CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19922

ADMINISTRATIVE DOCUMENTS

RHPM Overview of NDA 19-922
Corlopam (fenoldopam mesylate) 10 mg/mL Infusion
July 11, 1997

Type: 1 S
Receipt Date: June 25, 1996
Major Amendment: May 6, 1997
PDUFA Goal Date: September 25, 1997

Background
Corlopam (fenoldopam mesylate) Infusion is a systemic and renal vaso dilator that stimulates postsynaptic dopamine DA_1 receptors. This NDA was originally filed by Smith Kline and French (now SmithKline Beecham) on December 12, 1988. A not approvable letter issued on November 15, 1991. Neurex subsequently purchased the rights to the drug in 1994 and resubmitted the application on June 21, 1996. An Advisory Committee was held on June 26, 1997 wherein the Committee recommended 9-yes, 1-no, that fenoldopam be approved for treatment of hypertension when oral therapy is not practical and 8-yes, 2-no, that fenoldopam be approved for use in hypertensive crisis. Concern about absence of data on co-administration of fenoldopam and beta-blockers was expressed. The Committee was evenly divided (5-5) on a recommendation to require such a study prior to approval.

Medical Reviews
In his review dated February 20, 1997, Dr. Rodin did not make a recommendation as to whether the application should be approved.

In his review dated March 7, 1997, Dr. Karkowsky did not make a recommendation as to whether the application should be approved.

There was no recommendation as to approvability of the application in the global review dated May 6, 1997.

DSI - Dr. Lipicky said an inspection of the new study was not needed. Seven inspections of clinical investigators were done for the original submission.

Statistical -
In his review dated June 16, 1997, Dr. Jin did not make a recommendation as to whether the application should be approved.

Biopharmaceutical Review
In his draft review, Dr. El-Tahtawy concluded that the submission is acceptable provided the requested changes are made in the proposed labeling. See Dr. Tahtawy's review, page 14.

Pharmacology Review
In her review dated August 8, 1996 stated that the NDA is approvable with some labeling changes, see pages 8 and 9.

Chemistry Review

In his review dated September 4, 1996, Dr. Short recommended approval.

EER - The Establishment Evaluation Report found the two establishments acceptable of May 5, 1997.

Methods Validation -A memo from Mr. Beckwith dated April 4, 1997 stated that the methods have been validated and found acceptable.

EA - Acceptable - see Environmental Assessment and Finding of No Significant Impact dated July 25, 1996

Tradename - Acceptable - see review attached to request for trademark review dated January 16, 1996

RHPM Summary

Dr. Lipicky is still writing his memo to Dr. Temple and believes the application is approvable. Other than labeling changes, to my knowledge, there are no outstanding issues that might prevent action on this application.

Zelda McDonald 7/11/97

Zelda McDonald, RHPM

cc: Orig. NDA
HFD-110
HFD-111/McDonald

CSO OVERVIEW OF PACKAGE

NOV 15 1991

NDA 19-922
Corlopam (fenoldopam) Injection
Smith Kline & French Laboratories
Class: 1C

Chemistry

All Chemistry issues have been dealt with satisfactorily except the deficiencies outlined in review # 4 regarding labeling. These issues can be addressed in the approvable letter if the application is found to be approvable.

Pharmacology

The application is approvable from the Pharmacologist's point of view. The reviewer has made several labeling recommendations (see the attached comments).

Microbiology

This application is not approvable from the Microbiologist's perspective. The deficiencies are outlined in the review in a draft letter to the applicant (see the attached list). Dr. Lipicky said that they should not be conveyed to the firm yet, and could be included in a not approvable letter.

Biopharmaceutics

The Biopharmaceutics review is not completed.

Medical

The Medical Officer recommends that this application not be approved. An extensive list of deficiencies is attached.

David Roeder

David Roeder, CSO

cc: NDA 19-922
HFD-110
HFD-110/CSO

ITEM 13./14.

PATENT INFORMATION

Pursuant to the provisions of 21 U.C.S. 355(b), the applicant states that the only U.S. patent which claims the drug for which this application is being submitted or a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of the drug is U.S. Patent 4,197,297, expiration date, April 8, 1997.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

APPEARS THIS WAY
ON ORIGINAL

IND 22,837

EXCLUSIVITY SUMMARY for NDA # 19-922 **SUPPL #** _____

Trade Name Corlopam **Generic Name** fenoldopam mesylate
Applicant Name Neurex **HFD-** 110

Approval Date September 23, 1997

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 /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /___/

   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 /✓/ 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 /___/ NO /✓/

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

_____

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 /✓/

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 /✓/

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 /✓/

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

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: _____

_____

_____

_____

Signature

Title: Regulatory Affairs Project Manager

7/11/97
Date

Signature of Division Director

8/12/97
Date

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

8/8/95

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 19-922 Trade (generic) names Corlopam (fenoldopam mesylate) I.V.

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

__✓__ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. 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.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

The drug is approved [illegible] for [illegible] limited [illegible] Other drugs are available.

BEST POSSIBLE COPY

Ken Kocy
Signature of Preparer

9/10/96
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

CERTIFICATION OF COMPLIANCE

This is to certify that during the course of the development of Corlopam®, Neurex has not employed any individual named on the debarrment list. In addition, Neurex has not utilized any of the investigators on the list of ineligible clinical investigators.

Bonnie Horner
Senior Director, Regulatory Affairs

NDA 19-922

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 9, 1997

FROM: Director, Office of Drug Evaluation I

SUBJECT: Fenoldopam mesylate (Corlopam, Neurex)

TO: Dr, Lipicky

Your approvable memo was very helpful. Fenoldopam plainly has a dose (infusion rate)-related BP lowering effect that is present at 0.04 mcg/kg/min and probably at 0.01 mcg/kg/min. Study 94-004 by eyeball (mine) and at least two analytic approaches shows that the full effect of any given infusion rate is more-or-less achieved by one hour (actually, pretty close to this in 15 minutes) and is reasonably stable after that. There seems no apparent reason to use infusion rates past 0.4 mcg/kg/min. It seems possible that the tachycardia that occurs contributes to BP maintenance and use of a beta blocker might well exaggerate the BP effect (although tachycardia at 0.1 mcg/kg/min, a reasonable starting dose) is not very great.

The on-off properties of Fenoldopam are not well-described in either the Jin or El-Tahtawy reviews, but should be available as BP/HR were taken q five minutes during the first hour after starting and stopping infusions, in each study (Avi's review of 94-006 says every 15 minutes), but that would be often enough. These properties need description because they can reveal how soon to titrate and how quickly excess BP lowering can be reversed. I do note your fig three which shows that the 15 minute and one hour effects of doses from 0.03 to 0.1 mcg/kg/min are about the same, which isn't too surprising, as in 2+ half lives the concentration is about 75% of steady state. I note that I don't think you need to wait four half-lives to titrate. You can get a very good idea of where matters are heading in, say two half-lives.

I have some comments on labeling, most on the draft, but a few others.

1. Indications:

I like your suggestion generally, but wonder what "when not practical or not feasible" means. Isn't the real point that you want a fast, reversible effect because the patient needs a fast reduction? If so, what about this:

"... of severe hypertension when raped but quickly reversible emergency reduction of blood pressure is clinically indicated..."

