suitable sample preparation.

Results:

The time-course profiles and kinetic parameters for pramipexole in various matrices were as follows:



Tab. D.1.d.1

Kinetic steady state parameters of pramipexole in rats after a multiple oral administration of 0.5 mg/kg
(calculated from geometric means of concentrations in Table 5)

parameter	dimension	brain	liquor	plasma
AUC (0-τ)	ng/ml·h	1131.00	79.24	129.57
AUC ratio (plasma=1)		8.7	0.6	1
half-life	hours	3.29	3.33	3.18
log-lin. regression.*)	hours	6-24	4-10	4-24
MRT_{ss}	hours	6.49	4.87	4.68
peak concentration	ng/ml	113.82	15.89	36.20
time to reach peak	hours	3	1	0.5

*) within the time period given the concentration data were used for the estimation of the terminal half-life ($t_{1/2}$ (λ_z))

D.1.e. Excretion of [^{14}C]-SND 919 CL2 into rat milk after a single oral dose of 0.5 mg/kg.

Document #(s):

Upjohn TR 7256-94-035

Sponsor Volume: 1.56

Summary:

This study determined the excretion of [^{14}C]-PPX and/or its metabolites into rat milk following oral administration of 0.5 mg/kg. Greater levels of radioactivity were detected in milk than in plasma, and the rates of elimination from the two compartments were relatively similar. Most of the radioactivity appeared to be metabolites of pramipexole.

Methods:

Test article: 0.5 mg/kg, p.o. (ca. 30-35 μCi/rat)[^{14}C]-pramipexole labeled at the 2-position of the thiazole ring (Batch 14; 7800 KBq/mg = 210.8 μCi/mg)

Animals: Six nursing female rats (Chbb:THOM, weight 320-390g) with pups (12-14 days old).

Procedure: Pups were weaned 4 hrs before first milking. Samples were collected at 1, 4 and 8 hrs after drug administration (n=2/time point). Lactation was stimulated in the mothers by oxytocin, and milk collected using a vacuum pup (under anesthesia). After milking, blood was collected by exsanguination and a portion was processed to plasma. Radioactivity in the milk, blood, and plasma samples was determined by LSC. A fraction of each sample was also chromatographed for determination of metabolites.

Results:

Levels of radioactivity in the milk were 3-6 times higher than in plasma. The milk:plasma concentration ratio did not change over time suggesting relatively equivalent rates of elimination from the two compartments (Fig. D.1.e.1).

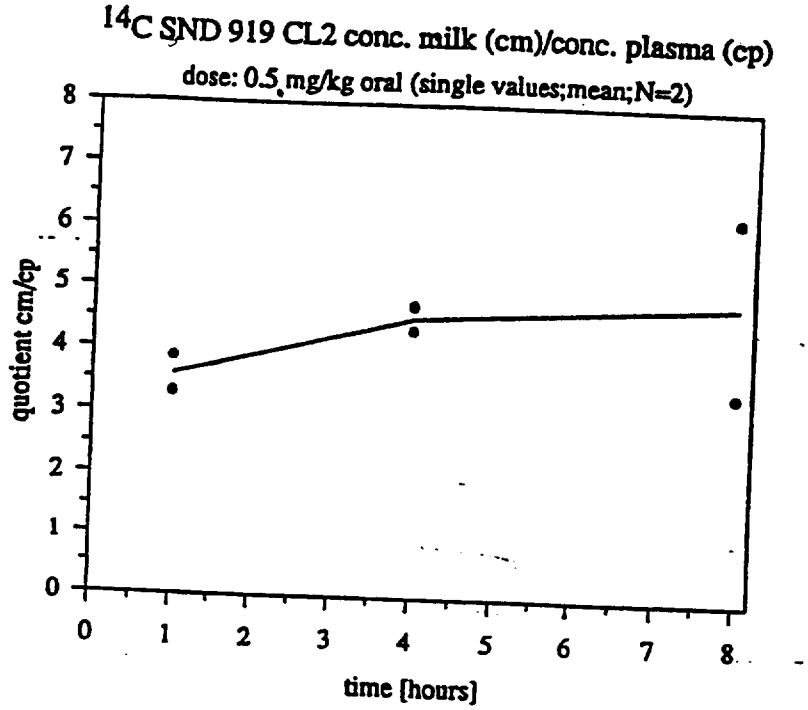
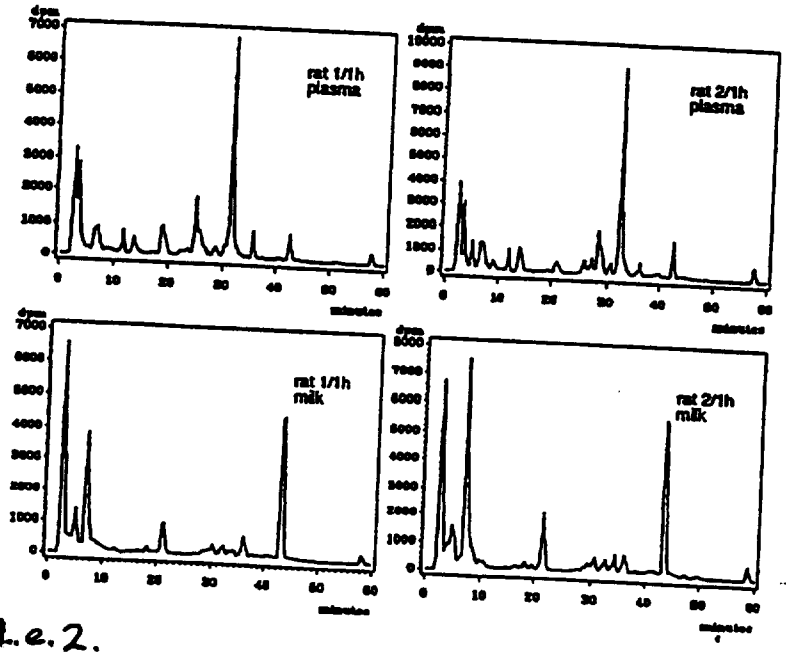


Figure : Distribution of radioactivity between milk and plasma in albino rats after oral D.1.e.1. administration of 0.5 mg/kg [^{14}C]SND 919 CL_2 (• individual values).

Chromatographic analysis indicated that the primary radioactive peak in the plasma extracts is pramipexole. In contrast, very little pramipexole was present in rat milk extracts. The primary chromatographic peak in milk extracts was an apparently lipophilic metabolite. Several smaller polar metabolites were also evident (Fig. D.1.e.2).



D.1.e.2.

Figure : Chromatographic pattern of 14C activity in extracts of plasma and milk at 1 h after oral administration of 0.5 mg/kg [^{14}C]SND 919 CL_2 in 2 albino rats.

D.2 Rabbit Pharmacokinetics

D.2.a. Pramipexole: Pharmacokinetics and metabolism in the rabbit after intravenous and oral administration of a single dose of 1 mg/kg.

Document #(s):

Upjohn TR 7256-94-102

Sponsor Volume: 1.56

Summary:

Plasma concentration and balanced excretion determinations of parent compound and radiolabel were made in rabbits following the intravenous or oral administration of 1 mg/kg [^{14}C]-PPX. Absorption after oral administration was rather slow (Tmax = ca. 6 hrs), but relatively high (F = 68.7). The radiolabel was slowly excreted in urine and feces as indicated by long mean residence times. The degree of metabolism of PPX is more extensive in rabbits than in other species on both a qualitative and quantitative basis.

Methods:

Drug Lot: Batch II (non-radioactive material) used to prepare Batch 7 of [^{14}C]-PPX labeled in the 2-position of the thiazole ring (7.8 MBq/mg).

Dosages: 1 mg/kg/day (prepared in distilled water)

Route of Administration: oral (gavage) or intravenous

Species/Number: 4 female Himalayan rabbits

Mean initial weights/age: ca. 2.8 kg

Parameters measured:

Plasma concs -	pramipexole and [^{14}C]-activity
Excretion -	urine (pramipexole and [^{14}C]-activity) and feces ([^{14}C]-activity) from 0-192 hrs
Metabolic profile -	0-24 and 24-48 hr urine analyzed by HPLC with radiochemical detection

Results:

Plasma concentrations:

PK parameters for 1 mg/kg pramipexole (i.v. or p.o.) in rabbits

	AUC (ng.ml/hr)	Cmax (ng/ml)	MRT (hr)	Cl (ml/min)	Vd (l)	$t_{1/2}$ (hr)	Tmax (hr)	F (%)
i.v.	1243	486.2	8.6	32.2	16.6	12.1		
p.o.	990	64.1	12.0			11.0	6	68.7

* Peak concentration of [^{14}C]-activity after oral dose was 282.8 ng/ml, 4.4-fold higher than parent compound, indicating a high degree of biotransformation.

Excretion Balance (0-192 hrs):

	% Dose (Radioactivity)		
	urine	feces	total
i.v.	74.3	14.7	89.0
p.o.	74.4	14.6	89.0

Metabolic Profiles:

In addition to the parent compound, 7-9 metabolites are present in urine after 24-48 hrs. None were identified in this study, but one appears to be rabbit specific.

D.3 Monkey Pharmacokinetics

D.3.a. SND 919 CL 2 Y: Plasma concentrations and Renal Excretion in Rhesus Monkeys after administration of three single intragastric doses (0.1, 0.5 and 1.0 mg/kg) and one intravenous dose (0.5 mg/kg).

Document #(s):

Upjohn TR 7256-94-042

Sponsor Volume: 1.59

Summary:

Plasma and urine concentrations of PPX in rhesus monkeys were determined after oral (0.1, 0.5 and 1.0 mg/kg) and intravenous (0.5 mg/kg) administrations. PPX was readily absorbed from the gut, had a high bioavailability (79-92%), and demonstrated linear kinetics. Tmax was approximately 2 hrs, and the half-life of elimination from plasma was 3 hr. The plasma concentration:time profile suggested enterohepatic circulation of PPX. The renal clearance of PPX was 4.3 ml/min.kg, and the degree of biotransformation is moderate (p.o.: 35-42%, iv: 48%; based on amount detected as unchanged in urine).

Methods:

Dosages: intragastric: (i.g.) 0.1, 0.5, 1.0 mg/kg PPX (Batch II, in water)
intravenous: 0.5 mg/kg (in saline)

Subjects: 4 rhesus monkeys (2M, 2F)
Average weights: M = 6.8 kg, F = 6.4 kg

Parameters measured:

Plasma concs	-	HPLC-EC
Urine concs	-	HPLC-EC

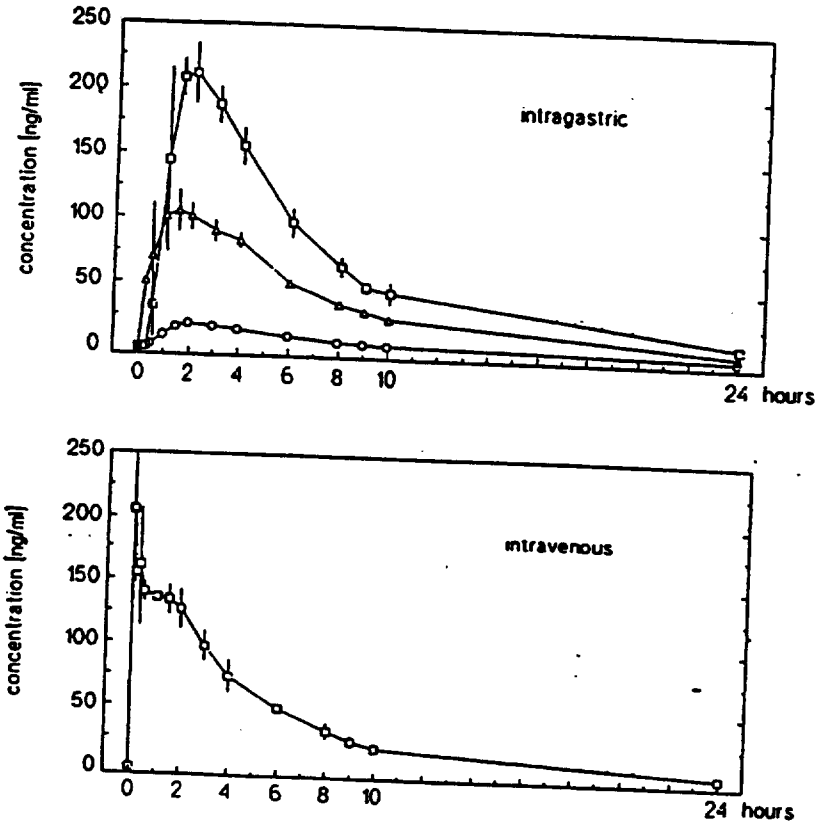
exhalation, excretion balance (urine, feces), blood levels, plasma protein binding (different species), biliary excretion, metabolite profiles (urine, feces).

Results:

Single Dose Pharmacokinetic Parameters in Rhesus Monkeys:

	AUC (ng.ml/hr)	Cmax (ng/ml)	Tmax (hr)	MRT (hr)	Cl (ml/min) (ml/min/kg)	Vd(l) (l/kg)	$t_{1/2}\lambda$ (hr)	F (%)
0.1 i.g.	141.9	19.0	1.9	6.2			3.7	79.2
0.5 i.g.	832.9	106.3	1.6	6.0			3.6	93.0
1.0 i.g.	1519.9	218.6	2.0	6.2			3.3	84.6
1.0 i.v.	886.6			4.8	61.5	17.6	3.0	
					9.4	2.7		

Increases in AUC were approximately dose proportional. The $t_{1/2}$ calculation was based on data from 3-10 hrs postdose, i.g., or 2-10 hrs postdose, i.v. Elimination kinetics were not uniformly monotonic. A small secondary maxima was evident in the plasma concentration:time profile following i.v. administration suggesting enterohepatic recirculation (Fig. D.3.a).



D.3.a:

Fig.: Mean plasma concentrations of pramipexole [ng/ml] ± SD in the rhesus monkey after single dose intragastric: 0.1 (-o-o-), 0.5 (-Δ-Δ-), 1.0 (-□-□-) mg/kg intravenous: 0.5 mg/kg

Renal Excretion:

Cumulative Renal Excretion as Percent Dose

	0-24 hr	0-96 hr
0.1 mg/kg, i.g.	30.8	34.9
0.5 " , i.g.	37.6	42.0
1.0 " , i.g.	37.1	41.7
0.5 " , i.v.	44.1	47.8

Renal Clearance

ml/min
24.6
25.2
27.0
24.5

D.4 Human Pharmacokinetics (provided for comparisons to animal pharmacokinetics)

D.4.a. Pharmacokinetics and metabolism of [^{14}C]-pramipexole after single intravenous and oral doses in healthy volunteers.

Document #(s):

Upjohn TR 7215-94-014

Sponsor Volume: 1.57

Summary:

The single dose pharmacokinetics of orally (0.304 mg) and intravenously (0.099 mg) administered [^{14}C]-PPX were determined by monitoring levels of radiolabel and parent compound over 24 hrs in healthy volunteers. Following oral administration, PPX was quantitatively absorbed from the GI tract (F = ca. 90%), and peak plasma concentrations were achieved in approximately 1 hr. Elimination from the plasma was rather slow $t_{1/2}\gamma$ = 12.8 hrs). Renal excretion is the primary route of elimination (ca. 90%; Cl_{ren} = 409 ml/min), and the major fraction is unchanged parent compound. Plasma protein binding was low (14.1%). The only clinical change were slight decreases in systolic pressure and pulse rate.

Methods:

Drug Lot: Batch VI (non-radioactive)
Radioactive Batch 6 (labeled in the 2-position of thiazole ring)

Subjects: Oral/IV cross-over design with 6 subjects. Washout period of 5 weeks between administrations.

Doses: 0.099 mg [14C]-pramipexole, i.v. (0.812 MBq), or
0.304 mg [14C]-pramipexole, p.o. (2.15 MBq)

Parameters measured:

Plasma concs	-	pramipexole and [^{14}C]-activity over 24 hrs
Ce/Cp	-	erythrocyte/plasma distribution
Excretion balance	-	0-96 or 0-120 hrs
Plasma protein binding	-	
Metabolic profile	-	0-24 and 24-48 hr urine analyzed by HPLC with radiochemical detection

Results:

Human PK parameters for PPX (0.099 mg, i.v., or 0.304 mg, p.o.):

(PK data for the parent compound, pramipexole, were analyzed using both a 3-compartment open model and a moment analysis, but [14C]-activity data were analyzed only by moment analysis. PK parameters for the parent compound were similar by both methods. In order to compare the PK parameters for parent compound and [14C]-activity, the values obtained by moment analysis are presented, except where indicated*).

	AUC (ng.ml/hr)	Cmax (ng/ml)	MRT (hr)	Cl (ml/min)	Vd (l)	$t_{1/2}\lambda$ (hr)	Tmax (hr)	F (%)
PPX (iv)	3.64		16.1	506.2	451	12.6		
[^{14}C] (iv)	4.75		18.8	355.6	395	14.4		
PPX (p.o.)	10.43	0.85*	17.0			12.1	1.0	93.3
[^{14}C] (p.o.)	15.84	0.91*	24.8			17.6	1.0	108.6

PPX was still present in plasma at 24 hrs.
F calculations based on AUCs corrected for dose:

$$(AUC_{po})(0.99/3.04)/AUC_{iv}$$

Absorption/Bioavailability:

Absorption of [14C]-activity and bioavailability of PPX were determined by two methods:

- normalization of AUCs (as described under PK parameters Table), and
- renal excretion

$$\frac{\text{renal excretion } (^{14}C, \text{ oral})}{\text{renal excretion } (^{14}C, \text{ iv})} \times 100$$

By either method, the absorption of radioactivity and bioavailability of PPX were essentially quantitative:

	AUC method	renal excretion method
[^{14}C] absorption	108.6	98.3
PPX bioavailability	93.3	95.6

Erythrocyte/Plasma Distribution:

Most values were in the range of 1.3-2.6, indicating slight enrichment of [^{14}C] activity in erythrocytes.

Excretion:

		% Dose		
		urine	feces	total
[^{14}C] (0-96 hr)	i.v.	89.1	2.0	91.1
	p.o.	87.6	1.6	89.2
Pramipexole (0-24 hr)	i.v.	61.8	nd	
	p.o.	56.3	nd	
Pramipexole (0-inf)	i.v.	81.5	nd	
	p.o.	77.9	nd	

Small amounts of radioactivity were excreted later than 120 hrs.
Mean renal clearance of PPX was 409 ml/min (exceeds GFR).

Plasma Protein Binding: (Assessed at two concentrations of PPX)

[PPX]	% Bound (Range)
2.5 ng/ml	12.8 - 15.8
5.0 "	16.6 - 19.9

Metabolism pattern:

In chromatograms of urines collected after dosing, very little of the radioactivity was NOT PPX (0-24 hrs: 4-9% of dose; 24-48 hrs: 1-2% of dose).

Vital Signs:

Small decreases in systolic blood pressure and heart rate were evident between 1-8 hrs after dosing by either route. No clear changes in ECG, diastolic blood pressure, or laboratory values were observed.

D.4.b. A single dose tolerance and pharmacokinetic study of intravenous pramipexole in healthy male volunteers.

Document #(s):

Upjohn TR 7217-94-014

Sponsor Volume: 1.58

Summary:

This study was primarily a dose tolerance study with limited pharmacokinetic evaluations. PPX (10 - 300 μg) was administered by intravenous infusion and plasma levels were determined over 24 hrs; levels were below the LOD by 24 hrs. Increases in AUC were slightly greater than dose proportional. Cardiovascular changes were increases in pulse rate after doses of 200 and 300 μg, and decreases in diastolic blood pressure after 300 μg. Orthostasis occurred in 1/5 patients after 200 μg, and 2/4 patients after 300 μg. No other drug-related effects on ECG or laboratory parameters were observed.

Methods:

Drug Lot: Batch 802203

Subjects: Healthy, adult male volunteers; three groups of eight subjects.

Group A: 10 and 50 μg
Group B: 25 and 100 μg
Group C: 50, 200 and 300 μg (50 μg administered as a pretest)

Five subjects per dose received active drug, three received placebo.
Drug administered as an i.v. infusion over 20 min.
Washout period was 6 days.

Parameters measured:

Plasma concs - by RIA
Laboratory - hematology, clinical chemistry, urinalysis
Vitals - blood pressure, ECG, etc.

Results:

Pharmacokinetics:

The pharmacokinetic data were not subjected to rigorous analysis.

Dose (μg)	AUC (ng.ml/hr)	C_{20min} (ng/ml)	$t_{1/2}$ (hr)
50	1.01	0.40	
100	2.06	0.64	4.8
200	4.94	1.89	7.9
300	7.35	2.26	6.6

Increases in AUC were generally dose proportional, although slightly nonlinear (slope > 1). Plasma PPX levels were below LOD at 24 hrs. The $t_{1/2}$ calculation was based on plasma levels determinations between 2-8 hrs

Clinical Determinations:

Increases in pulse rate lasting up to 4 hrs occurred following doses of 200 and 300 μg. A decrease in diastolic blood pressure was noted 40 min after 300 μg infusion. Orthostasis occurred in 1/5 patients after 200 μg, and 2/4 patients after 300 μg. The cardiovascular changes suggest a vasodilating effect of pramipexole. No significant drug-related effects on ECG or laboratory determinations were observed.

D.5 Multiple Species Pharmacokinetic Studies

D.5.a. Balanced excretion studies and metabolic profile following oral administration of [14C]-SND 919 CL2Y to the mouse, rat, rabbit, dog, monkey and pig.

Document #(s):

Upjohn TR 7256-94-036

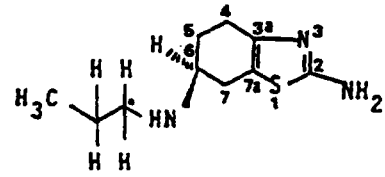
Sponsor Volume: 1.59

Summary:

The excretion and metabolism of [^{14}C]-PPX were evaluated in several species following oral administration. In general between 50-80% of administered label was recovered in urine and 5-30% in feces. The urinary metabolic profile in mouse, rat, dog, monkey and pig were relatively similar on both a quantitative and qualitative basis. The rabbit had the highest proportion of radioactive metabolites, and a species-specific polar metabolite.

Methods:

Substance administered: [^{14}C]-PPX labeled at C1 of the propyl group (Batch 2) or the 2-position of the thiazole ring (Batch 3). Batch 2 was used in all studies except in the rabbit study.



x 2 HCl

$C_{10}H_{17}N_3S$ + 2 HCl

* = labelling with ^{14}C

Molecular weight: 284.25 (base)

357.17 (dihydrochloride)

Parameters measured:

Excretion balance (urine, feces) - collect samples at 24 hr intervals for 96 hrs (rat), 168 hrs (mouse, dog, monkey, pig), or 192 hrs (rabbit). Analyze for radioactivity by liquid scintillation spectroscopy.

Metabolic profile - analyzed 0-24 hr urine samples by HPLC with radiometric analysis

Animals:

Species	n (sex)	weight (ca.)	dose (mg/kg, ca.)	dose (MBq, ca.)
mouse	10M, 15F	22 g	0.5	0.09
rat	2M, 2F/dose	208-232 g	0.01, 0.1, 1.4, 10.8 79.1	0.02 - 0.21
rabbit	2M, 2F	2.5 kg	0.5	3.44
dog	4F	14.0 - 16.1 kg	0.1 - 0.5*	2.27 - 10.75*
monkey	2M, 2F	10.3 - 11.5 kg	0.5	12.95
minipig	2M, 2F	8.0 - 9.5	0.5	9.59

*variation in dog dose due to emesis

Results:

Excretion balance:

Tab. ●: Mean balances of excretion in % of dose after oral administration
D.S.a.1 of [^{14}C]-SND 919 CL 2 Y in 6 animal species

species	N	mg/kg	collection period [h]	urine	feces	sum
mouse	25	0,6	0 - 168	68,42	27,79	96,21
rat	4	0,01	0 - 96	51,87	28,71	80,58
"	4	0,1	"	64,78	38,26	103,04
"	4	1,4	"	48,16	41,15	89,31
"	4	10,8	"	52,14	28,29	80,43
"	4	79,1	"	43,61	25,81	69,42
rabbit	4	0,6	0 - 192	79,25	12,88	92,13
dog*)	4	0,1 - 0,5	0 - 168	60 - 87	1,5 - 5,6	65,4 - 88,3
monkey	4	0,5	0 - 168	69,07	8,43	77,5
minipig	4	0,5	0 - 168	58,88	12,72	71,5

*)strong emesis in 3 out of 4 animals

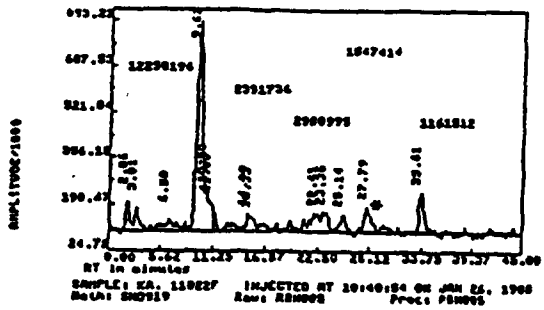
The sponsor suggests that adsorption of [^{14}C]-material to surfaces may contribute to low recovery. The fact that the rabbit studies were conducted with material labeled at a different (more metabolically stable) position, and 3 of 4 dogs experienced emesis, hinders species comparisons. In general, 50-80% of material was eliminated in the urine, and 5-30% was excreted in the feces.