This in not too far from SNP ("immediate reduction"), and that's appropriate as only those two "go away" fast. If you overshoot badly with nicardipine, labetalol, enalaprilat, or dearoxide, you're into pressors.

2. Dosing and Administration

The past-developed labeling indicates how hard this can be. In the present case, study 94-006 gives very good, and rather simpler, guidance. One can say (your figure three) that an initial rate of 0.03 (or is it 0.04) mcg/kg/min gives a response that is, on the whole, not sufficient in this population, but that a starting infusion of 0.1 mcg/kg/min gives an average response of seven mmHg or so on DBP and is a reasonable starting point. One can also say that response at one hour is no better than at 15 min so that a titration at that point, if response is insufficient, is reasonable, either to 0.2 or 0.3 mcg/kg/min. Whether doses past 0.4 or so are useful is hard to say from available data.

3. I note in Dr. Karkowsky's discussion of the PK/PD analysis of study 94-006 the slower progressive drop (contrasted with the immediate response) in BP (review page 26) with a half-life of about seven hours. I see no good reason at all to attribute this late phase response to the drug. It is seen in all Rx groups (there is no placebo) and probably represents "cooling off" of patients in the treatment setting. It perhaps could represent the gradual addition of additional therapy (but that doesn't occur in the 0.3 mcg/kg/min group, which also falls over time about as much as the other groups).

4. Labeling: See marked-up copy.

Robert Temple

Robert Temple, M.D.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION **Public Health Service**
Division of Cardio-Renal Drug Products

Memorandum

DATE : AUG 8 1997

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approvable of NDA 19-922, Fenoldopam mesylate (Corlopam), Neurex

TO : Director, Office of Drug Evaluation I, HFD-100

Introduction

This memo and its attachments constitute the Division's recommendation that fenoldopam be approved for the parenteral treatment of hypertension. A clean draft package insert that incorporates most of the Division's initial suggestions, additional mark-ups of that draft, as well as an approvable letter are also attached.

Fenoldopam (a mixture of R- and S- racemates; the R- form being the biologically active one) was originally developed by as an antihypertensive agent (starting clinical trials in about 1981), resulting from a screen of many benzazepine renal vasodilators. submitted an NDA (19-922) in 1988, which resulted in a not-approvable letter in November 1991. Neurex obtained rights to fenoldopam and right to reference to NDA 19-922 in 1994 and following completion of 2 additional clinical trials (94-005 and 94-006) resubmitted NDA 19-922 (an administrative decision on our part, rather than having a new NDA number) in June, 1996. The results of study 94-006 were submitted to the NDA in March, 1997. The results of study 94-006 are essential to the Division's approval recommendation. Therefore, the "User Fee Deadline" has been extended to September 25, 1997.

Overall Total Data Base

Pharmacology. The original (1988) submission contained complete pre-clinical evaluation, including rat and mouse carcinogenicity studies (by the oral route of administration). Of note is that dose-dependant chromosomal aberrations in Chinese Hamster Ovary cells were observed, with none of 5 other standard assays showing mutagenic or chromosomal aberration potential. The oral dosing carcinogenicity studies found no tumorigenic potential, but found a subgroup of rats with interstitial nephritis.

Rats (but not dogs, nor monkeys) were found to be susceptible to medial necrosis of medium sized arteries following intravenous administration of fenoldopam.

Because of the heat sterilization of the product, descholorofenoldopam appears in the final product at about a 0.6% level. It (i.e., descholorofenoldopam) has been the subject of independent subacute toxicology studies and was found to not differ remarkably from fenoldopam itself.

All-in-all, the animal chronic toxicology studies are complete and give no reason for concern.

Chemistry. There are no issues remaining to be resolved for manufacturing and controls. chemistry finds the application approvable.

Clinical. In Dr. Friedman's June, 1990 review of NDA 19-922, he cites (page 223, Integrated Summary of Safety, Volume 3 of the 3 volume attachment) 2131 patients or subjects who had received oral or intravenous fenoldopam (1635 oral, 553 IV and 57 by both routes). Nine hundred seventy (970) having a

variety of pathology other than hypertension, mainly congestive heart failure.

Including the Neurex trials, over 1,000 patients with a variety of disorders have been exposed to intravenous fenoldopam at cumulative doses of 0.12 to 523 mg, with infusion times from 2 to 146 hours. So, in total there is a "safety" data-base that amounts to over 3000 patients/subjects for both the oral and intravenous formulations. Experientially, this is a "rich" NDA.

In the original intravenous NDA data-base, 96% of patients had a total duration of infusion between 1 and 12 hours (median about 4 hours), with infusion rates between 0.1 and 1.5 micrograms/kg/min, and 86% of patients had a total cumulative dose of less than 0.25 mg/kg. The most common adverse reactions among the 383 patients exposed to fenoldopam were headache (9%), flushing (8%), ventricular extrasystoles (3%), hypotension (6%), dizziness (3%), serum potassium decreases (3%).

hypoten-sive

In the original intravenous studies there were 27/383 (7%) withdrawals from study mainly because of symptoms associated with hypotension. There were no deaths in the 383 patients while receiving intravenous fenoldopam. One of these 383 patients died 10 days after receiving intravenous fenoldopam from an intracranial bleed.

There were 800 patients with congestive heart failure receiving oral fenoldopam. Thirty six (5%) died while on therapy. The deaths are not decipherable (none in controlled trials) and contribute nothing to our deliberations.

The clearest potential adverse effect (studies 239 and 088) was a dose related increase in intraocular pressure produced by fenoldopam infusions over a range of 0.2 to 1.0 micrograms/kg/min. The increases were in the mean range of 4 to 6 mm Hg (as great as 10 to 12 mm Hg in some individuals, which could be clinically meaningful over a period of years (ophthalmology consult, Wiley Chambers, M.D., December 5, 1996); usual diurnal variations are in the range of 3 to 5 mm Hg. Dr. Chambers did not think this needed to be monitored unless drug treatment was to be continued for longer than a week. We concur with his opinion.

Metabolism. The Division of Clinical Pharmacology (FDA/CDER/OTR) did the in-vitro studies of drug metabolism (sulfation, methylation and glucoronidation) that characterize fenoldopam. The in-vitro metabolic profile correlated well with the human in-vivo characterization. This was a useful collaboration that we hope to see again in the future.

Evidence that fenoldopam is an antihypertensive

The number of studies and number of patients and number of reviews is almost overwhelming (a 3 volume transmittal package, without any of the Neurex provided text). That fenoldopam is an antihypertensive agent is without doubt; that evidence exists in every study and every review. For purposes of our deliberation at this time, it is appropriate to restrict all attention only to the "new" studies that were conducted by Neurex, namely studies 94-005 and 94-006. These two studies are the major content of the 2nd volume of the attached documentation, and a statistical review of study 94-005 by Dr. Kun Jin is in the 1st volume, under the statistical reviews.

Study 94-005. This was a randomized, parallel group, placebo controlled, fixed infusion rate, dose ranging trial that involved a total of 32 patients with mild to moderate hypertension. The simplest graphical expressions of the results of that trial are shown in appended Figures 1 and 2, where placebo subtracted diastolic blood pressure decrease and placebo subtracted increase in pulse are shown as a function of the infusion rate of fenoldopam.