Metabolic Profile:

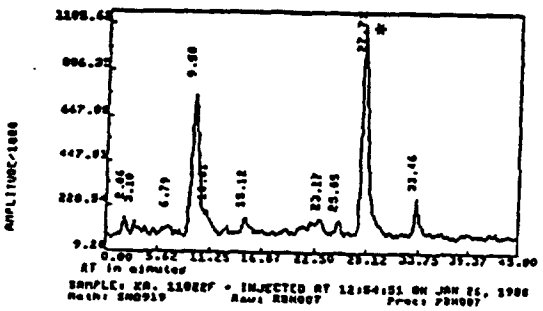
Generally similar chromatographic profiles are obtained with 0-24 hr urine specimens from the rat, mouse, dog, minipig, and monkey in that a primary peak, identified as the parent compound, and several (5-8) minor peaks are present. However, the major peak in the rat sample elutes approximately 3 min after the major peaks in samples from other species. The sponsor did not indicate how the major peak was identified as pramipexole, or the reason for this discrepancy in elution times for the major peaks.

The chromatograms of the rabbit 0-24 hr urine samples were markedly different from other species examined (e.g. Fig. D.5.a.1; comparison with rat). The largest peak in most of the rabbit chromatograms is not PPX, but appeared much earlier in the elution profile (9-10 min). In addition, numerous smaller peaks were present in these chromatograms. The variation in the position of the radiolabel on the PPX moiety (i.e., ring-labeled material used in the rabbit studies versus side-chain-labeled material in other species) did not appear to contribute to the differences in metabolic profile.

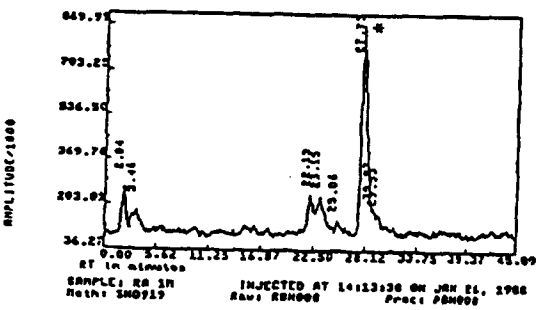
Fig. D.5.a.1.



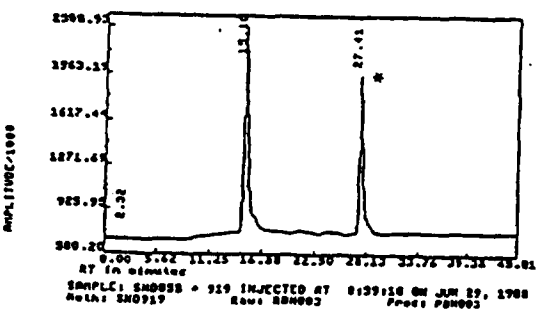
rabbit: No. 11022f
dose: 0.6 mg/kg po



rabbit: No. 11022f
dose: 0.6 mg/kg po
spiked with 14000 dpm SND 919 CL 2 Y-14



rat: 1m
dose: 0.5 mg/kg iv
(exhalation experiment with batch no. 3 [2])
0 - 24 hour urine, $3 \cdot 10^4$ dpm injected



chromatographic separation of SND 855 BS (depropyl derivative of SND 919) and SND 919 CL 2 Y
detection: UV, 254 nm

Fig. 8: Pattern of 14C activity in 0 - 24 hour urines of rabbit (original and spiked) and rat after administration of SND 919 CL 2 (14C label in position 2 of thiazole ring) and chromatogram of reference substances (SND 855, SND 919)

D.5.b. Studies on the metabolism of pramipexole including experiments to detect a potential metabolic inversion at the optical active center of the molecule.

Document #(s):

Upjohn TR 7256-95-057

Sponsor Volume: 1.60

Summary:

These studies were conducted to chromatographically separate and purify pramipexole metabolites in rat and rabbit urine, and determine the propensity for chiral inversion of PPX in rat and human.

Methods:

Substance administered: [^{14}C]-pramipexole (batch and position of label not identified)

Animals/Dosing: according to the scheme:

running no.	species	subjects N	treatment dose	regimen	route	MBq/subject
1	rat	3	12 mg/kg	single dose	oral	1.6737
2	rat	2	0.5 mg/kg	single dose	oral	0.743
"	"	2	"	"	"	0.743
3	rabbit	1	1 mg/kg	single dose	oral	3.66
4	rabbit	1	1 mg/kg	single dose	oral	13.16
5	man *) (male,subj. 2)	1	1.5 mg t.i.d.	steady state	oral	—
"	man *) (female, subj. 9)	1	1.5 mg t.i.d.	steady state	oral	—

*) samples from study M/2730/0047, ref. [6]

Note: the dose in rabbit study is in conflict with the dose stated in the text (0.5 mg/kg)

Experimental Procedures: Samples were subjected to appropriate extraction techniques then analyzed by various methods for metabolite identification (Ion spray MS, GC-MS, HPLC-GC/MS). Enantioselective chromatographic techniques were used to determine the occurrence of chiral inversion from the (6S)-(-) configuration to the (6R)-(+) configuration.

Results:

Metabolite Identification:

Rabbit urine: 6 chromatographic peaks were separated and tentatively identified.

M1	-	may be a labile conjugate
M2	-	N-dealkylated metabolite
M3,M4	-	hydroxylated metabolites (4 and 5 position of the thiazole ring)
M5	-	parent compound
M6	-	glucuronic acid conjugate

Rat urine: 2 chromatographic peaks were separated and tentatively identified.

M2	-	N-dealkylated metabolite
M3,M4	-	hydroxylated metabolites (4 and 5 position of the thiazole ring)

The "species-specific" polar metabolite suggested in the preceding study was identified as M1. The proportion of total metabolites, M1, and PPX in rat and rabbit urine were as follows:

The proportions of total metabolites, M1 and parent compound in the urines used for metabolite isolation were in % of 14C activity registered:

species	figure	Total metabolites	Metabolite M1	Pramipexole
rabbit	1	70.5	12.4	29.5
rabbit	3	96.1	42.8	3.9
rat	4	45.8-49.6	2.3-4.6	50.4-54.2

The proposed metabolic pathways are shown in Fig. D.5.b.1.

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Chiral Inversion Studies:

In rat and human urine, very minor peaks that coeluted with the (6R)-(+) enantiomer of pramipexole were detected (≤ 3% total peak area; Tab. D.5.b.1).

Table ● D.5.b.1

Evaluation of data from stereoselective chromatography of extracts of rat urines

Estimation of apparent SND 919 R(+) concentration

measured/calculated:	dimension	rat no1	rat no.2	rat no. 3
concentration pramipexole	µg/ml	17.935	15.391	41.655
	%	100	100	100
R(+) region standard (background)	dpm/region	484	484	484
R(+) region in vivo urine	dpm/region	685	427	761
R(+) region (net)	dpm/region	201	0	277
S(-) region (no background correction possible)	dpm/region	53761	44070	65153
sum: R(+) + S(-)	dpm/2 regions	53962	44070	65430
apparent SND 919 R(+)/R(+) region *)	ng/region	4.8	0	6.6
apparent SND 919 R(+)/ml urine	ng/ml	66.8	0	176
apparent SND 919 R(+) as % of pramipexole concentration	%	0.4	0	0.4

*) specific activity: 42.371 dpm/ng ; f=0.0236 ng/dpm

Table ●

Stereoselective separation of extracts from human urine after oral steady state administration of 1.5 mg t.i.d. pramipexole (SND 919 S(-) CL2)

subject/ gender	fraction [hours]	pramipexole [ng/ml]	region1 SND 919 R(+)	region2 SND 919 S(-)	ratio [%]
2 (male)	0-4	1860	3962	234497	1.7
	4-8	1270	3273	169776	1.9
	8-12	472	1598	67211	2.4
*intercept *)*	*8-12*	*472*	*491 *)*	*76575 *)*	*0.6*
9 (female)	0-4	899	3619	122147	3.0
	4-8	551	2188	76818	2.9
	8-12	811	1080	119556	0.9
intercept)*	*8-12*	*811*	*390 *)*	*132950 *)*	*0.2*

*)The areas given result from the the linear regression of peak area data of the spiking experiments in Figure 20 (peak area ratio vs. ng/ml SND919 R(+) added). They were calculated using the intercept of the regression line and a mean value (N=5 injections) of the SND 919 S(-) peak areas

ischemia in gerbils or high doses of methamphetamine to mice. PPX also prevented the loss of TH-positive cells due to micromolar concentrations of L-DOPA in primary cultures of rostral mesencephalic tegmentum cells. While these studies are interesting from a mechanistic standpoint and may be considered preliminary evidence of neuroprotection, they are not sufficient to support the sponsor's proposed labeling claim that pramipexole "reduces dopamine-induced neuronal degeneration."

Safety Pharmacology

The safety pharmacology studies of PPX revealed relatively few safety concerns. The most significant issue arose from early clinical studies where hypotensive effects of PPX were identified. Because of concerns that combining PPX with other PD drugs may potentiate this effect, the cardiovascular effects of PPX in combination with Sinemet and Eldepryl were evaluated in rhesus monkeys. The modest bradycardia and blood pressures decreases produced by PPX (0.05 mg/kg, p.o.) were not potentiated by either Sinemet (100 mg/kg L-DOPA/10 mg/kg carbidopa, p.o.) or Eldepryl (0.2 mg/kg, p.o.). Other notable effects of PPX in safety studies were sedation in monkeys, sleep suppression in cats and rats, and emesis in dogs. PPX doses of 0.005-0.025 mg/kg lowered basal plasma prolactin levels in male rats. Similar effects of PPX were demonstrated as part of the chronic toxicology studies because of the speculated role of prolactin inhibition in some of the observed histopathological and reproductive changes.

Toxicology

Acute Studies

The acute toxicity of PPX was evaluated in mice, rats and dogs following oral and intravenous administration. Animals were observed for 14 days. In rodents, signs of toxicity were exophthalmus, piloerection, irregular breathing, and tremors/convulsions. The ratios of LD_{50}s by the p.o. and i.v. routes were approximately 10 in mice (p.o. = 1700, i.v. = 169) and greater than four in rats (p.o. > 800, i.v. = 210). The most prominent toxicity in dogs was emesis at doses of 0.001-0.01 mg/kg, i.v., and 0.001-1 mg/kg, p.o.

Chronic Studies

The toxicity and toxicokinetics of PPX administration for one year were evaluated in rats at doses of 0, 0.5, 3.0 and 15.0 mg/kg. The lowest test dose resulted in slight behavioral activation and decreased body weight gain in both sexes. Decreases in cholesterol and triglycerides occurred at all doses in females. Other sporadic clinical chemistry changes were modest elevations in transaminases, alkaline phosphatase and urea, and decreases in serum potassium at the mid and high doses; these were generally more frequent in females than in males. Hematological changes were slight thrombocytopenia (MD, HD) and slight-to-moderate increases in the granulocyte/lymphocyte ratio in females. Ovarian weights were increased at all dosage levels, and enlarged corpora lutea were observed at the mid and high

dose. Histopathological changes in the uteri (dilatation, serous contents, pyometra) and changes in the glandular epithelial pattern of mammary tissue were also evident in MDF and HDF. The female reproductive changes were attributed to inhibition of prolactin secretion. Eleven animals (4 controls, 7 PPX-treated) were identified with tumors, none of which could be clearly attributed to PPX treatment. The decreases in serum cholesterol, shift in granulocyte/lymphocyte ratios, and ovarian changes were consistent with observations in previous subchronic rat studies (5-week i.v., and 13-week oral studies reviewed under IND 34,850). Rat plasma concentrations at the "No Toxic Effect" dose level of 0.5 mg/kg are near the anticipated steady-state Cmax in humans (5.5-7.2 ng/ml).