The plots (Figures 1 and 2) are not data. Rather, the points are the estimates that come from a linear, mixed-effects model used by Dr. Kun Jin. Note that the standard error of each estimate is in the range of 2 mm Hg, which can be interpreted as meaning that the model accounted for the data reasonably well. The lines connecting the points in Figures 1 and 2 are simple splines (used only to keep the symbols straight for the eye to follow). To my eye, it is reasonably clear that there was a dose related decrease in diastolic blood pressure (systolic behaved similarly, but is not shown), as well as a dose related increase in pulse rate. From Dr. Jin's analyses, this intuitive statement is supported by analytical p values < 0.0001.

Dr. Jin's analysis would require many paragraphs to lay a background that would defend the approach in detail. It is one of the approaches that our ABPM project will be applying to Ambulatory Blood Pressure Monitoring data, where diurnal variation is present in the collected data. From my point of view, the approach taken by Dr. Jin is reasonable (although there are others that may be equally reasonable), does not misrepresent the data and easily allows for estimates of effect at various arbitrary times (e.g., 1-16 hours, 17-32 hours, 33-48 hours), allows for quantitative tests of significance and otherwise deals with data that is not collected at exactly the same clock time or exactly the same time following the beginning of dosing and where there is diurnal variation in both the control and treated groups. The "model" has no particular biological meaning but does allow for data description and statistical testing using established, well defined statistical tests.

Another approach to data analysis was taken by Dr. El-Tahtawy, his review is also in Volume 1 of the attached documentation, under Biopharm Reviews. Here, the principal focus was on providing a quantitative description of the relationship between plasma concentrations and drug-effect. As can be gleaned from his review, which also used established methods of analysis, this was a frustrating endeavor and no clear quantitative description emerged.

For sure, the relationship between infusion rate and plasma concentrations was fairly orderly, was basically linear over the infusion rates studied and a reasonable quantitative description between infusion rate and plasma concentrations could be written. Fenoldopam, at a constant rate of infusion, reaches steady-state concentrations in about 20 to 25 minutes (the half life of each racemate being about 6 minutes). The steady-state concentrations reached in the first 30 minutes of a constant rate infusion is maintained for up to 48 hours. Upon discontinuation of an intravenous infusion, the decline in plasma concentration declines with the half-life of about 6 minutes).

The relationship between blood pressure lowering and plasma concentration was also fairly orderly. It does not appear that there is much "hysteresis" although this is not well documented in any review; rather, there are comments that state there was no "lag". The blood pressure decreases rapidly (time constant in minutes) upon starting an infusion and the blood pressure increases rapidly (time constant in minutes) upon discontinuation of an infusion. Qualitatively, it is clear that there is a definite relationship between the concentration of racemic fenoldopam and a decrease in blood pressure, and it is also clear that whatever the relationship, the two variables are closely linked.

So, all analyses of Study 94-005 establish that the blood pressure lowering effects of fenoldopam are related to the infusion rate and plasma concentration of fenoldopam, that the blood pressure lowering effects are reasonably prompt (time constant of minutes), and that the effects go away upon discontinuation of fenoldopam reasonably promptly (time constant of minutes). Yet, a good quantitative description of how these variables relate to one another is difficult to express. Whether this is a conceptual problem, an analytical problem, a numerical problem or some other problem is not clear. The lack of being able to quantitatively describe the relationships does not detract from the conclusion that fenoldopam lowers blood pressure and that the dose range studied covered the clinically usable dose range.

Of note is that, over 48 hours, the antihypertensive effect of fenoldopam decreases (some tolerance or tachyphylaxis occurs; there is not enough data to differentiate between these terms as I understand them). The diminished effect, although real, is not of appreciable magnitude. So, it is not a significant limitation and has no great clinical importance. Of course, with infusions longer than 48 hours this could become a significant limitation, but at the moment that is unknown. Practically, infusions should not be recommended to exceed 48 hours.

Study 94-006. This was a randomized, double-blind, 4-arm, fixed infusion rate (for 4 hours) study of patients that were judged to have "hypertensive crisis or emergency hypertension" by the physician at time of enrollment. There were 107 patients randomized, 13 did not receive medication. So this was a study of 94 randomized subjects. Their average age was 44.9 years, 55% were male, 79% were african-American, and their mean blood pressure was 208/134 mm Hg at baseline. Eight of the 94 were randomized on the basis of blood pressure alone (diastolic blood pressure > 140 mm Hg). The remainder were randomized on the basis of a diastolic blood pressure >120 mm Hg and evidence of end organ involvement (cardiovascular, or renal, or neurological or ophthalmological). Thirty patients (32% of the 94 randomized patients) had papilledema, Grade III-IV retinopathy or acute changes in vision, 56 (60% of the 94 randomized patients) had chest pain, shortness of breath, pulmonary edema, or ECG evidence of ischemia, 39 (41% of randomized patients) had oliguria, elevated BUN and/or creatinine, or hematuria. This was a population that was pretty sick, but as pointed out by Dr. Karkowsky, exact protocol criteria were not uniformly met. I do not think that is a significant factor with respect our evaluation of the merits of this study.

There was neither a placebo, nor a positive-control arm in this trial. The four fixed-dose infusion rate arms were 0.01, 0.03, 0.10, and 0.3 micrograms/kg/minute. All statistical comparisons were made with respect to the effects measured in 0.01 micrograms/kg/minute arm. Only for the 1st hour of study was there absolute need to maintain only the randomized, fixed-dose infusion, for the next 3 hours dose was allowed to be doubled (once an hour). After 4 hours of infusion, the clinician could do as he or she thought warranted. At the end of 4 hours, 76% of patients had received no dose increase and 15% had received one dose increase. So, 91% of randomized patients were within a factor of 2 of their randomized dose (fixed-dose increments were by a factor of 3). All formal analyses were done for 0 to 4 hours after infusion was begun and were "intention-to-treat".

There were no events (i.e., death, stroke, myocardial infarction, etc.) observed during the entire trial. This was planned as a blood pressure trial, and it is not possible to (even retrospectively) look at clinical event rates. That does not matter with respect to our current decision making process.

Appended Figure 3 shows the results on diastolic blood pressure. The Figure shows the decrease from baseline over and above that occurring with the 0.01 microgram/kg/minute infusion. The p value for a difference from the lowest infusion rate at 4 hours for the 0.3 microgram/kg/minute infusion group was

0.0001. The absolute magnitude of reduction was -29.1 mm Hg at 4 hours (that of 0.01 group being -11.5). There is no question about fenoldopam's ability to lower blood pressure in a population of hypertensive patients that most would agree required hospitalization and required blood pressure to be lowered promptly.

Other studies. There are at least 10 other studies (part of the NDA submitted in 1988) that reproducibly show a decrease in systolic and diastolic blood pressure associated with intravenous fenoldopam infusions. Some are more convincing than others. Some are patients who were undergoing surgery and/or post-operative hypertension. The reviews are attached. I see no reason to detail them one by one. In 1991, we were sure fenoldopam lowered blood pressure, but were unsure of the dose and were unsure that an appropriate patient population had been studied. At this point, all of my uncertainty is gone.

Safety

Dr. Karkowsky has summarized the safety data base (starting on page 17 of his review dated May 8, 1997). Of the 1226 patients enrolled in hypertension studies, there were a total of 2 **deaths** that occurred during fenoldopam infusions (one patient with congestive heart failure who died of ventricular fibrillation and another who died of complications associated with rejection of a heart transplant). There were, in the total data base associated with intravenous fenoldopam, an additional 22 deaths that occurred from 1 to 23 days following infusion of fenoldopam. None of these 22 deaths seem even remotely attributable to exposure to fenoldopam.

A careful look at **drop-outs** for reasons other than death, similarly leaves no impression that fenoldopam has effects (other than decreasing blood pressure) that are of any concern, save the increase in intraocular pressure. The latter also being of insufficient magnitude over a short duration (e.g. 48 hours) of infusion to be of any concern other than to mention.

Tachycardia. Part of the cardiovascular effect of fenoldopam is tachycardia, that is also dose-related. At present there is almost no systematic study of the hemodynamic interaction between beta-blockers and fenoldopam. It is a little embarrassing to me that it took 9 years to recognize that tachycardia occurs, but it surely does; mean increases of pulse as great as 26 beats/minute. The tachycardiac effects present two potential concerns.

First, tachycardia is generally believed not be "good" in patients who are ill and have coronary-artery disease, especially in the face of elevated blood pressure. The lack of clinical events in the more than 1000 hypertensive patients actually studied give considerable reassurance in that regard.

Second, because of the perception that tachycardia is undesirable, beta-blockers are likely to be used when the tachycardia occurs. There is no assurance, at all, that the dose-response relationships for blood pressure described by the studies that support approval would be the same in patients pretreated with a beta-blocker or that the hypotensive effect of beta-blockers might be greater than expected if the beta-blocker was given to treat the fenoldopam induced tachycardia; not to mention the possible additive or potentiating effect to the dose of fenoldopam already on-board.

I cannot realistically see the first issue being resolved by any clinical trial I can imagine. The second issue is an "Instructions for Use" issue and could be very well addressed by controlled clinical trials. Neurex has agreed to contemplate the design of such trials and has agreed to conduct mutually agreeable trials post-marketing. The approvable letter acknowledges these agreements and recommends meetings with the Division to work out the details.

In the meantime labelling should be clear with respect to the indeterminate effects that beta blockers might have on how fenoldopam should be used.

Speed of lowering blood pressure. There is no evidence, that I am aware of, that supports the notion that blood pressure in patients with malignant hypertension and hypertensive emergencies needs to lowered over a time course of minutes.

Indications

I look forward to seeing your recommendation for Indications. For background, there are 5 parenteral antihypertensive products approved. Their Indications sections are reproduced below as they appear in the 1997 PDR.

1) Nicardipine (Cardene IV).

Indication: Cardene IV is indicated for the short-term treatment of hypertension when oral therapy is not feasible or not desirable.

For prolonged control of blood pressure, patients should be transferred to oral medication as soon as their clinical condition permits (see "Dosage and Administration").

Nicardipine is also available in oral dosage forms, that are indicated for the treatment of hypertension and angina.

2) Labetalol hydrochloride (Normodyne Injection).

Indication: Normodyne (labetalol Hcl) injection is indicated for control of blood pressure in severe hypertension.

Labetalol is also available in oral dosage forms, that are indicated for the treatment of hypertension.

3) Enalaprilat (Vasotec IV).

VASOTEC I.V. is indicated for the treatment of hypertension when oral therapy is not practical.

VASOTEC I.V. has been studied with only one other antihypertensive agent, furosemide, which showed approximately additive effects on blood pressure. Enalapril, the pro-drug of enalaprilat, has been used extensively with a variety of other antihypertensive agents, without apparent difficulty except for occasional hypotension.

In using VASOTEC I.V., consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and available data are insufficient to show that VASOTEC I.V. does not have a similar risk. (See WARNINGS.) In considering use of VASOTEC I.V., it should be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, it should be noted that black patients receiving ACE inhibitor monotherapy have been reported to have a higher incidence of angioedema compared to non-blacks. (See WARNINGS, *Angioedema*.)

Enalapril, the pro-drug of enalaprilat, is available in oral dosage forms, that is indicated for hypertension and congestive heart failure.

4) Diazoxide (Hyperstat IV).

Indication: Hyperstat IV injection is indicated for short-term use in the emergency reduction of blood pressure in severe, non-malignant and malignant hypertension in hospitalized adults; and in acute severe hypertension in hospitalized children, when prompt and urgent decrease of diastolic blood pressure is required. Treatment with orally effective antihypertensive agents should not be instituted until blood pressure has stabilized. The use of Hyperstat IV injection for longer than 10 days is not recommended.

HYPERSTAT I.V. injection is ineffective against hypertension due to pheochromocytoma.

There is no oral dosage form available.

5) Sodium Nitroprusside has no package insert in the PDR (1997).

Indication: Sodium nitroprusside is indicated for the immediate reduction of blood pressure of patients in hypertensive crises. Concomitant longer-acting antihypertensive medication should be administered so that the duration of treatment with sodium nitroprusside can be minimized.

Sodium nitroprusside is also indicated for producing controlled hypotension in order to reduce bleeding during surgery.

Sodium nitroprusside is also indicated for the treatment of acute congestive heart failure.

There is no oral dosage form available.

My suggestion for fenoldopam INDICATIONS is:

Indications: CORLOPAM is indicated for the in-hospital, short-term (48 hours or less) management of severe hypertension when oral therapy is either not practical or not feasible and when emergency reduction of blood pressure is clinically indicated (e.g., malignant hypertension with deteriorating end-organ function). Transition to oral therapy with some other agent can begin at any time after the blood pressure appears stable during a fenoldopam infusion.

Dosing and Administration

Another difficult judgement call. Dosing and administration sections that exist for the above approved drugs follow. All are fairly complicated and very detailed.

1) Nicardipine (Cardene IV).
Cardene I.V. (nicardipine hydrochloride) is intended for intravenous use. DOSAGE MUST BE INDIVIDUALIZED depending upon the severity of hypertension and the response of the patient during dosing.

Blood pressure should be monitored both during and after the infusion; too rapid or excessive reduction in either systolic or diastolic blood pressure during parenteral treatment should be avoided.

PREPARATION

WARNING: AMPULS MUST BE DILUTED BEFORE INFUSION

Dilution: Cardene I.V. is administered by slow continuous infusion at a CONCENTRATION OF 0.1 MG/ML. Each ampul (25 mg) should be diluted with 240 mL of compatible intravenous fluid (see below), resulting in 250 mL of solution at a concentration of 0.1 mg/mL.

Cardene I.V. has been found to be compatible and stable in glass or polyvinyl chloride containers for 24 hours at controlled room temperature with:

Dextrose (5%) Injection, USP
Dextrose (5%) and Sodium Chloride (0.45%) Injection, USP
Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
Dextrose (5%) with 40 mEq Potassium, USP
Sodium Chloride (0.45%) Injection, USP
Sodium Chloride (0.9%) Injection, USP

Cardene I.V. is NOT compatible with Sodium Bicarbonate (5%) Injection, USP or Lactated Ringer's Injection, USP.

THE DILUTED SOLUTION IS STABLE FOR 24 HOURS AT ROOM TEMPERATURE.

Inspection: As with all parenteral drugs, Cardene I.V. should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Cardene I.V. is normally light yellow in color.