The toxicity and toxicokinetics of orally administered PPX (0, 0.1, 0.5 and 2.0 mg/kg/day) for one year were evaluated in rhesus monkeys. Prominent clinical signs of toxicity were behavioral changes (agitation, jumping, swinging, gripping) that diminished over the course of treatment. Body weight and food consumption were not affected by PPX. Dosing was limited to 2.0 mg/kg because of drug-induced injurious behavior in the animals during the early phase of the study. The most significant drug-related effect was bradycardia with increased R-R and Q-T intervals recorded at various times during the study; however, this effect was only observed in mid-dose males. No treatment-related hematological or urinary changes were evident, and only some modest changes in clinical chemistry occurred. Organ weights were not altered and no histopathological findings were attributed to PPX. One death, a low-dose female, occurred late in the study and did not appear to be drug-related. Plasma concentrations of PPX were approximately 2- (low test dose) to 80-fold (high test dose) higher than the anticipated human steady-state Cmax. Thus, oral administration of 0.1-2.0 mg/kg/day PPX for 52 weeks does not produce significant pathologic effects in monkeys. PPX was also devoid of toxicities in 4-week intravenous toxicity study at doses up to 0.6 mg/kg.

Reproductive Toxicology

In a rat Segment I study, PPX (0.1-2.5 mg/kg, p.o.) was given to males for 70 days prior to mating, and females for 14 days prior to mating through gestation (C-section on day 22) or weaning (spontaneous delivery group). The most notable reproductive toxicities in the HD dams were prolongation of estrus in HDF, and reductions in the number of implantations, pregnant females and successful deliveries. Body weight development was impaired in pups of MD and HD dams, possibly because of reduced suckling opportunities or inhibition of prolactin secretion by PPX. Teratogenic effects of pramipexole were not evident, although the data were limited by the low number of evaluable pups. A follow-up Segment I study was conducted which identified PPX-treated females rather than males as the source of infertility. These findings were expected since PPX, like other dopamine agonists, inhibits secretion of prolactin which is necessary for the maintenance of rat pregnancy.

In the rat Segment II study, PPX (0.1-1.5 mg/kg, p.o.) was administered from day 7 to 16 of gestation. Dams were either sacrificed on day 22 for delivery of pups by Caesarean section, or allowed to raise the pups to weaning (21 days). Significant embryolethality

occurred with the high dose as only 7 of 32 pregnant females had viable offspring. The other 25 pregnancies were classified as complete "early" resorptions. Abnormalities identified in fetuses of drug-treated dams included one case each of anal atresia (LD), sirenomelia and gastroschisis (LD), and a cleft vertebra (MD). Teratology information from the high-dose group was limited by the low number of evaluable pups. Body weight development was not impaired in this study, which suggests that PPX administration during lactation is responsible for this effect.

In contrast to the rat Segment II study, oral administration of PPX (0.1, 1.0, 10 mg/kg) to rabbits from day 6 to 18 of gestation did not produce any embryotoxic, fetotoxic or teratogenic effects.

In a Segment III study, oral administration of PPX (0, 0.1, 0.5 and 1.5 mg/kg/day) to female rats from day 16 of gestation to day 21 of the rearing phase (lactation) caused an impairment of pup development as indicated by a decreased body weight gain during the lactation/rearing phase. As in the Segment I study, reduced suckling opportunities or impaired milk production in the dams may underlie this effect. Fertility of the F_1 offspring was not impaired. No other remarkable drug-related changes in litter parameters or at necropsy of the pups were evident.

Taken together, these data suggest that PPX has toxicological consequences on reproductive and developmental parameters in rats but not rabbits. The prolongation of estrus, impairment of female fertility and early resorptions are likely related to the D_2 receptor-mediated suppression of prolactin, a hormone necessary for the maintenance of rat pregnancy, and may not necessarily be a great human concern. However, a significant consequence of this effect is a low number of evaluable pups from dams treated with the highest dose of PPX (2.5 mg/kg in Segment I study, 1.5 mg/kg in Segment II study), which drastically limits conclusions on the teratogenicity of PPX. Although the Segment III study produced a relatively large sample of pups with no drug-related effects on skeletal, visceral or external abnormalities, these animals were not exposed to drug until after the critical period of organogenesis. Since some relatively rare fetal abnormalities were present in PPX-treated pups in the Segment I and II studies (anal atresia, sireniform malformation and gastroschisis, and cleft vertebra), teratogenic effects of PPX cannot be discounted in the absence of data from a larger pup population.

The impairment of body weight development in the Segment III study is clearly a PPX-related effect. The sponsor suggests as a basis for this finding that pups are inadequately nursed because of behavioral activation in the dams. Inadequate milk production due to insufficient prolactin levels in the dams is an alternative possibility. However, a direct effect of PPX on pup development cannot be discounted.

Genotoxicity

PPX was tested for mutagenic effects in four standard *in vitro* assays (Ames test, SHE cell transformation assay, chromosomal aberrations in CHO cells, V79 gene mutation assay) and the *in vivo* mouse micronucleus test. The testing procedures were generally adequate; where deficiencies existed (i.e., SHE cell assay, micronucleus test), further testing will not be recommended.

No reproducible mutagenic responses to PPX were observed. The only positive signal in any assay was a small, non-reproducible clastogenic effect with S9 activation at the highest test dose (3300 µg/ml) in the CHO chromosomal aberration study.

Carcinogenicity

In the two-year mouse study, no neoplastic and few non-neoplastic lesions were associated with PPX administration (0.3, 2.0 and 10 mg/kg/day in diet). However, the validity of this study as an assessment of the tumorigenicity of PPX is questionable because of the marked impairment of body weight deveolopment (37-45%) at the intermediate and high test dosages. Plasma exposures at the lowest test level (equal to or less than expected human exposures) were not considered adequate for valid risk assessment.

The rate of premature decedents was higher in PPX-treated animals, primarily because of unscheduled sacrifices due to eczema; a sufficent number of survivors remained at termination. Drug-related clinical observations were increased spontaneous activity at the mid and high dose levels. No statistically significant increases or trends for increases in the incidence of neoplastic lesions in drug-treated animals were apparent according to the sponsor's analysis. A pooled analysis of all mesenchymal/epithelial uterine neoplasms was not presented, although a possible dose-related positive trend was noted (controls: 10%; LD: 10%; MD: 14%; HD: 16%). Unusual histopathological findings in PPX-treated animals were fibro-osseous proliferative lesions in the femurs of females (all dosage groups). This lesion occurred at a relatively high rate in control females (28%), but approximately doubled in incidence in treated animals (56-62; similar at the three dosage levels). This type of lesion is known to occur spontaneously in female mice. However, administration of the prostaglandin E analogue misoprostol has also been associated with this lesion in mice, and the issue is addressed in the labeling of that product. A hormonal basis for this effect is suggested, but no experimental evidence was presented. A similar lesion was not observed in long-term studies of PPX in rats or monkeys.

As in the mouse study, a marked impairment of body weight gain in MDF and HDF prevents conclusions regarding the tumorigenicity of PPX (0.3, 2.0 and 8.0 mg/kg/day) in female rats. Body weight gain reductions in males were less than 10%. Mortality occurred in all treatment groups at various times during the study, but no clear drug relationship was evident. An adequate number of survivors remained at termination. The only tumors found at a statistically significant greater incidence in PPX-treated animals were Leydig cell adenomas in MD (44%) and HD (44%) males. A relatively high incidence of these tumors also occurred in control animals (Group 0: 26%, Group 4: 18%). Leydig cell hyperplasia was also increased in MD and HD rats. Changes in females were enlarged corpora lutea (HD

rats), uterine lesions and hemorrhage (MD and HD), alterations in mammary gland patterns from female-like to male/female-like (MD and HD), and diffuse hepatocellular fatty changes (MD and HD). Retinal degeneration occurred in MD and HD males and females.

The proposed basis for the neoplastic and nonneoplastic lesions in reproductive and endocrine structures is PPX-induced inhibition of prolactin secretion, which was demonstrated at week 60 and 69 (ca. 10-fold decrease in females, 100-fold decrease in males). Reductions in serum prolactin in males purportedly trigger an elevation in LH production and release leading to the Leydig cell adenomas and hyperplasia. Direct evidence for a PPX effect on serum LH was not provided. Nonetheless, the finding is suggested to be of questionable relevance to humans given the high background incidence of this tumor in rats (as demonstrated in this experiment), and since several widely-used compounds also produce Leydig cell tumors in rats but are not known to do so in humans (cimetidine, hydralazine, vidarabine, israpidine). The female reproductive changes (corpora lutea enlargement, uterine lesions, and mammary gland pattern changes) were also observed in the one year rat study. The sponsor contends that the potential human relevance of these findings is questionable because of the divergent influences of prolactin on female hormone levels in rats and humans. However, the effect of PPX on estrogen and progesterone was not shown in any study. Thus, the proposed mechanisms for the pathological changes in rodents are plausible and supported in the literature by studies with other dopamine agonists, but direct support for these mechanisms specifically in the case of PPX is not present in this submission.

Retinal degeneration was the most notable non-neoplastic finding of this study. Follow-up studies to address this issue were reviewed under IND 34850, and were independently reviewed by an FDA consultant (Dr. Tim O'Neill). Briefly, the sponsor has provided evidence that treatment with PPX (25 mg/kg, p.o.) for 13 weeks in combination with constant light exposure produces retinal degeneration in non-pigmented albino rats, but not in pigmented Brown-Norway rats. Retinal degeneration was not observed after long-term treatment of minipigs and monkeys. Thus, pigmentation may protect against the retinotoxic effects of PPX. The proposed mechanism for this effect is inhibition of retinal disk-shedding, which occurs universally in vertebrates. This leaves open the possibility that a similar effect could occur in humans.

Pharmacokinetics/ADME

The absorption, distribution, metabolism, and excretion of pramipexole were evaluated in several species (mouse, rat, rabbit, monkey, human, dog, and minipig) following oral and intravenous administration of single or multiple doses. Only the single dose pharmacokinetic studies conducted in species used for animal toxicology (rat, monkey, rabbit) studies are reviewed here. Human studies are included for comparitive purposes. Toxicokinetic studies were reviewed as part of the main study review.

The analytical methodologies included the use of radiolabeled [^{14}C]-PPX, HPLC with electrochemical detection, radioimmunoassay, or GC with chemical ionization mass spectroscopy. The former two methods were used for the majority of analyses, and provided adequate sensitivity.

In most test species, PPX is absorbed rapidly and nearly completely following oral administration. Peak plasma concentrations are generally reached within 2 hrs of treatment, except for the rabbit (tmax = 6 hrs.). The calculated bioavailabilities in all species exceeded 69%, and in humans this value was greater than 90%. After intravenous administration, the systemic clearance of PPX was high, and terminal half-lives were relatively short (<4 hrs), except for rabbits and humans ($t_{1/2}\gamma$= 12-13 hr). The excretion and metabolism of [^{14}C]-PPX were evaluated in several species following oral administration. In general, between 50-80% of administered label was recovered in urine and 5-30% in feces. Renal excretion of PPX is the primary route of elimination in humans (ca. 90%; Cl_{ren} = 409 ml/min). Except for the rabbit, the major urinary fraction is unchanged parent compound. Significant biliary excretion of radioactivity was detected in cannulated rats. The plasma concentration:time profile of PPX in monkeys suggested enterohepatic circulation of the drug. The degree of biotransformation is low to moderate in most species, and the urinary metabolic profile in mouse, rat, dog, monkey and pig were relatively similar. Biotransformation in rabbits differed from the other species on both a qualitative and quantitative basis. The rabbit had the highest proportion of radioactive metabolites, and a species-specific polar metabolite. Plasma protein binding of PPX was relatively low in all species (dog, pig, monkey, man). PPX did not undergo chiral inversion *in vivo* in rats or humans.