DOSAGE

As a Substitute for Oral Nicardipine Therapy

The intravenous infusion rate required to produce an average plasma concentration equivalent to a given oral dose at steady state is shown in the following table:

Oral Cardene Dose	Equivalent I.V. Infusion Rate
20 mg q8h	0.5 mg/hr
30 mg q8h	1.2 mg/hr
40 mg q8h	2.2 mg/hr

For Initiation of Therapy in a Drug Free Patient

The time course of blood pressure decrease is dependent on the initial rate of infusion and the frequency of dosage adjustment.

Cardene I.V. is administered by slow continuous infusion at a CONCENTRATION OF 0.1 MG/ML. With constant infusion, blood pressure begins to fall within minutes. It reaches about 50% of its ultimate decrease in about 45 minutes and does not reach final steady state for about 50 hours.

When treating acute hypertensive episodes in patients with chronic hypertension, discontinuation of infusion is followed by a 50% offset of action in 30 ± 7 minutes but plasma levels of drug and gradually decreasing antihypertensive effects exist for about 50 hours.

Titration: For gradual reduction in blood pressure, initiate therapy at 50 mL/hr (5.0 mg/hr). If desired blood pressure reduction is not achieved at this dose, the infusion rate may be increased by 25 mL/hr (2.5 mg/hr) every 15 minutes up to a maximum of 150 mL/hr (15.0 mg/hr), until desired blood pressure reduction is achieved. For more rapid blood pressure reduction, initiate therapy at 50 mL/hr (5.0 mg/hr). If desired blood pressure reduction is not achieved at this dose, the infusion rate may be increased by 25 mL/hr (2.5 mg/hr) every 5 minutes up to a maximum of 150 mL/hr (15.0 mg/hr), until desired blood pressure reduction is achieved. Following achievement of the blood pressure goal, the infusion rate should be decreased to 30 mL/hr (3 mg/hr).

Maintenance: The rate of infusion should be adjusted as needed to maintain desired response.

CONDITIONS REQUIRING INFUSION ADJUSTMENT

Hypotension or Tachycardia: If there is concern of impending hypotension or tachycardia, the infusion should be discontinued. When blood pressure has stabilized, infusion of Cardene I.V. may be restarted at low doses such as 30-50 mL/hr (3.0-5.0 mg/hr) and adjusted to maintain desired blood pressure.

Infusion Site Changes: Cardene I.V. should be continued as long as blood pressure control is needed. The infusion site should be changed every 12 hours if administered via peripheral vein.

Impaired Cardiac, Hepatic or Renal Function: Caution is advised when titrating Cardene I.V. in patients with congestive heart failure impaired hepatic or renal function (see "Precautions").

TRANSFER TO ORAL ANTIHYPERTENSIVE AGENTS

If treatment includes transfer to an oral antihypertensive agent other than Cardene capsules, therapy should generally be initiated upon discontinuation of Cardene I.V. If Cardene capsules are to be used, the first dose of a TID regimen should be administered 1 hour prior to discontinuation of the infusion.

2) Labetalol hydrochloride (Normodyne Injection).

NORMODYNE (labetalol HCl) Injection is intended for intravenous use in hospitalized patients. DOSAGE MUST BE INDIVIDUALIZED depending upon the severity of hypertension and the response of the patient during dosing.

Patients should always be kept in a supine position during the period of intravenous drug administration. A substantial fall in blood pressure on standing should be expected in these patients. The patient's ability to tolerate an upright position should be established before permitting any ambulation, such as using toilet facilities.

Either of two methods of administration of NORMODYNE (labetalol HCl) Injection may be used: a) repeated intravenous injections, b) slow continuous infusion.

Repeated Intravenous Injection: Initially, NORMODYNE (labetalol HCl) Injection should be given in a dose of 20 mg labetalol HCl (which corresponds to 0.25 mg/kg for an 80 kg patient) by slow intravenous injection over a 2-minute period.

Immediately before the injection and at 5 and 10 minutes after injection, supine blood pressure should be measured to evaluate response. Additional injections of 40 mg or 80 mg can be given at 10-minute intervals until a desired supine blood pressure is achieved or a total of 300 mg labetalol HCl has been injected. The maximum effect usually occurs within 5 minutes of each injection.

Slow Continuous Infusion NORMODYNE (labetalol HCl) Injection is prepared for intravenous continuous infusion by diluting the contents with commonly used intravenous fluids (see below). Examples of methods of preparing the infusion solutions are:

The contents of either two 20 mL vials (40 mL), or one 40 mL vial, are added to 160 mL of a commonly used intravenous fluid such that the resultant 200 mL of solution contains 200 mg of labetalol HCl, 1 mg/mL. The diluted solutions should be administered at a rate of 2 mL/min to deliver 2 mg/min.

Alternatively the contents of either two 20 mL vials (40 mL), or one 40 mL vial, of NORMODYNE (labetalol HCl) Injection are added to 250 mL of a commonly used intravenous fluid. The resultant solution will contain 200 mg of labetalol HCl, approximately 2 mg/3 mL. The diluted solutions should be administered at a rate of 3 mL/min to deliver approximately 2 mg/min.

The rate of infusion of the diluted solution may be adjusted according to the blood pressure response, at the discretion of the physician. To facilitate a desired rate of infusion, the diluted solution can be infused using a controlled administration mechanism, eg graduated burette or mechanically driven infusion pump.

Since the half-life of labetalol is 5 to 8 hours, steady-state blood levels (in the face of a constant rate of infusion) would not be reached during the usual infusion time period. The infusion should be continued until a satisfactory response is obtained and should then be stopped and oral labetalol HCl started (see below). The effective intravenous dose is usually in the range of 50 to 200 mg. A total dose of up to 300 mg may be required in some patients.

Blood Pressure Monitoring: The blood pressure should be monitored during and after completion of the infusion or intravenous injections. Rapid or excessive falls in either systolic or diastolic blood pressure during intravenous treatment should be avoided. In patients with excessive systolic hypertension, the decrease in systolic pressure should be used as indicator of effectiveness in addition to the response of the diastolic pressure.

Initiation of Dosing with NORMODYNE (labetalol HCl) Tablets: Subsequent oral dosing with NORMODYNE (labetalol HCl) Tablets should begin when it has been established that the supine diastolic blood pressure has begun to rise. The recommended initial dose is 200 mg, followed in 6-12 hours by an additional dose of 200 or 400 mg, depending on the blood pressure response. Thereafter, *inpatient titration with NORMODYNE (labetalol HCl) Tablets* may proceed as follows:

Inpatient Titration Instructions

Regimen	Daily Dose*
200 mg b.i.d.	400 mg
400 mg b.i.d.	800 mg
800 mg b.i.d.	1600 mg
1200 mg b.i.d.	2400 mg

*If needed, the total daily dose may be given in three divided doses.

While in the hospital, the dosage of NORMODYNE (labetalol HCl) Tablets may be increased at 1-day intervals to achieve the desired blood pressure reduction.

For subsequent outpatient titration or maintenance dosing see NORMODYNE (labetalol HCl) Tablets Product Information **DOSAGE AND ADMINISTRATION** for additional recommendations.

Compatibility with commonly used intravenous fluids:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

NORMODYNE (labetalol HCl) Injection was tested for compatibility with commonly used intravenous fluids at final concentrations of 1.25 mg to 3.75 mg labetalol HCl per mL of the mixture. NORMODYNE (labetalol HCl) Injection was found to be compatible with and stable (for 24 hours refrigerated or at room temperature) in mixtures with the following solutions:

Ringers Injection, USP
Lactated Ringers Injection, USP
5% Dextrose and Ringers Injection
5% Lactated Ringers and 5% Dextrose Injection
5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
5% Dextrose and 0.2% Sodium Chloride Injection, USP
2.5% Dextrose and 0.45% Sodium Chloride Injection, USP
5% Dextrose and 0.9% Sodium Chloride Injection, USP
5% Dextrose and 0.33% Sodium Chloride Injection, USP

NORMODYNE (labetalol HCl) Injection was NOT compatible with 5% Sodium Bicarbonate Injection, USP.

3) Enalaprilat (Vasotec IV)

FOR INTRAVENOUS ADMINISTRATION ONLY

The dose in hypertension is 1.25 mg every six hours administered intravenously over a five minute period. A clinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to four hours after dosing. The peak effects of the second and subsequent doses may exceed those of the first.

No dosage regimen for VASOTEC I.V. has been clearly demonstrated to be more effective in treating hypertension than 1.25 mg every six hours. However, in controlled clinical studies in hypertension, doses as high as 5 mg every six hours were well tolerated for up to 36 hours. There has been inadequate experience with doses greater than 20 mg per day.

In studies of patients with hypertension, VASOTEC I.V. has not been administered for periods longer than 48 hours. In other studies, patients have received VASOTEC I.V. for as long as seven days.

The dose for patients being converted to VASOTEC I.V. from oral therapy for hypertension with enalapril maleate is 1.25 mg every six hours. For conversion from intravenous to oral therapy, the recommended initial dose of Tablets VASOTEC (enalapril maleate) is 5 mg once a day with subsequent dosage adjustments as necessary.

Patients on Diuretic Therapy

For patients on diuretic therapy the recommended starting dose for hypertension is 0.625 mg administered intravenously over a five minute period. A clinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to four hours after dosing,

although most of the effect is usually apparent within the first hour. If after one hour there is an inadequate clinical response, the 0.625 mg dose may be repeated. Additional doses of 1.25 mg may be administered at six hour intervals.

For conversion from intravenous to oral therapy, the recommended initial dose of Tablets VASOTEC (enalapril maleate) for patients who have responded to 0.625 mg of enalaprilat every six hours is 2.5 mg once a day with subsequent dosage adjustment as necessary.

Dosage Adjustment in Renal Impairment

The usual dose of 1.25 mg of enalaprilat every six hours is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥3 mg/dL), the initial dose is 0.625 mg. (See WARNINGS.)

If after one hour there is an inadequate clinical response, the 0.625 mg dose may be repeated. Additional doses of 1.25 mg may be administered at six hour intervals.

For dialysis patients, see below, *Patients at Risk of Excessive Hypotension.*

For conversion from intravenous to oral therapy, the recommended initial dose of Tablets VASOTEC (enalapril maleate) is 5 mg once a day for patients with creatinine clearance >30 mL/min and 2.5 mg once daily for patients with creatinine clearance ≤30 mL/min. Dosage should then be adjusted according to blood pressure response.

Patients at Risk of Excessive Hypotension

Hypertensive patients at risk of excessive hypotension include those with the following concurrent conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology (see WARNINGS). Single doses of enalaprilat as low as 0.2 mg have produced excessive hypotension in normotensive patients with these diagnoses. Because of the potential for an extreme hypotensive response in these patients, therapy should be started under very close medical supervision. The starting dose should be no greater than 0.625 mg administered intravenously over a period of no less than five minutes and preferably longer (up to one hour). Patients should be followed closely whenever the dose of enalaprilat is adjusted and/or diuretic is increased.

Administration

VASOTEC I.V. should be administered as a slow intravenous infusion, as indicated above, over at least five minutes. It may be administered as provided or diluted with up to 50 mL of a compatible diluent.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use whenever solution and container permit.

Compatibility and Stability

VASOTEC I.V. as supplied and mixed with the following intravenous diluents has been found to maintain full activity for 24 hours at room temperature.

5 percent Dextrose Injection
0.9 percent Sodium Chloride Injection
0.9 Percent Sodium Chloride Injection in 5 percent Dextrose
5 percent Dextrose in Lactated Ringer's Injection
McGaw ISOLYTE E

4) Diazoxide (Hyperstat IV).

HYPERSTAT I.V. Injection was originally recommended for use by bolus administration of 300 mg. Recent studies have shown that minibolus administration of HYPERSTAT I.V. Injection, i.e., doses of 1 to 3 mg/kg repeated at intervals of 5 to 15 minutes is as effective in reducing blood pressure. Minibolus administration usually provides a more gradual reduction in blood pressure and thus may be expected to reduce the circulatory and neurological risks associated with acute hypotension.

HYPERSTAT I.V. Injection is administered undiluted and rapidly by intravenous injections of 1 to 3 mg/kg up to a maximum of 150 mg in a single injection. This dose may be repeated at intervals of 5 to 15 minutes until a satisfactory reduction in blood pressure (diastolic pressure below 100 mmHg) has been achieved.

With the patient recumbent, the calculated dose of HYPERSTAT I.V. Injection is administered intravenously in 30 seconds or less.

HYPERSTAT I.V. Injection should only be given into a peripheral vein. Do not administer it intramuscularly, subcutaneously, or into body cavities. Avoid extravasation of the drug into subcutaneous tissues.

Following the use of HYPERSTAT I.V. Injection, the blood pressure should be monitored closely until it has stabilized. Thereafter, measurements taken hourly during the balance of the effect should indicate any unusual response. A further decrease in blood pressure 30 minutes or more after injection should be investigated for causes other than the action of HYPERSTAT I.V. Injection. It is preferable that the patient remain supine for at least one hour after injection. In ambulatory patients, the blood pressure should also be measured with the patient standing before surveillance is ended. Repeated administration of HYPERSTAT I.V. Injection at intervals of 4 to 24 hours usually will maintain the blood pressure below pretreatment levels until a regimen of oral antihypertensive medication can be instituted. The interval between injections may be adjusted by the duration of the response to each injection. It is usually unnecessary to continue treatment with HYPERSTAT I.V. Injection for more than four to five days.

Since repeated administration of HYPERSTAT I.V. Injection can lead to sodium and water retention, administration of a diuretic may be necessary both for maximal blood pressure reduction and to avoid congestive heart failure. (See **CLINICAL PHARMACOLOGY**.)

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

5) Sodium Nitroprusside has no package insert in the PDR (1996).

Reconstitution Directions for Univial:

1. Remove protective cap.

   Turn plunger-stopper a quarter turn and press to force sterile water for injection into lower chamber.

2. Shake gently to effect solution.

   Use only a clear solution.

3. Sterilize top of stopper with a suitable germicide.

4. Insert needle through the center of stopper until tip is barely visible.

   Withdraw dose.

Reconstitution Directions for Fliptop Vial:

Dissolve the contents of the Fliptop Vial with 2.3 mL of 5% Dextrose Injection, USP.

Dilution to proper strength for infusion: Depending on the desired concentration, the initially reconstituted solution containing 50 mg of NITROPRESS must be further diluted in 250-100 mL of sterile 5% dextrose injection. The diluted solution should be protected from light, using the supplied opaque sleeve, aluminum foil, or other opaque material. It is not necessary to cover the infusion drip chamber or the tubing.