The tissue distribution of PPX was evaluated in rat. A similar pattern was observed following i.v. or oral administration with highest concentrations detected in the lacrimal, salivary, and adrenal glands, kidney, pancreas, bone, liver and lung. At 24 hrs, radioactivity was still present in liver, kidney, and adrenals. Brain levels of radioactivity peaked at 2 hrs after i.v. PPX, and were detectable for up to 6 hrs. In a steady-state pharmacokinetic study of PPX, the highest levels of PPX were observed in brain tissue when compared to plasma and CSF. In a study of pregnant Wistar rats, [^{14}C]-PPX and/or its metabolites rapidly crossed the blood:placental and blood:brain barriers after i.v. or oral administration (1.0 mg/kg). PPX Concentrations of label tended to be higher in the placenta than in maternal blood or in the fetus. Highest fetal tissue concentrations of radiolabel were detected in the liver. In both dams and fetuses, brain levels were higher than plasma levels for up to 6 hrs postdose. In lactating rats, [^{14}C]-PPX and/or its metabolites were excreted into rat milk following oral administration of 0.5 mg/kg; higher levels of radioactivity were detected in milk than in plasma. Most of the radioactivity appeared to be metabolites of pramipexole.

EVALUATION

The following issues were identified in nonclinical studies as pertinent to the human use and labeling of pramipexole:

1. Carcinogenicity/Mutagenicity:

The carcinogenicity study in mice cannot be considered adequate for risk assessment purposes because of the marked impairment of body weight development (37-45%) at the intermediate (2.0 mg/kg/day) and high (10.0 mg/kg/day) dose levels, and inadequate plasma levels at the lowest test dose (0.3 mg/kg/day). Because of the potent effects of PPX on body weight development, it is likely that similar difficulties with study interpretation would be encountered at doses levels between 0.3 and 2.0 mg/kg. Thus, additional studies will not be recommended. The Carcinogenicity Assessment Committee will be consulted for a resolution.

A similar problem was encountered in the carcinogenicity study of female rats where body weight gain was reduced by 22-28% at the intermediate and high dose levels. In males, which received adequate exposures based on toxicity and plasma level determinations, the only tumor that occurred at clearly higher incidence in PPX-treated animals were Leydig cell adenomas (CON: 22%, 0.3 mg/kg: 34%, 2 mg/kg: 44%, 10 mg/kg: 44%). PPX did not appear to reduce the latency of tumor appearance. Because of the high background incidence of this tumor type in rats, and the possibility that species-specific hormonal mechanisms may be involved in their appearance, the significance of these findings in humans is questionable. The sponsor has included a description of the findings in the proposed labeling, which is an acceptable means of addressing this issue.

PPX did not cause significant mutagenicity in an appropriate test battery at acceptable concentrations.

2. Reproductive Toxicology

The reproductive toxicology studies do not adequately support the sponsor's proposed labeling of PPX in Pregnancy Category B. Three major concerns arose from the studies that are incongruent with the proposed labeling statements:

a. PPX is clearly embryotoxic in rats at doses of 1.5-2.5 mg/kg/day

b. Because of embryotoxicity, teratology information is severely limited by the low number of evaluable pups from HD dams

c. A developmental parameter, body weight gain, was significantly impaired in pups from HD dams in both Segment I and III studies

The data that forms the basis for statements a & b can be summarized as follows:

		# Dams w/ Viable Pups		# Viable Pups/Group	
Study	Delivery	Other Groups	HD Group	Other Groups	HD Group
Seg I[a]	C-Section Spontaneous	35/36 34/34	1/12 5/12	146-174 158-160	10 75
Seg I[b]	C-Section	46/48	6/48	308-330	31-53
Seg II	C-Section Spontaneous	58/72 32/36	4/24 3/11	222-250 133-138	51 39

Other Groups = controls, LD and MD combined; [a] = initial study, [b] = follow-up study

The impairment of rat pregnancy (i.e., low number of implantations, high number of early resorptions) by 1.5-2.5 mg/kg/day PPX was predictable based on the pharmacological effect of PPX as a dopamine agonist. The sponsor has demonstrated that PPX, like other dopamine agonists, inhibits prolactin secretion in rats. Prolactin is well-established as a factor necessary for the maintenance of rat pregnancy. In fact, dopaminergic inhibition of prolactin secretion is the basis for the proposed ICH guidelines stating that **the rat is an inappropriate model for reproductive toxicology studies of dopamine agonists.** Thus, the reproductive toxicology studies could theoretically be considered deficient since it is comprised of only of one Segment II study in a single "appropriate" species, the rabbit. The rabbit is also problematic since it is unique among all species with regard to pramipexole pharmacokinetics. Although the reproductive impairments in the rat were expected, the data cannot be completely disregarded because of design flaws on the part of the sponsor. The rat studies clearly demonstrated impaired fertility and harm to the fetuses, and thus the drug should be placed in Pregnancy category C according to CFR 21, Part 201.57.

The limitations on the teratogenicity study which arose as a consequence of embryolethality should also be mentioned in labeling, particularly in light of the occurrence of some rather rare malformations in fetuses of the Segment II study (LD: one case of atresia ani, one case of sirenomelia and gastroschisis; MD: one case of cleft vertebra), which may also merit a labeling statement.

(Note: The background incidence of cleft vertebra varies markedly depending the type of affected vertebra. Fetal incidences are 0.638% for cleft thoracic vertebra, and 0.033% for cleft lumbar vertebra -).

Body weight development was significantly impaired in pups from MD and HD dams in the Segment III study, which is not consistent with the sponsor's labeling statement that pups from PPX-treated dams develop normally. Body weight development in pups from HD dams in the Segment I study also appeared reduced, but could not be statistically evaluated because of the low pup number. A slight (insignificant) delay in eye-opening was also observed in the Segment I study. The sponsor's assertion that this impairment of body weight development is due to a drug

effect in the dam, and not a direct effect on pup development is plausible, and may be correct, but no experimental support is provided. The sponsor suggests that the basis for this finding is that PPX stimulates the dams and thereby reduces suckling opportunities by the pups; inhibition of lactation is another possibility. Irrespective of the mechanism, the question of whether the drug is affecting the dams or the pups could be addressed in a cross-fostering study. This study will not be required for approval, but until evidence is presented that argues against a direct effect of PPX on pup development, the labeling should accurately reflect the submitted findings.

Although the sponsor does not suggest inhibition of lactation as a basis for impaired pup development, the label states that PPX decreased lactation in rats. No reports addressing this effect were found in the submission. The sponsor needs to identify the pertinent reports that support this statement so that they can be reviewed.

Pharmacokinetic studies indicated that drug exposures in the rat and rabbit LD groups in the Segment II studies approximated the exposures of humans receiving the expected PPX maintenance dose of 1.5 mg, t.i.d.

3. Other Toxicology

a. Retinal degeneration

The sponsor has addressed the issue of retinal degeneration by submission of the original findings from the rat 2-year carcinogenicity study to an Expert Scientific Panel for review, and by conducting experiments suggested by the panel aimed at characterizing a potential mechanism of degeneration and the influence of pigmentation on the development of retinal lesions in two strains of rats. These studies were reviewed under IND and were also reviewed by an FDA consult, Dr. Tim O'Neill (see Appendix for Dr. O'Neill's review).

The sponsor's conclusion from these studies was that PPX inhibits retinal disk-shedding, a mechanism of disk turnover. Inhibition of this mechanism leads to degeneration of the retinal epithelium and photoreceptor cells. Degeneration occurred only in albino rats, and not in pigmented Brown-Norway rats suggesting that pigmentation may protect against this toxicity. This finding tends to reduce this concern with respect to human exposure. However, as concluded by the Expert Panel, disk-shedding is a universal vertebrate phenomenon. Thus, humans may still be at risk for this toxicity, albeit less sensitive due to the presence of pigmentation.

With respect to the sponsor' contention that retinal degeneration is a species/strain-specific effect, Dr. O'Neill raised the question of how closely the other species (monkeys, swine) were evaluated for retinotoxicity. The sponsor did not conduct ultrastructural or quantitative (e.g., thickness of cell layers) analyses in these species, which would have provided a more sensitive measure of toxicity. The sponsor emphasizes the point that the original findings in the rat carcinogenicity study was made during week 76, a long latency period. The monkey study was 52 weeks, and the minipig study was only 13 weeks, which may have been to short to create the

lesion. More sensitive indices of toxicity may have identified early stages of degeneration. The monkey and minipig studies were conducted several years before the 2-year rat study, so there was no reasonable basis to monitor for this lesion. However, a retrospective analysis of the tissues from these studies could have provided firmer support for the statement that retinal degeneration does not occur in these species. Thus, the sponsor's label will require modification to more accurately describe the studies in other species and their limitations. In view of the limitations, the possibility that pramipexole may damage human retinas cannot be discounted, and patients should be periodically monitored.

The proposed labeling statement that there is a long latency period for the effect is misleading since the sponsor has demonstrated that the effect can be produced in rats in 13 weeks.

The sponsor claims in the submission that the retinal lesions in Wistar rats are not indicative of retinotoxicity. Dr. O'Neill disagreed with this conclusion, and recommended (oral communication) the inclusion of a labeling statement to this effect.

b. Fibro-osseous proliferative lesions in mice

An unusual histopathological finding from the 2-year mouse study was the development of a bone lesion in female mice described as a fibro-osseous proliferative lesion. The spontaneous occurrence of this lesion was relatively high (28%), but its incidence rate approximately doubled in drug-treated mice. A dose-related trend was not evident. Similar lesions in mice have been described in the literature as arising spontaneously in aging females of certain strains (Sass and Montali, Lab Animal Sci, 30:907, 1980), and have also been observed following treatment with estrogen (Silberberg and Silberberg, Gerontology, 16:201, 1970), or the prostaglandin E1 analogue misoprostol (Dodd and Port, Vet Pathol., 24:545, 1987). The speculated mechanism for this PPX effect is an estrogen:progesterone imbalance, which is consistent with the positive effect of estrogens on bone deposition (i.e., osteoporosis therapy). No hormonal data was presented to support this mechanism.

Based on the literature descriptions, the toxicological consequence of this lesion is an invasion of marrow space by new bone and fibrous structures due to enhanced osteoblastic activity. This may be expected to reduce hematopoiesis, but this effect did not occur in this study. The potential significance of this lesion in humans is difficult to assess because of the paucity of information in the literature. The occurrence of this lesion in female mice following misoprostol appears in the labeling. Thus, inclusion of these findings in the PPX product labeling should also be considered.

4. "Neuroprotection" claim

The sponsor cites studies in which PPX protects against neurodegeneration in response to ischemia, methamphetamine (*in vivo*), and L-DOPA (*in vitro*). Only the ischemia model is generally recognized as a clinically relevant model, and in the best

case scenario this study would be acceptable evidence of efficacy to support a clinical trial for stroke. However, this data is inadequate to support a labeling claim with such widespread implications.

5. Application Deficiency

The sponsor's INDICATIONS AND USAGE statement does not specify that PPX is for use as an adjunct to any other Parkinson's disease medications (e.g. L-DOPA). Therefore, toxicology studies on the possible long-term, reproductive, or carcinogenic/mutagenic effects of PPX in combination with any other PD medications were not requested by the agency. A short-term cardiovascular study of PPX in combination with Sinemet or Eldepryl in monkeys was requested prior to the initiation of Phase I studies in patients stabilized on these drugs; no significant interactive effects occurred. Since combination therapies are frequently used in PD, and PPX may become part of that approach, the fact that the toxicological consequences of such interactions have not been evaluated in animals should appear in the label.

LABELING

CLINICAL PHARMACOLOGY

Para. 2, Sent. 2:

"Animal studies additionally suggest that pramipexole affect dopaminergic mesolimbic pathways thought to promote motivation."

This statement is very speculative should be deleted.

Para. 3 and 4:

These paragraphs address the potential neuroprotective effects of PPX in *in vivo* (transient forebrain ischemia, methamphetamine neurotoxicity) and *in vitro* (L-DOPA neurotoxicity) models of neurodegeneration. Only the ischemia model is generally accepted as clinically relevant, but it is not sufficient to support a labeling claim with such widespread implications.

PRECAUTIONS

Include a statement to this effect:

"The toxicological consequences (long-term, reproduction, carcinogenicity/mutagenicity) of using pramipexole in combination with other Parkinson's disease medications have not been evaluated in animals."

Carcinogenesis, Mutagenesis, Impairment of Fertility

Para. 1:

Control group B is indicated as having 60 animals. The number should be 50.

Para. 2:

The findings and significance of Leydig cell adenomas and hyperplasia in rats should be simplified since there is no experimental support for an effect of PPX on LH secretion or LH receptor number:

"These findings are of questionable significance in humans because of their high background incidence in rats, the absence of similar changes in mice treated with PPX for 2 years, and the probable involvement of endocrine mechanisms that are not relevant to humans."

Para. 4:

Para. 4:

The statements regarding the impact of PPX on fertility in rats and *potential* impact on fertility in humans should be reworded:

"In rat fertility studies, doses of 2.5 mg/kg/day pramipexole prolonged estrus cycles and inhibited nidation. These effects were associated with reductions of serum prolactin, a hormone necessary for implantation and maintenance of pregnancy in rats."

Pregnancy

The sponsor proposes that pramipexole should be placed in Pregnancy category B. Several factors argue against this proposal. The reproductive toxicology studies demonstrated a clear embryotoxic effect in rats at doses of 2.5 mg/kg/day. Because of the high rate of embryo loss, teratology information was very limited. The sponsor's contention that teratogenic effects were not observed is also disputable since 3 fetuses in the Segment II study (2 LD, 1 MD) had rare malformations. These facts are not clearly stated in the proposed labeling. In addition, the sponsor's statement that pups of pramipexole-treated dams developed normally, specifically referring to the Segment II study, is misleading since impairments of body weight development were observed in both the Segment I and Segment III studies. Therefore, the data presented only support a Pregnancy category C labeling:

"*Pregnancy Category C.* There are no adequate and well-controlled studies in pregnant women. Pramipexole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 2.5 mg/kg (28 times the human dose) pramipexole to rats during gestation inhibited nidation. Administration of 1.5 mg/kg (17 times the human dose) to rats on days 7-16 post-coitum (p.c.) resulted in early resorption of embryos. Because of the pregnancy impairment and embryolethality, limited teratogenicity data from the highest test dosages of pramipexole (1.5 - 2.5 mg/kg) were obtained. Rare malformations were observed in fetuses from dams treated on days 7-16 post-coitum. Of 250 fetuses from dams treated with 0.1 mg/kg pramipexole, one fetus with atresia ani, and one fetus with sirenomelia and gastroschisis were found. Of 222 fetuses from dams treated with 0.5 mg/kg pramipexole, one case of cleft vertebra was noted. Body weight development was impaired in pups from dams treated with 2.5 mg/kg pramipexole through gestation and weaning, or 1.5 mg/kg from day 16 p.c. through weaning. Other developmental parameters including fertility were normal in F_1 pups.

Administration of up to 10 mg/kg/day to rabbits on days 6 through 18 p.c. did not result in any embryotoxic, fetotoxic, or teratogenic effects."

Nursing Mothers

Experimental support for the statement that PPX decreased lactation in rats is not in the section of the Integrated Summary (Vol. 1.26, p. 5.1/126) indicated in the labeling statement. This statement should be deleted.

ANIMAL TOXICOLOGY

1. Retinotoxicity

1st Para.:

Modify as follows:

"Pramipexole was retinotoxic in albino rats in a 2-year rat carcinogenicity study. The incidence of lesions was dose dependent in animals receiving 2 or 8 mg/kg/day. The first retinal lesions were observed during week 76 of the study."

2nd Para.:

Modify as follows:

"Pramipexole was not retinotoxic in a 2-year carcinogenicity study in mice treated with similar or higher doses (0.3, 2, or 10 mg/kg)."

3rd Para.:

Modify as follows:

"Limited evaluation of the retina in other long-term animal studies did not reveal signs of retinotoxicity in monkeys that received pramipexole (0.1, 0.5, or 2.0 mg/kg/day) for 12 months, or minipigs that received pramipexole (0.3, 1, or 5 mg/kg/day) for 13 weeks."

4th Para.:

Modify as follows:

"Investigative studies demonstrated that pramipexole reduced the rate of disk shedding from the retinal photoreceptor cells of albino rats. In a comparative study, retinal degeneration occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day pramipexole and constant light (100 lux), but not in pigmented rats exposed to the same dose and even higher light intensities.

Thus, the retina of albino rats may be uniquely sensitive to the damaging effects of pramipexole. The potential significance of this effect in humans has not been established, but cannot be disregarded since retinal disk shedding is a universal vertebrate mechanism."

ANIMAL TOXICOLOGY (cont.)

2. Fibro-osseous proliferative lesion

"An increased incidence of fibro-osseous proliferative lesions occurred in the femurs of female mice treated for 2 years with 0.3, 2.0 or 10 mg/kg. Lesions occurred at a lower rate in control animals. Similar lesions were not observed in male mice, or rats and monkeys of either sex that were treated chronically with pramipexole. The significance of this lesion to humans is not known."

RECOMMENDATIONS

1. The NDA is approvable.

2. Labeling recommendations are in the preceding section. A major point of contention is the sponsor's proposed labeling of pramipexole in Pregnancy category B. The submitted data support category C labeling. The labeling could be amended if negative toxicological findings in appropriately designed Segment II and cross-fostering studies are obtained. An appropriate segment II design would involve either administration of pramipexole to rats on days 8-16 (after the prolactin-dependent stage on days 6-7), or the use of another species (hamster, mouse).

Thomas D. Steele, Ph.D.
Pharmacologist/Toxicologist

Original NDA 20667
cc.: /Division File, HFD-120
/G. Fitzgerald, Ph.D.
/J. Feeney, M.D.
/J. Purvis
/T.D. Steele, Ph.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products
5600 Fishers Lane
Rockville, MD 20857

Memorandum

Date: 13 February 1996

From: Glenna Fitzgerald, Ph.D. GFF
Pharmacology Team Leader
Division of Neuropharmacological Drug Products

Subject: Consultative review of rodent retinal degenerative findings; NDA 20-667

To: Timothy O'Neill, D.V.M., Ph.D.
Dept. of Veterinary Pathology
Armed Forces Institute of Pathology
Building 54
16th and Alaska Ave., NW
Washington, D.C. 20306-6000

Thank you so much for agreeing to review the drug-induced retinal degeneration findings that you have discussed with Dr. Lois Freed. Enclosed please find several documents we would like evaluated.

To briefly summarize the issue, pramipexole is a relatively selective dopamine D2 receptor agonist under development by Upjohn for the treatment of Parkinson's disease. An unexpected finding in the two-year rat carcinogenicity study was retinal degeneration in mid- (2 mg/kg/day) and high- (8 mg/kg/day) dose rats. This finding was first made in premature decedents during weeks 76/78. The primary contention of the sponsor is that this finding is a species-specific effect in albino rats due to the lack of "protective" pigmentation. To support this contention, the sponsor has conducted a comparative study of retinal degeneration in non-pigmented (albino) and pigmented (Brown-Norway) rats. In addition, the sponsor has conducted a study on the possible mechanism by which pramipexole produces retinal degeneration in albino rats. According to their hypothesis, dopamine D2 receptor activation by pramipexole effectively mimics conditions of constant light, which is known to damage the retinae of albino rats. The sponsor's bottom line is that pigmented species (i.e., humans) should not be subject to similar retinal degenerative effects of pramipexole.

The following documents contain the material for review:

1. is a discussion of the initial retinal degeneration findings in the 2-year rat carcinogenicity study, and a literature review of retinal degeneration

2. IND Amendment 107, contains:

   a. A literature review of retinal degeneration

b. An Expert Panel Report regarding the drug-induced retinal degeneration findings and their possible relevance to humans

c. A technical report (TR 7219-95-043) of a study in which a potential mechanism for drug-induced retinal degeneration (inhibition of disk shedding) was evaluated

d. A technical report (TR 7219-95-049) of a study in which the degenerative effects of the drug were compared in pigmented and non-pigmented rats

Color photocopies from the document (pages 32-34), and an original electron micrograph from the disk-shedding study (TR 7219-95-043) are provided. The histopathological evidence is rather limited, but according to the sponsor, this is the best they have at this point.

As you review the material, please consider the following questions:

1. In your opinion, has the sponsor provided convincing evidence that this is a species-specific effect that will occur only in non-pigmented animals? Bear in mind that albino mice did not show signs of retinal degeneration.

2. Are the retinal degeneration findings more likely a species-selective effect, as the sponsor contends, or a species-sensitive effect (i.e., does pigmentation merely prolong the latency for the degeneration)?

3. What are your recommendations for clinical monitoring for this effect, if any (type of monitoring, frequency)?

4. An issue that will arise during labeling is the description of the changes. The sponsor adamantly contends that the drug is not "retinotoxic", primarily citing the long latency for the changes. However, in the mechanistic and comparative studies, the retinal changes were produced in a much shorter period of time. should the drug be considered retinotoxic? In non-pigmented rodents only?

If you have questions please contact me at (301) 594-5501, or speak directly to the pharmacology/toxicology reviewer of the NDA (who put this package together and knows the data better than anyone else) Thomas Steele, Ph.D., at (301) 594-5508.

cc: NDA 20-667
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THE REGISTRY OF COMPARATIVE PATHOLOGY

Armed Forces Institute of Pathology
Washington, D. C. 20306-0001

July 15, 1996

Glenna Fitzgerald, Ph.D.
Pharmacology Team Leader
Division of Neuropharmacological Drug Products
HFD-120
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Fitzgerald:

Thank you, once again, for the opportunity to assist the Division of Neuropharmacological Drug Products in the review of NDA 20-667. I very much appreciate the occasions to collaborate with your group in this and past reviews. I do, however, apologize for the delay in reporting this review summary to you, as my work here has been very demanding lately.

Enclosed along with this review of NDA 20-667 are the original documents sent to me for review on 15 Feb. 1996, to include:

1. : discussion of the initial retinal degeneration lesions findings in the 2-year rat carcinogenicity study and literature review of retinal degeneration

2. IND Amendment 107, containing:
   a. Literature review of retinal degeneration
   b. Expert Panel Report discussing the drug-induced retinal lesions and relevance to humans
   c. Technical Report: TR 7219-95-043, SND 919 CL 2 Y: Influence on the Rod Outer Segment Disk Shedding Mechanism in the Retina of Albino Rats
   D. Technical Report: TR 7219-95-049, Pramipexole (SND 919 CL 2 Y) Influence on retinal degeneration in the albino rat with and without light as a cofactor

Phone: (202) 782-2440 ◆ Fax: (202) 782-9161/9150

Registry of Comparative Pathology activities are supported by a grant from the National Center for Research Resources, National Institutes of Health.

3. Color photocopies and black and white photos of histological and electron microscopic images of control and drug-induced lesions in experimental animals.

The materials are returned in their entirety and original condition. In no instance was the material duplicated or reproduced and in no case was the proprietary nature of material disclosed.

As part of my review, in addition to review of the provided printed materials listed above, I conducted and reviewed information from fairly exhaustive MEDLARS® database searches from 1990 to the present on: retinal degeneration in rats and mice; dopamine and retina; dopamine receptors and retina; and dopamine or dopamine receptors and retinal degeneration. Moreover, I consulted with members of the Department of Ophthalmic Pathology, AFIP, on several questions I had regarding retinal pathology as they related to the lesions described in this NDA.

Before I specifically address the questions posed in your letter of 15 February 1996, I would like you to gain an appreciation for some of the assumptions I performed my review of the materials under. Defining these will aid in how I address these questions and arrived at my conclusions.

Firstly, The term retinal degeneration is ill defined in the documents. At times the term is applied to photoreceptor cell loss and at other times refers to, I assume, total loss of the retina.

Secondly, I did not find in the materials provided a detailed histological description of the retinal degeneration in the affected (treated) rats other than that described in the "Report of Expert Panel Evaluation...". In that report only a fairly general description of the light microscopic pathology was eluded to, i.e. "..loss of photoreceptor cells, inner layers of the retina had lesions and vessels penetrated the retinal pigment epithelium", and in TR 7219-95-049: "reduction of photoreceptor cell nuclei...". Little information regarding the genesis (e.g. the earliest lesion observed were nuclear pycnosis followed by cytoplasmic vacuolation, etc) of the photoreceptor cell loss was provided. Therefore, one has to assume these photoreceptor cells just disappeared without premonitory changes.

Thirdly, no mention was made of pathology secondary or ancillary to photoreceptor cell loss (i.e. retinal degeneration began with photoreceptor cell loss followed by inner nuclear layer cell loss, etc.), but rather terms such as "severe retinal degeneration" or "photoreceptor cells of the entire retina were completely degenerated". Therefore, one again assumes lesions were either restricted to photoreceptors or, as indicated, the entire retina (all layers) in the most severe form and were degenerated without a stepwise or pathogenesis to loss of the

other layers of the retina.

Lastly, the literature review and discussion material provided in the technical reports was at times confusing and contradictory in reference to dopamine action and metabolism and D2 (dopamine receptor) activation of the photoreceptor and inner nuclear layer cells. I gained ancillary information and clarification from the MEDLARS® searches previously mentioned.

In response to your questions regarding my review, I provide the following responses:

1. Within the context of the studies conducted and reference materials included (or lack of information showing D2 agonist-induced retinal degeneration in other species), the sponsor has provided evidence to support their contention that this is a species and strain-specific effect in non-pigmented (albino) rats. Detailed information on the conduct of the histopathological examination for both affected and non-affected species is not available in the materials and, therefore, I cannot access what effort was put into looking for very early, inapparent or ultrastructural changes that may have been present in the other species/strains.

2. Again, within the context of the information provided or found, the absence of retinal degeneration in parallel 2-year studies in albino (non-pigmented) mice and pigmented rats would tend to support a strain-selective (i.e. Wistar rat) effect of the drug-induced retinal degeneration. As ultrastructural studies were not conducted in other species or 2-year studies using pigmented rats were not conducted the question of pigmentation prolonging latency of retinal degeneration cannot be answered.

3. Although this is not my area if expertise, I find the sponsor's plan for clinical monitoring of patients receiving the drug to be fairly inclusive of detecting untold effects on eyesight. A detailed clinical monitoring schedule to include parameters and periodicity of exams would be helpful.

4. From what I can conclude from the information on the drug, the drug is retinotoxic in Wistar rats. Albeit, the drug has not been shown to be retinotoxic in a limited number of other species of animals (including albino mice) or strains of rat, it is definitely toxic to the photoreceptor cells of the retina in Wistar rats.

In summary, after careful inspection and consideration of the provided and supplemental documentation I was able to retrieve on the subject matter, I conclude that the sponsor's claim: "that the retinal degeneration observed in association with pramipexole is species-specific and unique to albino rats" is correct within the limitations I have specified above. Without further information

regarding the histopathology of the retina in other species or future studies designed to better quantitate and characterize the effects of the drug on the retina in non-pigmented and pigmented species, I am unable to predict the effects of the drug in the human patient.

Once again, thank you very much for this opportunity to be of assistance to the FDA. Should you have any questions regarding this report or my conduct of the review, please do not hesitate to contact me directly at (202) 782-2442 or FAX at (202) 782-9150.

Respectfully Yours

Timothy P. O'Neill, D.V.M., Ph.D.
Chief Pathologist
Diplomate, American College of Veterinary Pathologists

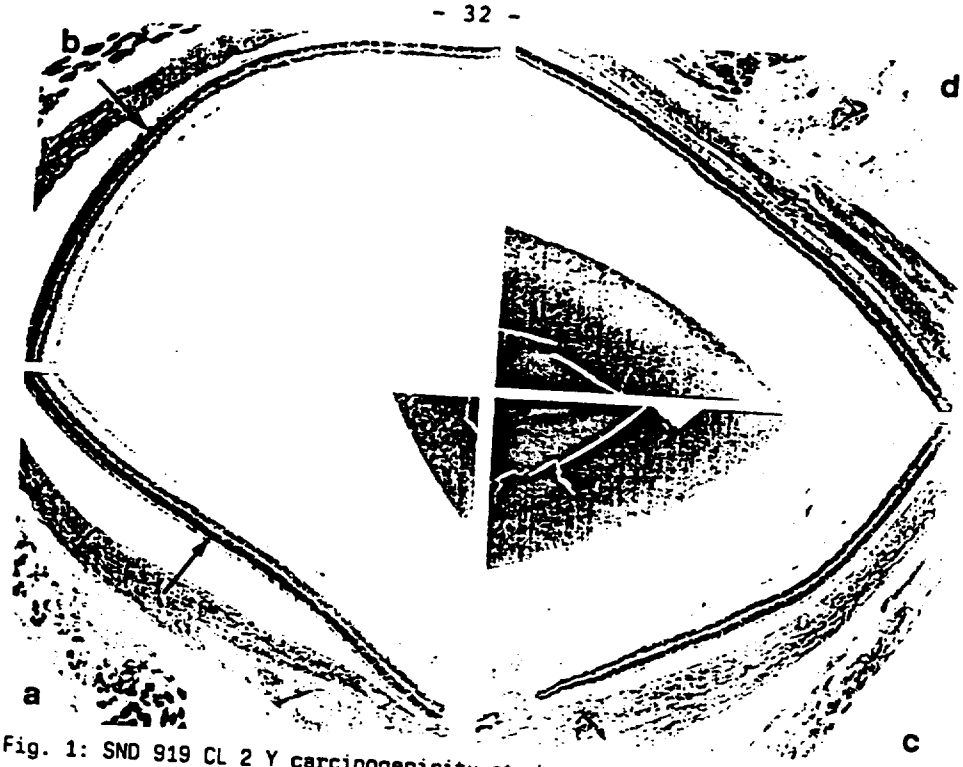

Fig. 1: SND 919 CL 2 Y carcinogenicity study rat: control rat no. 0014
a (central) and b (peripheral) represent one retinal hemisphere
c (central) and d (peripheral) the second of the same eye, HE, 43 x
——>= photoreceptor cell layer

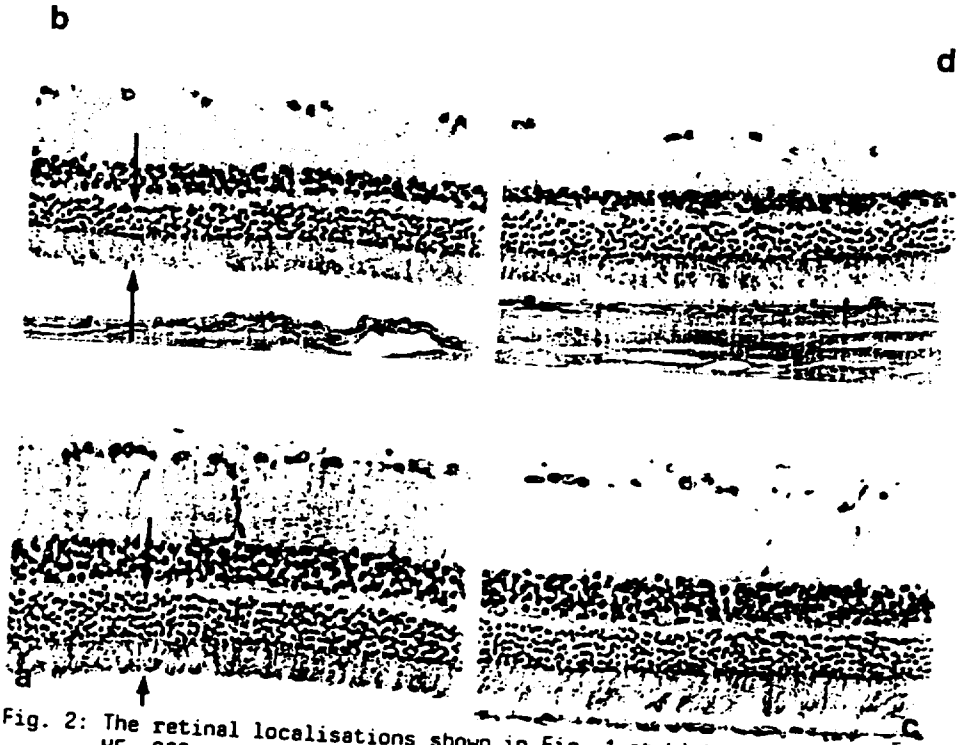

Fig. 2: The retinal localisations shown in Fig. 1 at higher magnification, HE, 260 x
——> <—— = photoreceptor cell layer

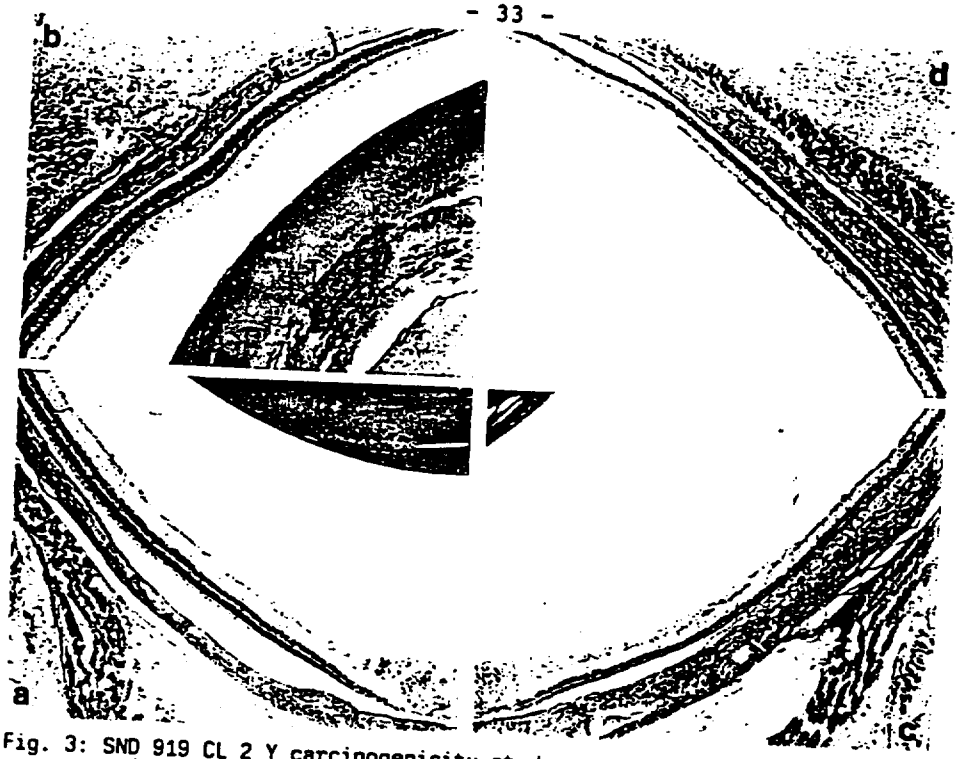

Fig. 3: SND 919 CL 2 Y carcinogenicity study rat: high dose rat no. 3526
a (central) and b (peripheral) represent one retinal hemisphere
c (central) and d (peripheral) the corresponding, HE, 43 x,
photoreceptor cell layer is present in one hemisphere
nearly missing in the other one.

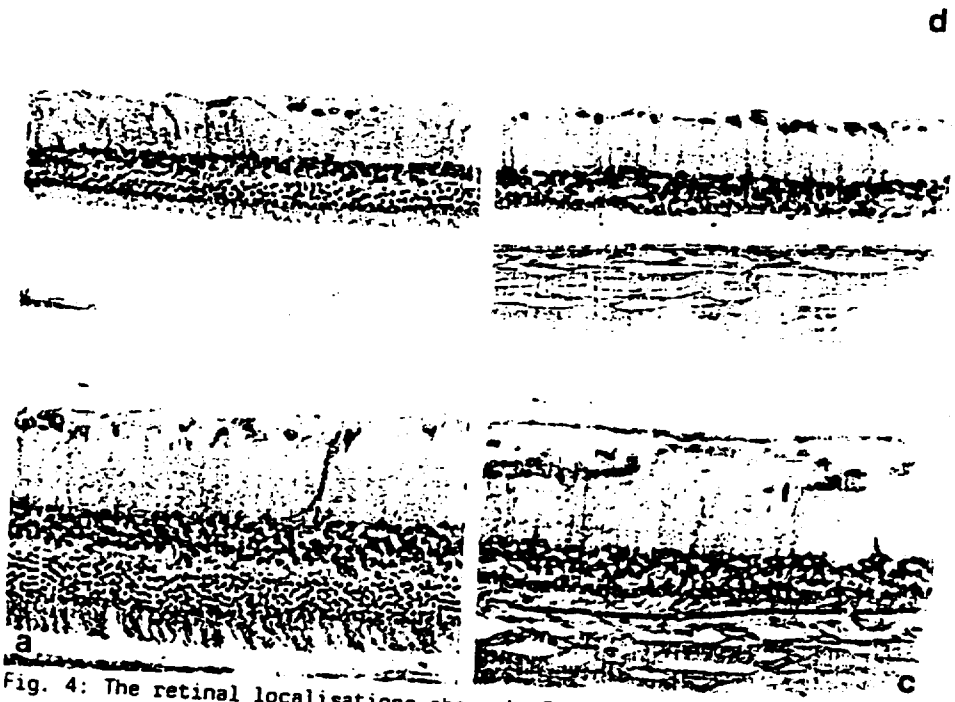

Fig. 4: The retinal localisations shown in Fig. 3 at higher magnification,
HE, 260 x, intact and degenerated photoreceptor cell layer

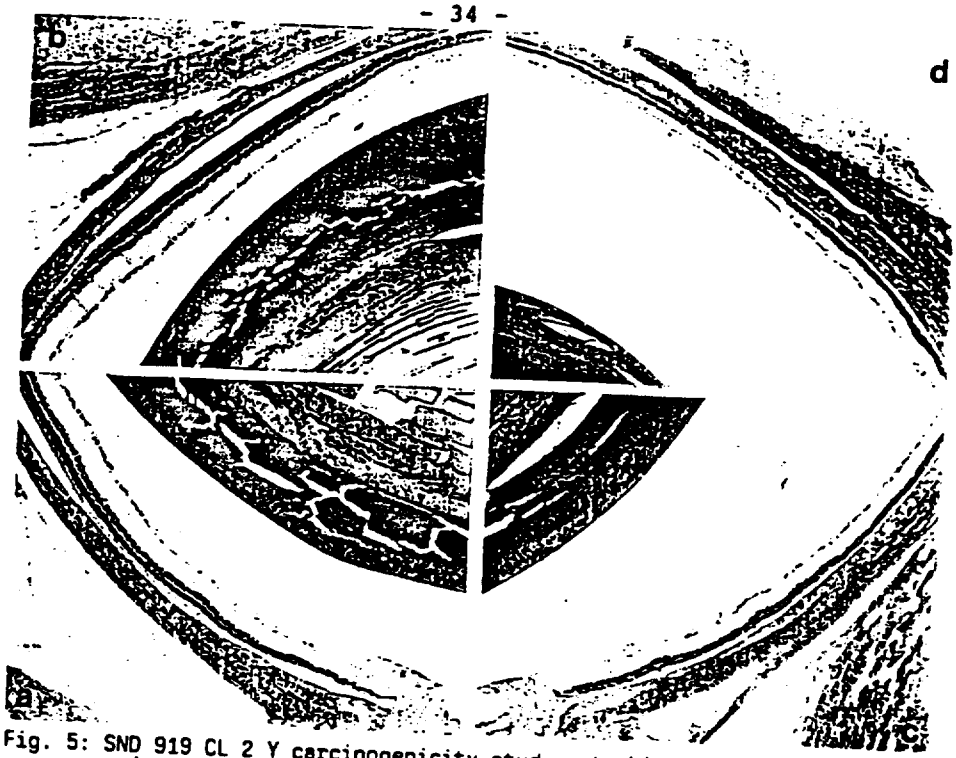

Fig. 5: SND 919 CL 2 Y carcinogenicity study rat: high dose rat no. 3535
a (central) and b (peripheral) represent one retinal hemisphere
c (central) and d (peripheral) the corresponding, HE, 43 x,
photoreceptor cell layer is present in one hemisphere
nearly missing in the other one.

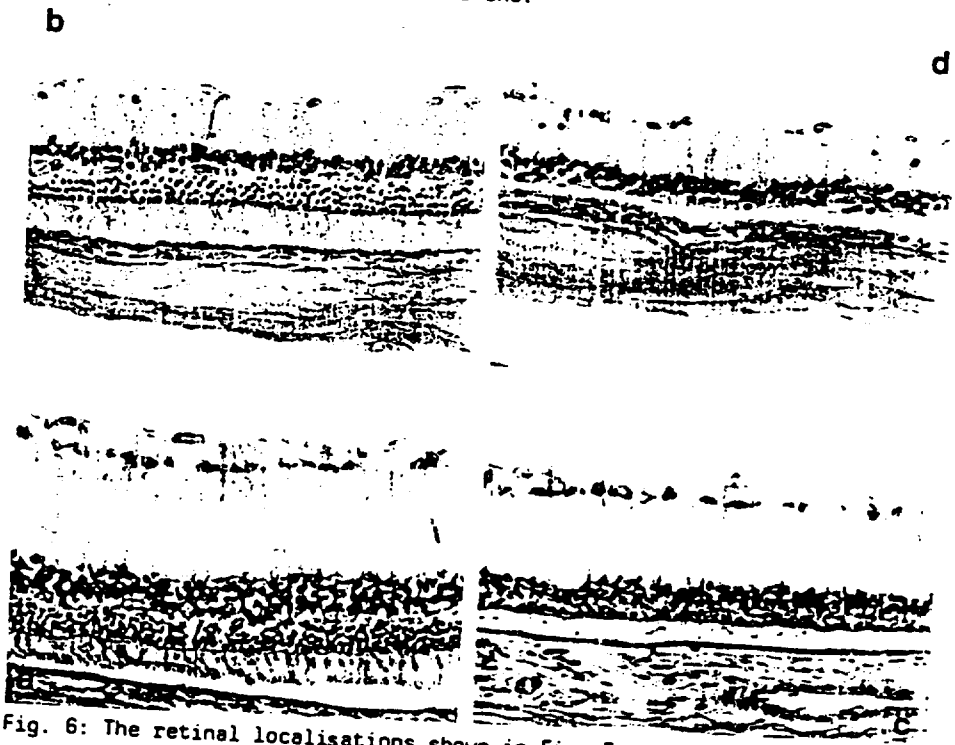

Fig. 6: The retinal localisations shown in Fig. 5 at higher magnification,
HE, 260 x, intact and degenerated photoreceptor cell layer.

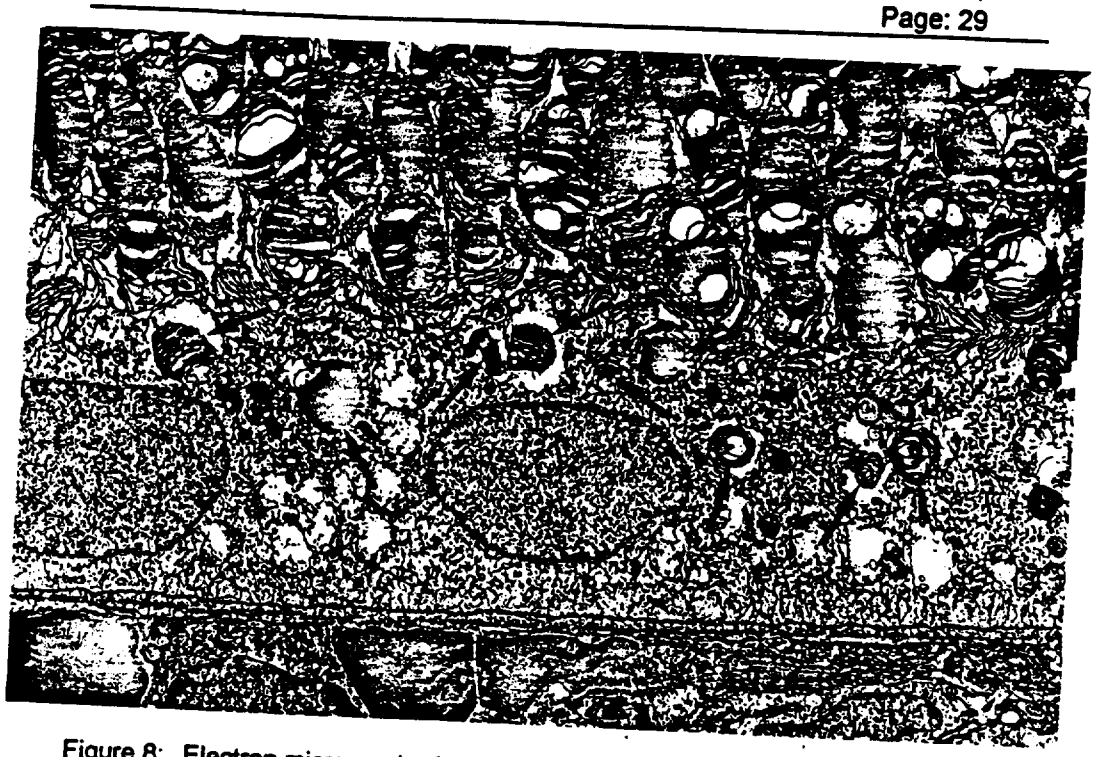

Figure 8: Electron micrograph of rod outer segments (ROS) and retinal pigment epithelium cells (RPE) from a control rat sacrificed at 8 am (early light phase). The RPE cells contain numerous phagosomes (←), magnification 5400 x

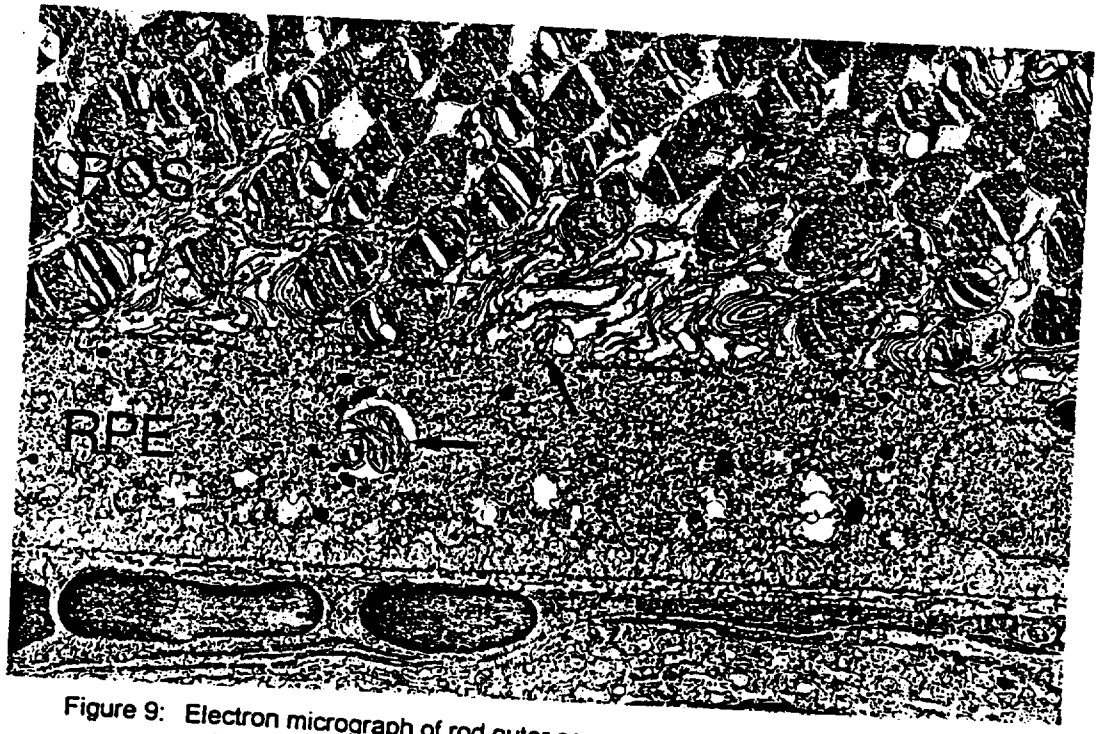

Figure 9: Electron micrograph of rod outer segments (ROS) and retinal pigment epithelium cells (RPE) from a SND 919 CL 2 Y-treated rat sacrificed at 8 am (early light phase). The RPE cells are nearly devoid of phagosomes (←), magnification 5400 x