Verification of the chemical integrity of the product: Sodium nitroprusside solution can be inactivated by reactions with trace contaminants. The products of these reactions are often blue, green, or red, much brighter than the faint brownish color of unreacted NITROPRESS. Discolored solutions, or solutions in which particulate matter is visible, should not be used. If properly protected from light, the freshly reconstituted and diluted solution is stable for 24 hours.

No other drugs should be administered in the same solution with sodium nitroprusside.

Avoidance of excessive hypotension: While the average effective rate in adults and children is about 3 µg/kg/min, some patients will become dangerously hypotensive when they receive NITROPRESS at this rate. Infusion of sodium nitroprusside should therefore be started at a very low rate (0.3 µg/kg/min), with upward titration every few minutes until the desired effect is achieved or the maximum recommended infusion rate (10 µg/kg/min) has been reached.

Because sodium nitroprusside's hypotensive effect is very rapid in onset and in dissipation, small variations in infusion rate can lead to wide, undesirable variations in blood pressure. **Sodium nitroprusside should not be infused through ordinary I.V. apparatus, regulated only by gravity and mechanical clamps. Only an infusion pump, preferably a volumetric pump, should be used.**

Because sodium nitroprusside can induce essentially unlimited blood-pressure reduction, **the blood pressure of a patient receiving this drug must be continuously monitored,** using either a continually reinflated sphygmomanometer or (preferably) an intra-arterial pressure sensor. Special caution should be used in elderly patients, since they may be more sensitive to the hypotensive effects of the drug.

When sodium nitroprusside is used in the treatment of acute congestive heart failure, titration of the infusion rate must be guided by the results of invasive hemodynamic monitoring with simultaneous monitoring of urine output. Sodium nitroprusside can be titrated by increasing the infusion rate until:

- measured cardiac output is no longer increasing,
- Systemic blood pressure cannot be further reduced without compromising the perfusion of vital organs, or
- the maximum recommended infusion rate has been reached, whichever comes earliest. Specific hemodynamic goals must be tailored to the clinical situation, but improvements in cardiac output and left ventricular filling pressure must not be purchased at the price of undue hypotension and consequent hypoperfusion.

The table below shows the infusion rates corresponding to the recommended initial and maximal doses (0.3 µg/kg/min and 10 µg/kg/min, respectively) for both adults and children of various weights. Some of the listed infusion rates are so slow or so rapid as to be impractical, and these practicalities must be considered when the concentration to be used is selected. Note that when the concentration used in a given patient is changed, the tubing is still filled with a solution at the previous concentration.

Avoidance of cyanide toxicity: As described in CLINICAL PHARMACOLOGY above, when more than 500 µg/kg of sodium nitroprusside is administered faster than 2 µg/kg/min, cyanide is generated faster than the unaided patient can eliminate it. Administration of sodium thiosulfate has been shown to increase the rate of cyanide processing, reducing the hazard of cyanide toxicity. Although toxic reactions to sodium thiosulfate have not been reported, the co-infusion regimen has not been extensively studied, and it cannot be recommended without reservation. In one study, sodium thiosulfate appeared to potentiate the hypotensive effects of sodium nitroprusside.

Co-infusion of sodium thiosulfate have been administered at rates of 5-10 times that of sodium nitroprusside. Care must be taken to avoid the indiscriminate use of prolonged or high doses of sodium nitroprusside with sodium thiosulfate as this may result in thiocyanate toxicity and hypovolemia. Incautious administration of sodium nitroprusside must still be avoided and all of the precautions concerning sodium nitroprusside administration must still be observed.

Infusion Rates (mL/hour) to Achieve
Initial (0.3 µg/kg/min) and
Maximal (10 µg/kg/min)
Dosing of NITROPRESS

Volume	250 mL		500 mL		1000 mL	
NITROPRESS	50 mg		50 mg		50 mg	
concentration	200 µg/mL		100 µg/mL		50 µg/mL	
pt	weight					
kg	**lbs**	**init**	**max**	**init**	**max**	**init**	**max**
10	22	1	30	2	60	4	120
20	44	2	60	4	120	7	240
30	66	3	90	5	180	11	360
40	88	4	120	7	240	14	480
50	110	5	150	9	300	18	600
60	132	5	180	11	360	22	720
70	154	6	210	13	420	25	840
80	176	7	240	14	480	29	960
90	198	8	270	16	540	32	1080
100	220	9	300	18	600	36	1200

Consideration of methemoglobinemia and thiocyanate toxicity: Rare patients receiving more than 10 mg/kg of sodium nitroprusside will develop methemoglobinemia; other patients, especially those with impaired renal function, will predictably develop thiocyanate toxicity after prolonged, rapid infusions. In accordance with the descriptions in ADVERSE REACTIONS above, patients with suggestive findings should be tested for these toxicities.

My suggestion for fenoldopam DOSAGE and ADMINISTRATION is:

Except for the 4 sentences I have added in my mark-up of the "clean draft", I like the fenoldopam better than any of the above. In particular, I think the reference to the clinical trials results for choosing infusion rates is a good idea and the tables in the clinical trials are similarly a good idea.

Summary

Everything seems in order, the labelling is suitable for your markup. We hope that the transmission package allows you to complete this action without having to contact the Division, but we would pleased to discuss any aspect that we did not make clear.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

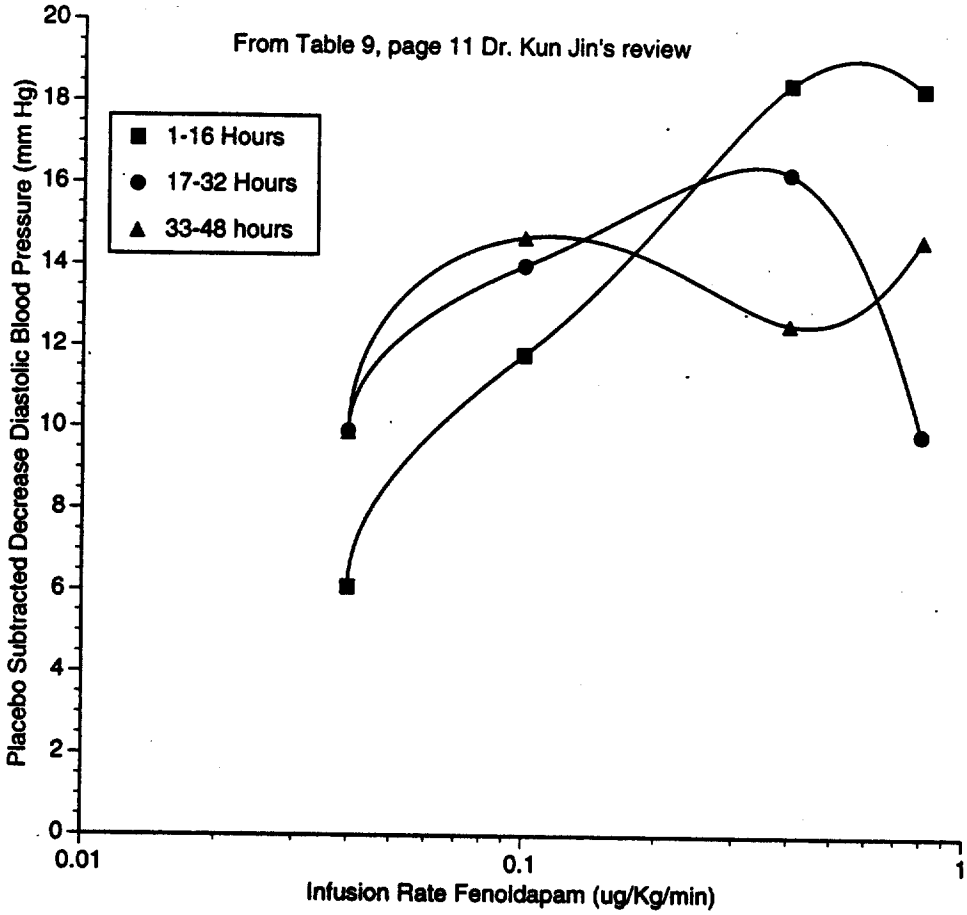

Figure 1. Results of Study 94-005. Diastolic blood pressure. Lines are spline.

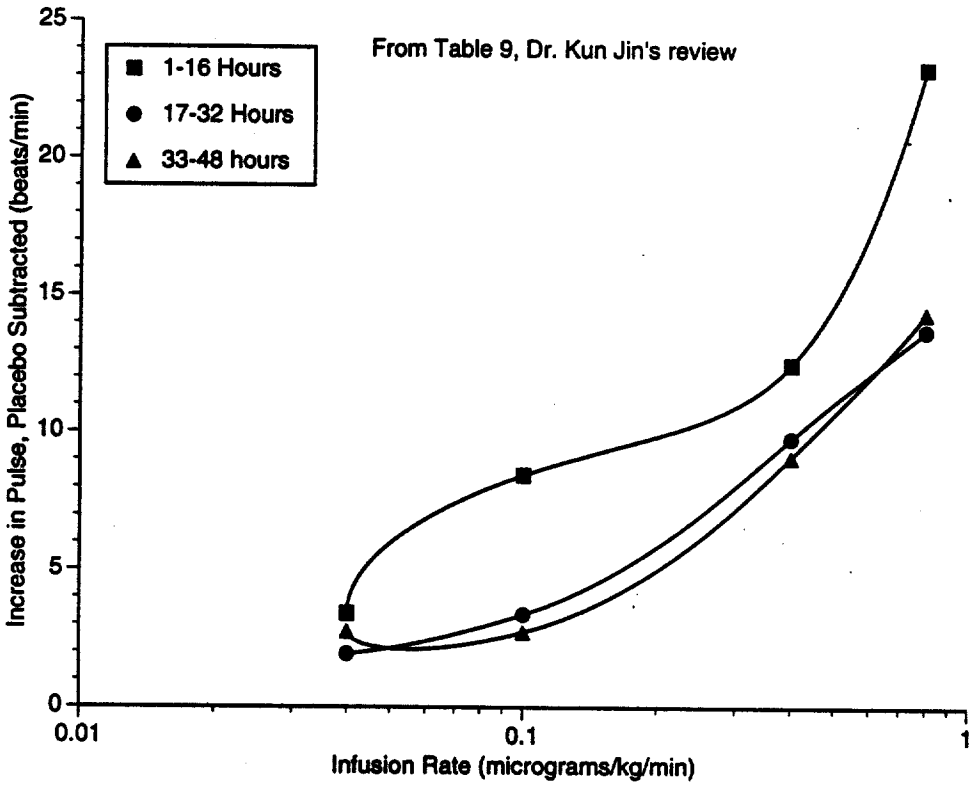

Figure 2. Results of Study 94-005. Pulse. Lines are spline.

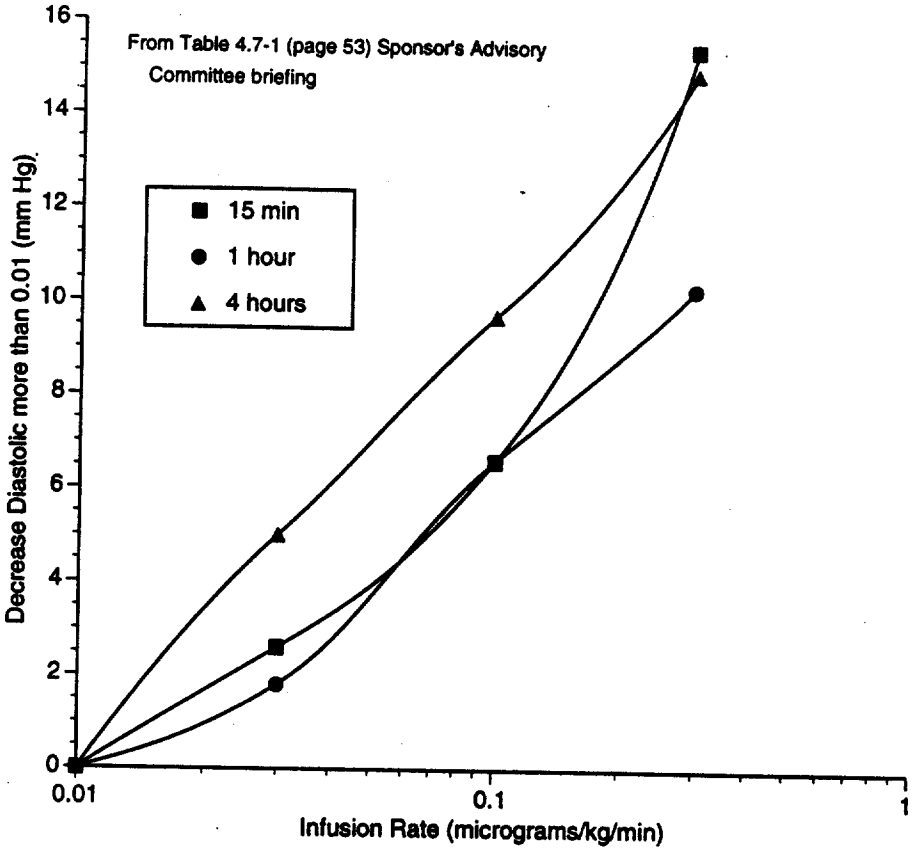

Figure 3. Results of trial 94-006. Diastolic blood pressure decrease. Plotted as decrease greater than that occurring in the 0.01 micrograms/kg/minute group, 15 minutes, 1 hour and 4 hours after the beginning of infusion. Lines are drawn by spline.

(527)

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Dan Boring HFD-530

FROM: Division of Cardio-Renal HFD- 110
Attention: Robert Wolters Phone 4-5376

DATE: January 16, 1996

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Corlopam NDA/ANDA# 19-922

Company Name: Neurex

Established name, including dosage form: Fenoldopam Injection 10 mg/ml

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy): Hypertension emergencies

Initial comments from the submitter: (concerns, observations, etc.)
This NDA was originally submitted by the then SKF in 1988. SFB withdrew the NDA and sold it to Neurex.

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 93

Consult #527 (HFD-T10)

CORLOPAM Fenoldopam Injection

A review no name which sounds like or looks like the proposed name.

The Committee has no reason to find the proposed name unacceptable.

CDER labeling and Nomenclature Committee

W Boring, Chair

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL