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NDA 20-664

10 June 1996

Pharmacia, Inc.
P.O. Box 16529
Columbus, OH 43216

Submission: 26,27 Dec 95

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original Summary

Dostinex (Cabergoline) [FCE 21336]

Long-acting dopamine (D_2) receptor agonist with antiprolactin activity.

Indicated Use: Treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas.

Related: INDs (HFD-120);

Dosage and Administration:

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(continued next page)

cc: Original NDA 20-664, IND [redacted] HFD-24 JDeGeorge; HFD-400 JContrera; HFD-345; HFD-510 NDA 20-664, IND [redacted] HFD-510 AJordan; HFD-510 DHertig

David H. Hertig
Pharmacologist

A Jordan
6/14

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(continuation)

REF - Original Review of IND (HFD-120) dtd. 12 Oct 89 (attached).
IND - Original Review of IND (HFD-510) dtd. 18 Jan 91 (attached).
2,3 etc. - This review.

Chemical Name:
N-[3-(Dimethylamino)propyl]N-[(ethylamino)carbonyl]-6-(2-propenyl)-8ß-ergoline-8-carboxamide (Code Name: FCE 21336)

Foreign Studies: Yes.

Preclinical Studies: Includes studies not covered in prior reviews.

Pharmacology and Dopaminergic Activity:

A study of the dopaminergic activity of FCE 21589, FCE 21590, and FCE 21904 (metabolites of cabergoline) in 6-OHDA lesioned rats showed only FCE 21904 to induce contralateral turning behavior at 0.5 and 1.0 mg/kg s.c. The effect was shorter by about 5 hr than that of cabergoline. The rotational affect of FCE 21904 was completely inhibited 99% by the selective D-2 agonist 1-sulpiride and only 30% by D-1 antagonists SCH 23390.

The effects of cabergoline were tested on MPTP (1-methyl-4-phenyl-1,2,36-tetrahydropyridine)-induced Parkinsonism in monkeys. Cabergoline administered s.c. and orally reversed the parkinsonian syndrome in all monkeys with minimal effective doses being 0.1 mg/kg s.c. and 2 mg/kg p.o. The effect was dose-dependent and long-lasting; higher doses inducing more intense and longer effects.

The acute behavioral effects of oral administration were investigated by [redacted] (Report 237i; Doc 9550032; KSI 42b/920600 dtd Oct 1992; Batch 9003C308; Q.A.: Present) in the Cynomolgus monkey.

CG-101 (cabergoline) administered orally at 10 mg/kg to 1M;1F naive monkeys produced no appreciable dose-related changes in behavior. Doses of 15, 20, and repeat 10 mg/kg administration produced behavioral changes principally comprised of hyperactivity and marked agitation from 24 hours post dose and up to 72 hours. Neither animal showed any consistent dose-related changes in bodyweight or rectal temperature. Food consumption was satisfactory.

An assessment of the effects on the morphine- and phenobarbitone-dependent and withdrawal in cynomolgus monkeys was carried out by (Report 236i, Doc 9550031; KSI 42d/920700 dtd Oct 1992; Batch 9003C308; Q.A.: Present).

Assessment was made of the ability of a single 20 mg/kg oral dose of CG-101 (cabergoline) to suppress the opioid and barbiturate withdrawal syndrome in each of 4 morphine- and 4 phenobarbitone-dependent withdrawal cynomolgus monkeys.

Single doses of phenobarbitone sodium and morphine sulphate clearly suppressed the majority of the behavioral changes observed. Minimal increases in rectal temperature were seen with these drugs in contrast with notable decreases seen with CG-101.

Both CG-101 (cabergoline) and vehicle (phosphoric acid) failed to overtly modify the withdrawal syndrome in any monkey. Thus, it was concluded that under the conditions tested 20 mg/kg CG-101 is unlikely to show any opioid- or barbiturate-like dependence liability.

ADME:

Additional ADME findings included the following information:

Rats received an oral dose of 0.5 mg/kg (as base) of [^{14}C]FCE 21336 and total radioactivity was collected over 192 h. The main part was excreted in the feces (ca 91% of the dose), less than 11% of the dose was recovered in the urine. The urinary excretion was 7.8% after 24 hours and 10.0% after 72 hours; the fecal excretion accounted for 66.6% and 86.6% after 24 hrs. and 72 hrs. Radioactivity in expired air was 0.04% of the dose in the 0-24 hour interval and not detected later. It is reported that data are in good agreement with previous [^{3}H]-FCE 21336 studies.

[^{3}H]-FCE 21336 was given to female rabbits at 1 mg/kg orally and 0.1 mg/kg i.v. Urinary excretion within 168 hr (after lyophilization of the samples) accounted for 6.48% (po) and 11.89% (iv) of the total radioactivity. Fecal excretion at the same period accounted for ca 69% after po and 63% after iv adm. Thus, biliary excretion appears to be the major route in rabbits. Most of the radioactivity was excreted within 96 hours.

Monkeys were given an oral dose of 0.25 mg/kg [^{14}C]-FCE 21336 and total recovery of radioactivity amounted to 83.8 ± 4.2% after 10 days. Fecal excretion accounted for 70.2 ± 5.1% of the dose while urinary excretion accounted for 12.7 ± 2.9%. Fecal elimination occurred mainly within 96 hr after dosing (67.6%) while most of the renal excretion occurred within 48 hrs (10.8%). Findings were similar to that seen previously with tritium-labelled drug. [The excretory balance in the monkey appeared to be less than that found in the rat.]

Urinary metabolism showed FCE 21336 to amount to 9.0% at 24 hrs. An acid derivative , FCE 21589 accounted for 20.5% and 6-deallyl FCE 21589 accounted for 11.1%. The major part of radioactivity was polar unidentified metabolites (28.2%); remaining radioactivity accounted for ca 5 or less percent. There was an increase in relative percentage of FCE 21336 in 24-72 hour urine with a concomitant decrease in polar compounds.

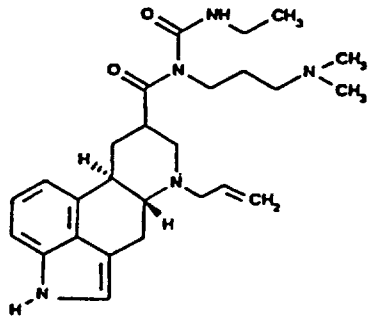
Pregnant Rat:

Pregnant rats were given a single oral 0.5 mg/kg dose of [^{14}C]-FCE 21336 (batch L-900920) on day 19 of gestation and killed at 15', 30', 1, 2, 4, 8, 24, hours afterwards. Blood, plasma and tissue radioactivity were measured in the dam and fetus.

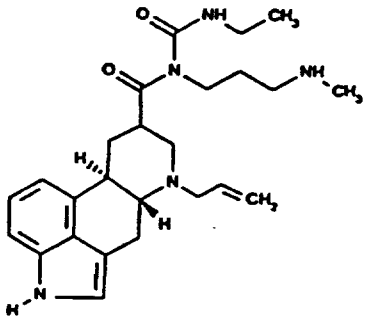
Mean concentrations of radioactivity in plasma were highest for those rats sacrificed at 0.25 hr (19.2 ng equivalent FCE-21336/ml) after which mean concentrations declined to 0.9 ng eq./ml at 24 hrs. In many tissues the maximum radioactivity concentration occurred in rats sacrificed at 4 to 8 hrs. Highest concentrations were in liver (2363.0 ng eq/g at 4 hr), kidney (413.5 ng eq/g at

Figure 1

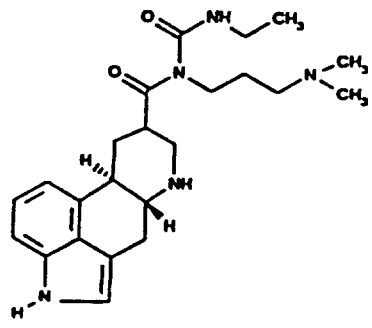
Molecular structures of cabergoline and of nine of its potential metabolites



FCE 21336



FCE 27395



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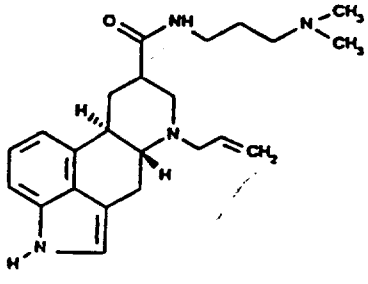

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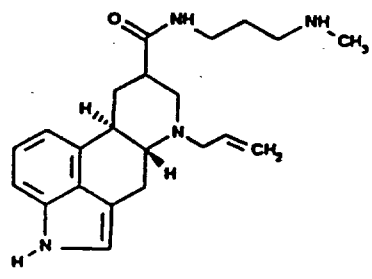
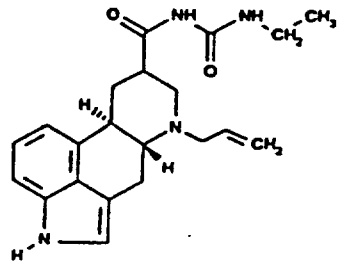


FCE 27393

Figure 1 (continued)



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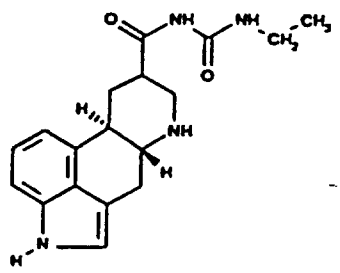
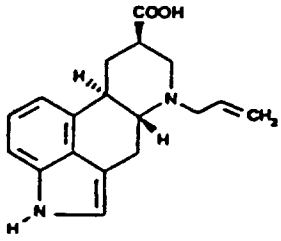
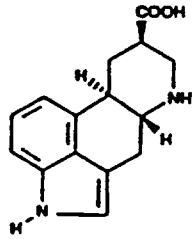


FCE 27400



FCE 21589



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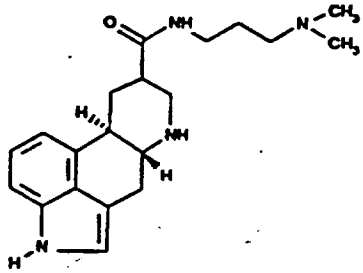

FCE 27390

8 hr). Concentrations in other areas included hypophysis (331. 4 ng eq./g at 8 hr), mammary gland (160.3 ng eq./g), placenta (134.2 ng eq./g), uterus (123.6 ng eq./g at 8 hr) and heart (122.0 ng eq./g at 4 hr.). The maximum radioactivity in brain, amniotic fluid and fetus were lower than that of plasma.

The ratio of liver concentrations/plasma concentrations in pregnant rats increased from 74 at 15' to 600 at 24 hours. Other tissues also showed increases of this ratio as a function of time. The ratio of blood concentrations in fetus/blood concentrations in the pregnant rat was 0.2-0.4 until 4 hours after dosing and 0.7 at 8 and 24 hours.

Biliary excretion and metabolism of radioactivity of [^{14}C]-FCE 21336 were studied in female rats following oral administration of 0.5 mg/kg diphosphate.

Bile radioactivity accounted for 7.06 ± 4.78% of the dose at 0-4 hrs, for 4.86 ± 1,08% at 4-8 hrs and for 7.35 ± 2.25% at 8-24 hrs for a total recovery of 19.27 ±4.09% of the radioactive dose.

No appreciable amount of unchanged drug was in the bile, the N-demethyl derivative FCE 27395 accounted for 12% of biliary radioactivity at 0-4 hrs, 7% in 4-8 hrs and 4% in 8-24 hr bile. About 9% was the acid derivative FCE 21589 for each time interval, and the N-deallyl derivative FCE 27391 accounted for 3-4%. The amide FCE 21590 was not detectable, the N-demethyl derivative FCE 27393 was ca 7% at 0-4 hrs, 5% at 4-8 hrs and 4% in the 8-24 hr bile. The remaining radioactivity was constituted by many unknown metabolites.

Rat Liver Inducing Enzyme Properties:

Cabergoline was given daily by gavage to male and female CD(SD)Br rats at doses of 0.1, 0.5 or 1.5 mg/kg for 14 days.

The cyanide-insensitive ß-oxidation determined as a marker for peroxisomes was slightly diminished in male rats (70% of control). The cystolic epoxide hydroxylase as measured using the diagnostic substrate trans stilbene oxide was weakly but statistically enhanced in female rat livers (2.7 fold). There was no detectable influence of cyctosolic flutathione S-transferase activity. There was a marginal (1.3 fold) increase in microsomal epoxide hydroxylase activity in female liver. Some enzyme activities of different cytochrome P-450 dependent monoxygenases were moderately affected. 15ß-Hydroxylation of testosterone (specific for P-450 3A family) was decreased 2 fold. O-dealkylation of 7-pentoxyresorufin was moderately decreased to ca 30% of controls in males there was a 1.9 fold increase in 16ß-hydroxylation. In female rats the only statistically significant effects on monoxygenase activities were 1.5 fold increases in 7-ethoxyresorufin-deethylase activity and testosterone 2ß-hydroxylation (1.6 fold) and the 3 fold increase in 7-pentoxyresorufin O-dealkylation.

Effects of Cabergoline of Rat Hepatic Microsomal Cytochromes P450:

Interaction between FCE 21336 and liver cytochromes p450 from rats treated by various inducers of monooxygenases was studied.

Cytochromes p450 from rats treated with phenobarbital (PB), 3-methyl-cholanthrene (3MC) and clofibrate (CLO) did not give significant spectral interactions. P450s from dexamethasone and untreated rats gave weak type I interactions corresponding to the formation of a P450 substrate complex (only formed with less than 7% of microsomal p450.

No destruction of P450 was seen after oxidation of FCE 21336 by rat liver microsomes in the presence of NADPH. Microsomes from untreated or rats treated by PB, 3MC, CLO showed no formation of any P450-iron-metabolite complex during oxidation.

Oxidation of FCE 21336 by DEX-treated rat liver microsomes and NADPH led to an unknown complex structure (possibly P450-iron(III)-metabolite).

Study of Metabolite Dopaminergic Activity:

The dopaminergic activity of FCE 21589, FCE 21590 and FCE 21904 (metabolites of Cabergoline) administered s.c. at doses of 0.5 and 1 mg/kg were studied in 6-OHDA lesioned rats (unilateral lesion of the substantia nigra) in comparison to parent compound.

Only FCE 21904 induced contralateral turning behavior at 0.5 and 1.0 mg/kg (effect shorter by ca 5 hr than that of cabergoline).

The FCE 21904 rotational effect was 99% inhibited by the selective D-2 antagonist l-sulpiride but only 30% by the D-1 antagonist SCH 23390.

Thus only FCE 21904 showed dopaminergic properties mostly of the D-2 type.

Measurement in Milk:

The secretion of radioactivity in milk from lactating female rats was investigated following 0.5 mg/kg [^{14}C]FCE 21336 (batch 1-900920) p.o. on the 14th day after parturition. Rats were sacrificed at 0.5, 1, 2, 4, 8, 24, 48 and 168 hours after dosing and plasma and milk radioactivity concentrations were measured.

Plasma radioactivity was highest at 1 hour (8.7 ng equivalents of FCE-21336/ml) after which it decreased to 0.9 ng equivalent/ml at 24 hours.

Mean concentrations of radioactivity in milk were highest in rats sacrificed at 8 hrs after dosing (53.6 ng eq. of FCE-21336/ml) after which radioactive concentration decreased to 6.6 ng eq./ml at 168 hours; terminal half-life for radioactive concentration in milk was 54.7 hours.

Radioactivity was much higher in milk than in plasma at all times with the ratio of milk/plasma increasing from 2 to 50 from 30' to 48 hours. It appears from this study that Cabergoline and/or its metabolites tend to accumulate in milk.

Toxicokinetics: Additional Information.

Mouse - Cabergoline plasma levels in mice at the 1st, 7th and 28th day at doses of 0.14 and 0.96 mg/kg/day (two highest doses employed in mouse CA study) showed large inter-individual differences. The AUCs after 0.96 mg/kg/day were 9-17x higher than those after 0.14 mg/kg/day. Plasma levels and AUCs were lower for females than for males. [It is reported that in parkinsonian patients treated daily with cabergoline doses of 7 mg (one of the highest employed for treatment of Parkinson's disease) shows that in mice AUC and (C_{max}) values were 2 and 5 times higher than those in humans, respectively.]

Rat - Cabergoline plasma at the Days 1, 7 and 28 in rats treated with 0.32, 3.2 and 5 mg/kg/day showed substantial inter-individual variability. At 0.32 mg/kg/day mean $AUC_{(0-24h)}$ values were similar at the different time periods. At 32 mg/kg/day the mean $AUC_{(0-24h)}$ increased substantially in both sexes. At 5 mg/kg/day male rats showed an increase in mean $AUC_{(0-24h)}$ after the 7th dose and a further increase after the 28th dose; there was an increase after the 7th dose in females with values remaining practically the same after the 28th. Exposure even after the lowest dose was fairly prolonged and measurable up to 24 hrs. after dosing.

According to the sponsor, rats in subchronic and chronic studies were adequately exposed to compound, the AUC values observed at 3.2 and 5 mg/kg/day being 36-72 times higher and C_{max} values being 66-148 times higher than those measured in humans (7 mg in Parkinson's). Also, in animals treated with the highest dose used in ratthe carcinogenic study (0.32 mg/kg/day) the exposure to the test compound was fairly prolonged, covering the interval between doses, and AUC and C_{max} values in rats were 2-3 times higher than those measured in humans.

Pharmacokinetics - Brain:

Radioactivity levels and cabergoline (batches 11267/6 and 11267/13) metabolism were determined in the brain of female rats at 4h, 8h, 16h, 24h and 48h after single, oral, nominal dose of 6 mg/kg [^{14}C]-cabergoline (free base) given to female rats. Total radioactivity levels were also evaluated in the substantia nigra, frontal cortex and nucleus accumbens at all time points, while the metabolism was determined in the frontal cortex and the nucleus accumbens, 8 h post-dosing. A number of areas were also studied 8 h after a 1 mg/kg dose.

Peripheral tissue showed the highest total radioactivity. The brain showed a major accumulation at all time points in the hypothalamus. Levels were high in the hippocampus, nucleus accumbens and striatum., but not at all time points. In the striatum the peak occurred at 8 hours. The metabolic profile was quite similar in the various areas for both doses. Most of the radioactivity in the brain was accounted for by cabergoline, particularly in the striatum where it was higher than 80% even 48 hrs. post-dose. Except for residual brain, the cabergoline percentage in other brain areas decreased to 31-55% at 48 hours and peripheral tissues decreased to 61-67%. Other metabolites were mainly FCE 27395 (2-62%) and FCE 27392 (0-9%) in amounts which were higher at 48 hrs. than at 4 hrs after dosing. A metabolite which could not be assigned to any of the available standards appeared in the tissues at 4 and 8 hours but was no longer detectable at 48 hrs (13-0%). Cabergoline was detected unchanged in urine and whole blood extracts at 8 and 24 hrs. Main metabolites in urine were FCE 21589 and FCE 27395, and in whole blood the main metabolites were FCE 27395 and UK1. Regression analysis of total radioactivity levels 8 hr after 0.5, 1, 3.5, and 6 mg/kg (includes other studies) showed linear dose-concentration relationships in the cerebellum, cerebrum and hypophysis. The amount of cabergoline in the striatum 8 hrs after a 0.5 mg/kg dose was estimated at ca 2 nM. It is reported that this value is in good agreement with the IC_{50} of cabergoline for inhibition of the specific [^{3}H]-N-n-normopropyl-apomorphine binding in rat striatum, suggesting that cabergoline might be the active species that elicits striatal dopamine D_2 receptor activity in the brain.

Reproduction Studies:

Reproduction-Teratology studies were not covered under the original Pharmacology review. Coverage for this section under Pharmacology review of 18,23 Jan 91 (attached) relied on sponsor's summaries submitted to IND [redacted] Portions of that Pharmacology review will be repeated below and following perusal of the complete reports any additional comments added as deemed necessary.

Fertility and General Reproductive Performance of the Rat by Oral Administration of FCE 21336 Diphosphate:

Report 4141 dtd Apr 1985. Batch: A 11002. Q.A.: Present

The diphosphate salt of Cabergoline was administered orally in distilled water to groups of 24 female Sprague-Dawley/Tif: RAI f (SPF) rats (141-160 g) at doses (as FCE 21336-base) of 0, 3, 6 or 12 µg/kg/day (vol. 1 ml/kg) by gavage for two weeks prior to mating until the end of the lactation period. Males were untreated. 12 females/group to be sacrificed on gestation Day 20 and the remaining 12 to be allowed to litter spontaneously.

Animals showed no pharmacotoxic signs, mortality or effect on food consumption or body weight gain. Although vaginal smears were positive and the number of matings was not significantly different from controls, fertility was totally inhibited. No other drug-related findings were reported. Study was discontinued at the end of the control's lactation period.

Seq.I: Fertility and General Reproductive Performance of the Rat by Oral Administration of FCE 21336 Diphosphate:

Report 413i dtd Dec 1984. Batch: A 11002

Q.A.: Present.

The study was performed in two parts (integrated report) with different dose-levels. In the first part only the male rats were treated with the test compound, in the second part only the female animals.

Fertility and breeding capacity were studied in Sprague-Dawley/Tif:RAI f (SPF) rats using a diphosphate in water solution (vol. 1 ml/kg) administered by gavage.

24 Males (60-80 g) were dosed for ten weeks prior to and during the mating period with 0, 20, 80 and 320 µg/kg/day (referring to FCE 21336-base) and then mated to untreated females (170-180 g).

24 Females (170-180 g) received 0. 0.5, 1 and 2 µg/kg/day (3 µg/kg/day caused complete inhibition of implantation - study above) for 2 weeks prior to mating with untreated males (250-270 g) and during the pregnancy and lactation periods.

For both parts of the study 12 Females per group were sacrificed on gestation day 20 and the remaining 12 females/group were allowed to litter and rear their young to weaning; 2 young rats/sex/litter were allowed to mature and used as filial F_1 generation breeding test with all of these dams being sacrificed on gestation day 20.

It is reported that fertility, breeding capacity and none of the standard reproductive parameters including behavior, general condition, food intake and body weight were impaired either in the treated males up to 320 µg/kg/day or in treated females of the F_0 generation or in the untreated F_1 generation at doses up to 2 µg/kg/day.

Testicle weights of the F_0 generation (part 1) were within the normal range and no treatment-related pathological changes were found at histological examination. One runt each was seen in part 1 at 20 and 80 µg/kg. In part 2 there was 1 runt at 1.0 µg/kg and all pups of 1 dam at 2.0 µg/kg were dead.

No pathological changes were reported in part 2 at the autopsy of the rats - dams and fetuses of both generations and pups of the F_0 generation. Histological examination of the reproductive organs of the dams of the F_0 generation were similar to that of control organs.

For part 2 F_0 spontaneous litters the fertility index and viability index of the high dose was slightly less than that of controls. For the part 2 F_0 laparotomy animals the resorption rate of the low and high dose were slightly greater than that of controls.

Part 1 F_1 generation fertility indices were 87.5, 79.2, 100 and 91.7% control thru high dose. There were 2 runts at the high dose. Part 2 F_1 fertility indices of 95.8, 83.3, 75.0 and 83.3% were somewhat lower than in part 1 but were reported to be within the spontaneous range. The number of fetuses reportedly showed no differences from controls.

2 µg/kg/day was reported as the maximum dose level which allows implantation in rats on repeated treatments.

Segment II - Influence of Cabergoline on the Pregnant Mouse and the Fetus by Oral Administration (Including postnatal behavioral/functional evaluation):

Report 6610/1/91 (Q 1232), Report 439i dtd Nov 1992 (Report 438i - Interim Report dtd Nov 1991) Batch: 7/90 Q.A.: Present.

Doses of 0, 0.5, 2.0, 8.0 mg/kg/day Cabergoline (base given as diphosphate aqueous soln.) were given orally by gavage to groups of 40 NMRI, HAN/BO (SPF) mice (22.7-34.0 g, 7 wks of age) Days 6 to 15 of pregnancy.

25 per group were sacrificed on Day 18 and 15 per group reared young to Day 22 of lactation. At weaning 1M;1F per litter were randomly selected and raised to maturity and evaluated for growth and development, behavior, learning and memory and reproductive performance prior to sacrifice. F_1 generation females were allowed to litter spontaneously and rear their pups to weaning.

F_0 Generation showed no drug-related clinical signs or deaths. Body weight gains of both the mid and high doses were affected. Food and water consumption also showed some reduced effects. No apparent drug-related changes were noted at autopsy.

Laparatomy on Day 18 showed no adverse effects on prenatal development. There were no apparent treatment-related fetal macroscopic abnormalities.

During the **Lactation** period one low dose dam died. Treated body weights were within normal range. High dose food and water consumption showed some decreases. Autopsy showed no treatment-related changes.

Spontaneous littering showed no treatment-related differences from control for low and mid-dose. There was a decreased number of pups at birth (including stillborn - 23 vs 1 control) for the high dose (2 dams with total dead litters); also reduction in number born vs implantation sites. Survival after 4 or 21 days were similar to that of controls.

Pup body weights were within normal at birth, however, high dose values were significantly below those of controls after 7, 14, and 21 days of lactation. No substance related changes were evident for viability and lactation indices, morphological landmarks and functional tests.

Compared to controls their were no abnormalities in number or pup weights or development during the 3-week lactation period. Autopsy of alive and stillborn showed no apparent drug-related changes.

F_1-reproduction test: F_1 brought to maturity did not show any definite differences from controls regarding clinical signs, body weight food and water consumption. Mating, pregnancy (1 low and 2 mid-dose were not pregnant), parturition and lactation phases showed no abnormalities. Fertility parameters were unchanged and development of the F_2 generation appeared normal. Although not statistically significant, the number of pups per dam at birth was slightly less for the high dose. Autopsy showed no apparent substance-related changes.

The drug showed no teratogenic properties.

According to the sponsor, the NOEL for dams was 0.5 mg/kg/day, that for embryos/fetuses was 8.0 mg/kg/day and that for pups was 2.0 mg/kg/day.

Oral Exploratory Teratology Test with Cabergoline on the Rat to Determine Effects on The Maintenance of Pregnancy:

Report 436i. Project 7173. Batch 7/90

Doses of 30 and 1000 mcg/kg were given orally by gavage to 5 fertilized female Crl:CD(SD) BR rats per group from Day 5, 6, 7, 8 or 9 to Day 13 of gestation. Maintenance of pregnancy was not affected at the dose of 30 mcg/kg starting from Day 7 or later of gestation and at 1000 mcg/kg starting from Day 9 and presumably later.

Prior to these dates adverse effects included vaginal bleeding and loss of pregnancy.

Preliminary Oral Teratology Study with Cabergoline in the Rat:

Report 401i dtd Aug 1982. Batch A 11002

This study was to determine the dosage range of cabergoline diphosphate (expressed as base) that would be compatible with normal gestation. The drug was given orally to female Crl: CD (SD) BR rats (10-11 per group) during the period of fetal organogenesis, according to the usual scheme for teratological studies using 5 dose levels from 100 to 6.25 τ/kg/day with administration Day 6 to 15 of gestation and sacrifice on Day 20.

Pregnancy was interrupted prematurely between days 8 and 10 at doses higher than 6.25 τ/kg with increasing frequency; significantly starting from 25 τ/kg.

Weight gain slightly reduced at 25 τ/kg was not modified at 6.25 and 12.50 τ/kg.

Resorptions increased slightly between 12.50 and 25.0 τ/kg. Other uterine content parameters did not vary significantly from controls.

Fetal body weight was slightly reduced at all doses.

The frequency of immature fetuses was increased (not significant at 6.25 τ/kg (due mainly to immaturity of fetuses in one litter).

Fetuses were viable with no external malformations (One 12.50 τ/kg fetus had moderate microsomia and acrocephalia).

Seq. I Teratology Study of FCE 21336 Diphosphate Administered Orally to Rats from Day 6 to 15 of Pregnancy:

Report 408i dtd June 1983. Batch: A 11001 Q.A.: Present.

Groups of 25 pregnant Charles River CD (SD) BR female rats (20-250 g) were given doses of 0, 6.25, 12.5, 25 µg/kg/day (as base) by gavage as the diphosphate in water on days 6-15 of pregnancy. Sacrifice was on day 20.

Fertility was not impaired and there were no drug-related symptoms. One Group 2 rat died due to pneumonitis ab ingestis. During the last few day of dosing body weight gains of the high dose were slightly lower than control values. Litter parameters were not affected at doses up to 12.5 µg/kg, however, at 25 µg/kg there was a very high increase of early resorptions (litters with early and late resorptions, 35%) with 6/20 litters having total implantation loss; there was also a slight increase (significant) in the incidence of fetuses with minor skeletal anomalies (mainly cranial bone retarded ossification) at this dose.

Malformations (within normal range) seen on examination included: micrognathia and microphthalmia in one 12.5 µg/kg fetus; micrognathia, arthrogryposis, renal and gonadal hypogenesis in one 12.5 µg/kg fetus; anasarca, renal and cardiac hypogenesis and gonadal agenesis in one 25 µg/kg fetus.

Wilson's examination of 50% fetuses per litter showed 2 fetuses at 12.5 µg/kg with minor visceral anomalies (one hypoplasia of the right testes and another with subdural hemorrhage). Skeletal examination of the remaining 50% showed retarded ossification in the skull of 3/145 controls, 3/140 low dose, 7/158 mid-dose, and 8/92 high dose. All groups including controls showed various other skeletal variants.

No teratogenic properties were reported at the doses tested.

Seq. II Preliminary Oral Rabbit Teratology Study of FCE 21336 Diphosphate (Cabergoline):

Report 402i dtd Jan 1983. Batch A 11002 Q.A.: Present.

Cabergoline was given orally (by gastric tube) to 6-8 per group female New Zealand HY/CR white rabbits (ca. 5 mo. of age weighing 3.204 ± 0.027 kg) from day 6 to 18 of gestation at doses of 0, 12.5, 25, 50, 100, 200 τ/kg/day (calc. as base). The vehicle was deionized water. Sacrifice was on day 28 of pregnancy.

Survival of treated rabbits was reduced (non-significant) compared to controls; the cause of death did not appear to be attributable to drug. Body weights were unaffected.

Conclusions included: at doses up to 200 τ/kg cabergoline did not interfere with pregnancy (one each case of abortion was seen at 12.5 and 200 τ/kg after 2 and 10 days); beginning with 25 τ/kg maternal findings included gastric ulceration in a considerable number of rabbits at all doses, splenomegaly was found at 25 and 200 τ/kg as well as slight kidney alteration which included variations in color and in the ratio of the cortico-medullar zones. No treatment-related alterations were seen at 12.5 τ/kg.

There were no significant embryotoxic or teratogenic effects; however, the number of resorptions were increased in low to medium doses (significant at low dose for late resorptions), and the medium to high doses caused delayed fetal development (several immature fetuses at doses over 25 τ/kg) and induced malformations in one fetus each for doses of 25, 50, 200 τ/kg which included acephalia, distortion of fore-paws and/or lost digits and omphaloschisis.

Seq. II Teratology Study - Influence of Oral Administration of FCE 21336 Diphosphate on the Pregnant Rabbit, Embryo and Fetus:

Report 412i dtd. Feb 1984.

Batch: A 11002. Q.A.: Present.
White Russian Rabbits: [A strain bred by

Groups of 12 pregnant White Russian rabbits age 4-5 mos., weight 2.0-2.7 kg were given 0, 5, 50, 500 µg/kg (as base) Cabergoline by gavage as the diphosphate in water solution (1 ml/kg) from Day 6-18 of pregnancy. Sacrifice was on day 29 of pregnancy. Doses up to 500 µg/kg showed no toxic effects on the pregnant rabbits and prenatal development was not interfered with.

No evidence of treatment-related teratogenic effects was reported for the doses tested. However, there were 3 fetuses with malformations at 5 µg/kg (scoliosis, hemicephalus and immobile, stretched hind limbs) and 1 at 50 µg/kg (omphalocele) - reported as spontaneous according to laboratory experience. No malformed fetuses were found at 500 µg/kg or in controls. The variation rate, not increased at the low and high dose, was slightly increased for the mid-dose, but reported to still be within a spontaneous range. Fetal and placental weights were not distinctly different from controls. Although not given as statistically significant the percent of post-implantation loss in treated animals (within range of each other) was greater than that of controls.

Seq II - Oral Teratogenicity Study of FCE 21336 in the Rabbit:

Project 519/11, Study Q 0972, Report 433i, 855-519/11 dtd April 1991. Batch A 16001 Q.A.: Present.

Groups of 18 inseminated New Zealand White rabbits (3.1 - 4.1 kg) received FCE 21336 (base - administered as diphosphate aqueous solution) by oral gavage at dosages of 0, 1000, 2000, 4000 mcg/kg/daily from Day 6-18 post-coitum. Controls received the distilled water vehicle (vol. 5 ml/kg). Sacrifice was on Day 28 post-coitum.

Mortalities, mainly due to respiratory system findings, included: 1 control day 20 pc (also had findings in kidney and spleen); 1 mid dose day 26 pc (also findings in kidney); 2 high dose one on day 20 pc and one on day 10 pc. One low dose died day 19 pc due to improper gavageing.

There were no treatment-related clinical observations or necropsy findings reported for the low and mid-dose. However, one 2000 mcg/kg dam aborted on Day 21 and another on Day 28 pc - food and water were reduced on several days prior to abortion. Necropsy followed: kidneys of one were slightly yellowish with granulated surface with light foci. One high dose also aborted on Day 22 pc - it had reduced food and water consumption for several days followed by diarrhea and bad physical condition. Necropsy showed a grossly granulated cut surface of the liver. Some animals from each group had ocular and nasal discharge. There was some hair loss and wounds.

Body weight from the low dose to the high dose (sig.) was slightly to markedly reduced from day 6 to 9 post-coitum.

Food and/or water consumption was reduced (particularly during the dosing period in the high dose group).

Necropsy findings included yellowish kidneys in 3 control, 1 low dose, 6 mid dose and 5 high dose. Other findings probably not treatment related included a control with the left uterine horn filled with greenish mucus, one control with head tilt (disposition of cervical vertebrae); findings in respiratory system, neck abscess, and grossly granulated cut surface of liver. One 200 mcg/kg animal showed kidney and respiratory findings along with several subcutaneous abscesses on the neck, and limbs - 100% intra-uterine deaths were detected. Another 2000 mcg/kg and one 4000 mcg/kg animal showed total intra-uterine deaths.

The incidence of pregnancy was normal and implantation (preimplantation loss slightly higher than concurrent controls, but individual values within normal range) showed no treatment effects. Post implantation loss was not affected (slightly increased for the low dose but high dose comparable to controls) and the mean number of fetuses per dam and sex distribution were comparable for all groups. Post implantation loss was increased in animals when total intra-uterine deaths are included (2-mid dose and one high dose dam).

Mean fetal and placental weights (not sig.) were reduced at the high dose.

There was a dose dependent increase in the number of various malformations. A retinal dysplasia and a scoliosis were seen in 3 fetuses of 2 litters at 1000 mcg/kg. At 2000 mcg/kg there were 5 fetuses from 4 litters with malformations. 3 fetuses showed visceral malformations as retinal dysplasia, with one of these with kinked tail. One fetus had scoliosis, another showed brachydactyly and proximally fused ribs and fused thoracic vertebral arches.

At 4000 ~~mcg/kg~~ 18 fetuses of 7 litters showed malformations. 3 fetuses from 2 litters showed adactly or kinked tail, and 2 fetuses from 2 litters had visceral malformations as retinal dysplasia. 4 fetuses had skeletal malformations as frontal(s) fused or ribs proximally fused and/or extra ribs(s) (vestigial) between existing thoracic ribs. Another 4 fetuses showed a scoliosis and/or rib branched and/or ribs proximately fused. 5 additional fetuses showed skeletal malformations as scoliosis and ribs proximally fused and thoracic vertebrae fused and unilateral thoracic hemivertebra with associated branched rib or ribs proximally fused and thoracic/lumbar vertebrae fused and thoracic vertebral arch(es) fused.

The sponsor indicates that the incidences of malformed fetuses in the low and mid-dose are lower than in the high dose and although there were no malformed fetuses in present controls they are within range and type of historical controls. Most of the high dose malformed fetuses were found in two litters only. However, the suspicion of a teratogenic potential cannot actually be denied from this study (see additional rabbit studies).

Seq. II - Oral Teratogenicity Study in the Rabbit:

Report FCE 20/901213, Sponsor Test Q1145, Report 4341 dtd Apr 91. Batch 9007L308 Q.A.: Present.

Doses of 0, 0.5, 2.0, 4.0 and 8.0 mg/kg (control 5 ml/kg distilled water) were administered daily by gavage to 25 (26 at 4.0 mg/kg) female time-mated New Zealand White rabbits per group from Day 6 to 18 post-coitum. Sacrifice was on Day 29.

Maternal effects at 4 and 8.0 mg/kg included increased nervousness, slight increase in signs of inappetence and anorexia, marked but transient reduction (sig.) in food and water consumption and an initial marked reduction in body weight.

Offspring showed a statistically significant reduction in mean fetal and mean placental weights at 4 and 8.0 mg/kg. Although not significant increases were seen in preimplantion loss (%) at 2.0 mg/kg and postimplantation loss (%) at 0.5 mg/kg.

Maternal effects with 0.5 and 2.0 mg/kg were the following: compared to controls a slight increase in nervousness, with some signs of inappetence and anorexia (noted to a lesser degree before treatment); a marked but transient reduction (sig.) in food and water consumption and an initial marked reduction (sig.) in body weight. Sponsor reports no treatment-related effects on litter parameters or embryofetal development at these doses.

The incidence of cold ears was slightly greater for treated in general and post-dose.

Mortalities after treatment commenced included one each in Groups 1 and 3 sacrificed due to intubation errors.

Macroscopic findings at terminal macroscopic examination did not suggest any overt treatment-related effects.

Litter Data:

Abortions: one each at 2 and 8.0 mg/kg towards end or at completion of treatment period.

Live young: 19, 22, 22, 22 and 24 for Groups 1-5.

Litter size, sex ratio, pre- and post implantation losses and embryonic deaths: There were slight intergroup differences in ovulation rate (corpora lutea count), implantation rate (unlikely to be influenced by start of treatment), embryonic losses and resultant litter size and sex ratio did not indicate treatment-related effects.

Litter weight, mean fetal weight, total placental weight and mean placental weights were lower than concurrent control values at 4.0 and 8.0 mg/kg. Mean litter values were statistically significant. These parameters showed no treatment-related effects at 0.5 and 2.0 mg/kg.

Malformations, anomalies and variants: For Groups 1-5, 154 (19), 172 (22), 174 (22), 194 (22) and 194 (24) fetuses (litters) were examined with the finding of malformations in a total of 3 (3), 5 (4), 7 (5), 5 (5) and 7 (7) fetuses (litters). The sponsor indicates incidences of changes were isolated and there was a lack of dose response.

It is reported that there were no adverse effects of treatment on the incidence and distribution of visceral and skeletal anomalies and of skeletal variants in any group.

Seg III - Oral Perinatal and Postnatal Study in the Rat:

Study N588-Q1349. dtd Mar 1995. Batch 1005E308 Q.A.: Present.

Cabergoline (base) was given orally by gavage as the diphosphate salt in aqueous solution to 25 fertilized rats from Day 17 of gestation to the end of lactation (Day 21 postpartum) at doses of 0, 1, 3, 10, 30 and 100 µg/kg/day.

There were no maternal deaths. Up to 100 µg/kg maternal toxicity and the duration of gestation and physiology of parturition were not affected.
Body weight and food consumption were not affected by treatment during late gestation. Food consumption decreased soon after birth with a dose relationship and statistical significance from 10 µg/kg up. Body weight and food consumption were not affected at 1 and 3 µg/kg.
Lactation was inhibited (antiprolactin activity) at 10 µg/kg and total suppression by the first week at 30 and 100 µg/kg. Death resulted due to undernourishment in 100% (early) at 30 and 100 µg/kg and 20% (late) at 10 µg/kg. There was a rebound influence on body weight, food intake and behavior of lactating dams as well as an inhibition of growth and development of surviving suckling. The drug did not appear to induce impairment of the main functions, including reproductive performance, of young adult F_1 rats at 10 µg/kg in the presence of decreased food intake and growth depression leading to death in some and inhibition of body weight curves from weaning to maturity which was more marked in males than in females. Post weaning development showed

a slight delay in testes descent and a significant delay in vaginal opening in the young rats. No drug-related findings or lesions were seen in F_1 offspring.

Doses of 1 and 3 µg/kg/day did not induce lactation inhibition and thus there were no important effects on F_0 treated dams or their offspring during pre-weaning until adult.

The sponsor indicates that the NOEL for the dam was 3 µg/kg/day based on pharmacological activity and for general toxicity 100 µg/kg/day. The NOEL for F_1 offspring was 3 µg/kg/day for postnatal development and 10 µg/kg/day for reproductive performance.

Carcinogenicity Studies:

Oral Carcinogenicity Study of FCE 21336 (Cabergoline) in CD-1 Mice: Report 430i; 198-0-124-014/T/006/91 dtd Jun 1991. Batch A16002 Q.A.: Present.

Dose: 0, 0, 20, 140 and 980 µg/kg/day orally by gavage. Groups 1-5 (2 control groups)

No. Animals: 65 mice/sex/group aged about 49 days. Crl:CD-1 (ICR)BR) mice - Swiss origin.

Male mice were sacrificed after 680 days treatment, because survival of Control Group 1 was approaching the 20% limit. Females were sacrificed after 730 days treatment.

Blood samples for hematology were taken at the end of study. For cholesterol and white blood cell parameters, blood was taken after 3 months.

Gross examination was performed on all mice. Microscopic examination was performed on all mice that died during study and on mice killed at termination for Groups 1, 2 and 5 only. Some additional tissues were examined for mice from Groups 3 and 4 killed at terminal sacrifice.

Mice were reported to show sensitivity to FCE 21336 in a 13 week toxicity study in mice (LSR-RTC Study 179-0-124-013) as a dose range finding study.

Results: [See also attached Statistical Review and Evaluation.]

Mortality of the Group 1 controls and high dose group males was higher than that of the other groups. Females did not show any significant intergroup differences. In general animals appeared to be in good health throughout the study.

Clinical signs apparently related to treatment included staining of the skin in 140 µg/kg males and in both sexes at 980 µg/kg. High dose females showed a slightly increased incidence of raised skin areas. The incidence of palpable masses was similar for controls and treated. No significant difference was reported for the mean day of onset of the first mass for controls or treated (slightly earlier in males).

Body weight and body weight gains were decreased in mid and high dose females throughout treatment. Low dose females also showed a reduction in bodyweight from day 189 on. High dose males showed a transient slight reduction in body weight gain.

Food consumption was in general comparable with controls, however all treated groups sporadically showed a statistically significant decrease which was not dose related.

Statistically significant variations were seen in a few blood parameters of treated compared to controls. The sponsor reports these differences to be in the range of normal values and to have no pathological significance. Compared to controls cholesterol values (taken only at 3 months) showed no statistically significant differences.

At necropsy both treated males and females had a slightly increased incidence of abnormal staining in the skin. Findings in the uterus of treated females appeared dose related and included a higher incidence of abnormal size, cysts, masses and abnormal color. Seminal vesicles in males also showed a slightly increased incidence of abnormal areas.

Histopathology showed females to have an expected range of findings reflecting a probable alteration in hormone ratios caused by treatment. Such alterations included a reduction in mammary gland hyperplasia and secretory activity, increased incidences in epithelial hyperplasia and/or stromal proliferation in the uterus, cervix and vagina, and a small increase in smooth muscle tumors in the cervix and ovary. According to the sponsor, the smooth muscle tumor incidence was similar to historical data for this strain of mice.

Other changes seen included decreases in porphyrin accumulation and adenomas in the Harderian glands, increase urinary bladder epithelial hyperplasia, a decrease in nephropathy, and an increase in fibrosis and secondary ossification in the sternum and stifle.

There was a small increase in the incidence of leiomyomas and/or leiomyosarcomas in the uterus and cervix (cervix P=.0418). The sponsor reports the incidence of these tumors to be similar to the historical data for this strain of mice. The incidence of benign tumor hepatocellular adenoma (P=.0280) in the female livers was 0, 0, 1, 2 control through high dose.
[See attach Statistical Review (including tables).]

Oral Carcinogenicity Study of FCE 21336 (Cabergoline) in CD-Crl:CD(SD) BR Rats: Report 429i; 181-0-124-015/T/020/90; Fice No. Q0775 dtd Jun 1991. Batch: A16001 and SC18H005 (week 76-termination) Q.A.: Present.

Dose: 0, 0, 20, 80, 320 µg/kg/day orally by gavage (2 control groups) Vol.: 5 ml/kg Groups 1-5

No. Animals: 60 rats/sex/group aged ca 44 days [CD-Crl:CD(SD) BR rats]

Blood samples for hematology were taken at the end of study.
Urinalysis not presented due to shipment mishap.
Gross and Histopathological examinations were carried out on all (specified) tissues for animals that died and for animals killed at termination.

Results: [See also attached Statistical Review and Evaluation.]

Females on 20 µg/kg showed a lower mortality than that of the other groups including controls; there was no difference between other groups.

Treatment related clinical signs included: staining of the perigenital area in males of the two higher dose levels and females of all three treated groups; vaginal discharge in females of the two higher levels; swollen abdomen in all female treated groups (because of distended uteri and peritonitis).

The incidence of palpable masses was reduced compared to controls.

Body weights (and weight gains) were decreased in female rats of all treated groups (evident mainly during second half of treatment). Food intake was also decreased during this period.

Hematology showed no apparent treatment-related effects. Bone marrow myeloid hyperplasia was increased in treated females.

Necropsy showed: an increased number of masses in the abdominal cavity in females on both 20 and 80 µg/kg and in males and females on 320 µg/kg; an increased incidence of enlarged testes in males on both 80 and 320 µg/kg and masses in the epididymides at 320 µg/kg. An increased incidence of uteri showing enlargement, distension or masses in treated females with evidence of a dose related effect was seen. There was also a similar dose related increase in the incidence of enlarged spleens (and increased incidence in extramedullary hemapoiesis, and reactive and lymphoid hyperplasia) in females.

The extent of non-neoplastic findings in both sexes reflected the inhibition of prolactin secretion. Female genital tract findings included increased incidence in the uterus of pyometra, dilatation, cystic endometrial hyperplasia, abscesses and squamous metaplasia and related peritonitis;

epithelial hyperplasia and squamous metaplasia in the vagina and cervix with a corresponding decrease in mucoid hyperplasia. The incidence of corpora lutea and of dilation of the ovarian bursa was increased. There was also a decreased incidence of telangiectasis in the adrenals, nephropathy and urolithiasis in the kidneys, and hyperplasia and secretory activity of the mammary glands. Consequences of suppression of prolactin secretion in males included reduced secretion of the mammary gland and an increase in testicular atrophy and interstitial cell hyperplasia along with increased incidence of epididymides showing an absence of sperm.

The two male high doses showed a slight increase in incidence of chronic liver inflammation.

Neoplastic changes were reflective of the pharmacological activity of the drug - pituitary adenomas were decreased in both males and females, mammary fibroadenomas were decreased in females and interstitial cell adenomas (according to the sponsor, chi-square value for intergroup differences and tests for trend with dose level and actual dose: $P<0.001$ in all cases) were increased in male testes. There also appeared to be a slight increase in skin malignant basal cell carcinoma in the skin of male rats.

Also probably related to a secondary response to the non-neoplastic changes was a slight increase in malignant tumors of the uterus and cervix. The sponsor reports stromal sarcoma (trend with actual dose only: $P<0.05$) and squamous carcinoma (chi-quare value for intergroup differences: $P<0.005$; Test for trend with dose level: $P<0.05$) in the uterus to be statistically significant.

[See attach Statistical Review (including tables).]

Life Span Oral Treatment with FCE 21336 (Cabergoline) and Determination of Hormonal Blood Levels in Rats: as of May 1991.

Report 431i; Report 182-0-124-016/T/005/91; Fice No. Q0815* dtd. Feb 92. Batch: A16001 and SC18H005 (week 76-termination). Q.A.: Present.

Report 432i - Hormone determinations -

Dose: 0, 20, 80, 320 mcg/kg/day orally by gavage for up to two years. Vol. 5 ml/kg. Controls distilled water.

No. Animals: 15M;15F per group Sprague-Dawley CD-Crl: CD (SD) BR rats ca 49-51 days old

NOTE: Reported that the hormonal levels contribute to the interpretation of a full carcinogenicity study (Report 181-0-124-015/T/020/90) which was undertaken at the same institute at the same time.

Blood Samples: During weeks 52, 78 and 104 blood samples (ca 3 ml) were withdrawn from the retro-orbital venous plexus from all surviving rats from each group, ca 24 hrs after dosing. For animals in extremis the maximum amount of blood was obtained in a similar manner prior to immediate sacrifice. Blood hormone determinations were carried out in the (Report 432i).

Vaginal smears: Prepared and examined from females for 14 consecutive days before treatment. At 3 monthly intervals thereafter the smears were obtained daily for about 11-14 days before samples of blood were taken for estimation of hormonal levels and on the day of blood sampling.

Results:

Mortality was comparable with controls and clinical signs showed no significant changes.

Palpable masses of treated males showed no changes in the incidence or onset time compared to controls. All treated female groups showed a reduction in the incidence of palpable masses compared to controls. There are too few data to establish any change in mean onset time.

Body weights of treated males were not significantly different from controls. For most of the study treated female body weights were statistically significantly lower (more apparent in Groups 3 and 4) than controls. Weights for mid and high dose groups were reduced up to ca 30% compared to controls during the second year. Body weight gains of treated males were comparable to that of controls while that of treated females was reduced (often statistically significantly) compared to controls.

Food consumption in males showed no important differences while it was generally reduced (sometimes statistically significantly) in Groups 2 and 3 females (less evident in the high dose).

Organ weights (adrenals, ovaries, pituitary, prostate, testes, uterus): Group 3 absolute testes weights showed a statistically significant increase. Group 2 absolute female adrenal weights were decreased. Relative organ weights of both sexes were not statistically different from controls. [However, pituitaries that were grossly enlarged were not weighed. According to the sponsor, if these weights had been included then the reduction in the incidence of pituitary tumors in the treated groups would have resulted in a reduced mean pituitary weight in treated animals compared with controls.]

Macroscopic observations showed a reduction in the incidence of enlarged or swollen pituitaries in treated of both sexes which was associated with a decreased incidence of depression of the ventral mid-brain. Testes showed an increase in abnormalities, the most significant being an increase in incidence of small size in the high dose. Treated female mammary glands showed a decreased incidence of thickening, cysts and subcutaneous masses compared to controls. The incidence of ovarian cysts, enlarged ovaries and enlarged, distended or thickened uterus was increased in treated females.

Preserved tissues for histopath [abnormalities (including palpable masses), adrenals, ovaries, pituitary, prostate, testes (with epididymides), uterus]:

Non-neoplastic changes included:

Adrenals - Cortical hyperplasia only in 2/14 control males and 3/15 low dose males;

Testes - the increased incidence of testicular atrophy and interstitial cell hyperplasia of treated groups was similar. There was a high incidence of absence of sperm in the epididymes of high dose males.

Ovaries - Corpora lutea were increased especially in unscheduled deaths (dose related). Only 2 high dose showed this change at final sacrifice, probably (according to sponsor) because in several cases there had been regression of corpora lutea with advancing senility. Dilation of ovarian bursa was seen in treated but not controls.

Uterus - endometritis and pyometra were seen at the two higher levels in unscheduled deaths. Such findings were seen at all dose levels but at a lower incidence at final sacrifice. Hyaline change in the endometrial stroma was seen in some of all treated groups but not in controls.

Mammary gland - In treated the drug appeared to suppress the hyperplasia, secretory activity and galactocele formation seen only in a portion of controls.

Neoplastic Changes:

Pituitary - the incidence of pituitary adenoma was reduced in both sexes with a corresponding decrease in the incidence of depression of the ventral mid-brain.

Adrenals - Only controls and low dose showed a few cortical adenomas (higher doses may have been suppressed).

Testes - interstitial cell adenoma showed a treatment-related increase.

Skin: There was a marked treatment-related decrease in mammary fibroadenomas.

Ovary and Uterus - reported no tumors which showed evidence of treatment-relationship. [Mid-dose, only, - 2 uterine squamous cell carcinomas]

Other tumors - were considered generally in the range of spontaneous findings.

Vaginal Smears - showed no effect on the estrous cycle during the first 14 weeks. The two higher dose levels showed a dose-related prolongation of estrus after 26 and 28 weeks of treatment which continued throughout treatment and by weeks 64-65 incidence rates were 90 to 100% in all treated groups. To a lesser degree, controls showed a tendency towards prolonging the estrous phase from weeks 39 up to 65 with acyclic or irregular cycles by weeks 76 to 78 indicating normal physiological senility.

Analysis of Hormone levels (Sponsor's Report FCE 21336/432i):
Blood Samples at 52, 78, 104 weeks treatment. [Variability was wide and at 104 weeks survival was low.]
0, 80, 320 µg/kg/day - Mean Percentage values compared to controls.

Females:
Prolactin - Reductions at all levels tested were: 52 weeks (61, 86, 93%); 78 weeks (83, 78, 96%); 104 weeks (77, 67, 98%).
LH - 52 weeks (-3, -9, -19%); 78 weeks (+3, -14, -16%); 104 weeks (-9, +17, -40%)
Progesterone - Reduced: 52 weeks (66, 52, 49%); 78 weeks (78, 79, 74%); 104 weeks (59, 66, 54%).
Estradiol - Increased: 52 weeks (130, 144, 78%); 78 weeks (90, 50, 175%); 104 weeks (86, 89, 16%)
Progesterone/Estradiol Ratio - Reduced: 52 weeks (85, 84, 76%); 78 weeks (88, 88, 91%); 104 weeks (54, 83, 28%).

Males:
Prolactin - Dose effective reduction at all time periods. 52 weeks (76, 86, 86%); 78 weeks (59, 86, 87%); 104 weeks (96, 99, 99%).
LH - Increased at all doses at 52 weeks and less markedly at 78 weeks. 52 weeks (55, 95, 109%); 78 weeks (33, 58, 19%); 104 weeks (87(very high in one rat), 7, 7%).
Testosterone - Lowered by treatment, although no statistically significant effect was seen. 52 weeks (-16, -34, -25%); 78 weeks (-37, +8, -13%); 104 weeks (+31, -37, +24%) mean + values influenced by abnormally high serum values seen in two rats.

CG-101 (Cabergoline): A Self-Administration Study to Evaluate the Psychological Dependence Liability by the Intragastric Route in the Cynomolgus Monkey. Report KSI 42B(e?)/92U6UU dtd Nov. 92 (Report 238i). Batch: 9003C308
Q.A.: Present.
Dose: 0.025, 0.05, 0.1 mg/kg/injection
No. Animals: 4 cynomolgus monkeys.

None of the animals showed a desire to self administer the drug at the doses tested. A further period of involuntary injections at 0.1 mg/kg/injection did not initiate lever pressing in 3/4 monkeys. An apparent drug-seeking behavior was demonstrated by the fourth animal during the involuntary injection period. The increased lever pressing activity persisted after the involuntary injection period but the animal did not continue self-administration following the increase in the fixed ratio to 3 lever presses per one injection.

The sponsor thus considered it unlikely that the drug, at the doses tested, possesses any overt psychological dependence in the cynomolgus monkey.

CG-101 (Cabergoline): Assessment of the Physical Dependence Liability in Naive Cynomolgus Monkeys following Two 28-Day Periods of Oral Administration. dtd Jan 93. Study KSI 42c/921028 Batch 9003C308 Q.A.: Present.

Four naive cynomolgus monkeys were treated orally with CG-101 twice daily for two 28-day periods. Severe CNS stimulation was produced by the starting dose of 5.0 mg/kg CG-101; after one monkey died the study was restarted with 1.0 mg/kg daily which produced continuous CNS stimulation and tremor.

Benzodiazepam antagonist, Ro 15-1788, failed to precipitate any withdrawal signs or enhance any of the CG-101 residual effects during the first challenge. During the second challenge Ro 15-1788 exacerbated agitation in one animal and pilo-erection in another. This significance was reported as unclear. At the end of the first 28-day dosing period, there were no signs of withdrawal nor were there any exacerbations of the residual effects of CG-101. Mild tremor and pilo-erection were observed in one animal each during the second withdrawal period (week 10) making it difficult to interpret.

The sponsor did not consider these signs as indicative of withdrawal since they were seen in conjunction with CG-101 residual effects.

Minimal body weight increases seen during dosing and withdrawal periods were reported as not indicative of dependence. Food consumption reduced during dosing periods, increased during withdrawal periods. Rectal temperatures at first increased, tended to reduce as the study progressed.

Diazepam, also tested (CNS depression and ataxia), was judged to have an intermediate physical dependence liability.

Effect of Cabergoline (FCE 21336) on Postpartum Lactation in the Mouse. Report 234i dtd June 1991. Batch 5/90 (free base)

Cabergoline, given orally to lactating mice for 10 consecutive days, starting within 24 hrs postpartum, at doses of 0.1, 0.3, 1 and 3 mg/kg/day, inhibited milk production at all doses tested, as evidenced by the reduced total litter weight and daily litter weight gain during treatment. The ED_{50} for lactation inhibition, calculated on the sum of litter weight gains during days 2-10 of lactation was 0.38 mg/kg/day.

Effect of Cabergoline on Postpartum lactation in the Rat and Long-term Effects on the Next Pregnancy and Lactation. Report 230i dtd Jan 1990. Batch SC 18G003 (free base)

Groups of 9-10 lactating rats treated within 24 hrs postpartum with single oral doses of 0.03, 0.1, 0.3 or 1 mg/kg showed a dose-related inhibition of lactation, as evidenced by the decrease in litter weight gain. 0.03 mg/kg was ineffective, inhibition was evident 24 hrs after treatment with 0.1 and 0.3 mg/kg, at 0.3 2/9 litters died day 4-5, and at 1 mg/kg all 9 litters died days 3-5 of lactation indicating a strong suppression of milk production. The ED_{50} calculated during the first 4 days after treatment was 0.089 mg/kg.

A new pairing took place - there was no long-term effects on fertility, fecundity and lactation in the dam.

Intravenous Studies of FCE 21336 Two-Week in Rats and Cynomolgus Monkey and CV Study in Monkeys: - Studies N637-Q1389 (May 95), N638-Q1390 (May 95), N630X (Mar 95).

Clinically, drug is to be given orally. In general findings were:

Doses up to 2500 mcg/kg/day i.v. in the rat were considered to be well tolerated and effects seen were similar to those seen with repeated oral administration in the same species.

Doses up to 1500 mcg/kg i.v. in the monkey produced effects similar to those obtained by repeated oral administration in monkeys.

A single 1.5 mg/kg dose i.v. in the monkey produced no significant changes in cardiac functions as revealed by ECG and blood pressure examinations, [Minimal changes in repolarization and the minimal decrease in blood pressure in the male monkey were ascribed by the sponsor to ketamine anesthesia.]

Reprints: Information Included:

Clinical termination of unwanted pregnancy can be achieved by inhibition of prolactin secretion in dogs. According to K. Onclin, et al. [J.Reprod. Fert. Suppl. '47(1993), 403-409], when 1.65 μg/kg cabergoline was injected s.c. for 5 days starting at day 40, pregnancy was terminated in 100% of dogs in <6 days. When started at day 30, 67% aborted and at day 25, 25% aborted. In all failures another treatment of cabergoline caused abortion.

According to W. Jöchle and M. Jöchle [J.Reprod. fert., Suppl. 47(1993), 419-424], 5-15 μg/kg cabergoline in the diet of feral cats for a mean of 4-9 days starting on day 25-48 resulted in reduction of the size of the mammary gland and abortions usually within 3-5 days. When given latter (44-56 days) early parturition was induced but not abortions. Females returned to fertile estrus after abortion or premature parturition. To explore safety aspects, five repeatedly aborted females were allowed to go to term; parturition occurred in all cases, an average of 64.5 days after the last observed mating.

J.P Verstegen, et al., [J. Reprod. Fert. 47(Suppl.): 411-417, 1993] showed that abortion was produced (usually through fetal resorption) in 4/5 cats treated on day 30 of gestation for 5 days with 1.65 μg/kg/day s.c. cabergoline. It is reported that there were no side effects or behavioral disturbances.

Labeling: Needs Revision - See Comments below.

Comments and Conclusion:

Dostinex (Cabergoline) is a long-lasting dopamine (D_2) receptor agonist with antiprolactin activity. It is indicated for oral treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas. It is usually given as an initial dose of 0.5 mg once a week which may be increased to a maximum of 4.5 mg (90 mcg/kg) per week. [Cabergoline has also been investigated for use in Parkinson's disease (reportedly doses have ranged up to 10.0 mg/day) under IND in HFD-120.] The secretion of prolactin by the anterior pituitary is mainly under hypothalamic inhibitory control, likely exerted through release of dopamine by tuberoinfundibular neurons. The properties of Cabergoline appear to be selective, potent and long lasting. It is reported that its prolactin-lowering activity, in normoprolactinemic rats was found to be longer than that of bromocriptine or pergolide. That 8 hours after oral treatment (maximal inhibition) Cabergoline is 11 times less potent than pergolide, whereas at 24 hours it is equipotent to pergolide and 195 times more potent than bromocriptine, and at 72 hours it is 4 times more potent than pergolide, bromocriptine being inactive. Receptor binding studies indicate that cabergoline has low affinity for dopamine D1, α1- and α2- adrenergic and 5-HT1 - and 5-HT2 - serotonin receptors.

Cabergoline's antiprolactin action appears to occur as a result of direct stimulation of dopaminergic receptors present in the lactotropic cells of the pituitary gland. Even at high doses, it is reported not to appear to be accompanied by an increased dopaminergic action at the CNS level.

Central dopamine agonism was reported to last up to 70 hours in MPTP lesioned monkeys. [MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyrodine) is a neurotoxic lipophilic molecule which readily penetrates into the brain where it causes destruction of the dopamine containing neurons of the substantia nigra.]

Studies in rats have implied that Cabergoline's long duration of action can be related to its slow rate of elimination from the pituitary. It has also been found to persist for a long time in vitro at the level of pituitary dopamine receptors. It is well absorbed and followed by a rapid and extensive tissue distribution which appeared to be the main determinant of low plasma radioactivity levels and slow elimination.

Cabergoline did not appear to affect LH response in various tests in rats. Studies in immature rats did not show any androgenic, antiandrogenic, estrogenic, antiestrogenic or antithyroid activity. No progestational activity was seen in rabbits. Studies in rabbits and dogs also showed Cabergoline to inhibit lactation.

Tests in monkeys showed cabergoline to be unlikely to show any opioid- or barbiturate-like dependence liability.

Liver enzyme studies show that there is some indication for moderate sex-specific effects of Cabergoline as obtained for monoxygenase activities. [It is reported that in contrast to many carcinogens cabergoline does not significantly influence the cytochrome P-450 1A family.]

It appears from the secretion of radioactivity in milk from lactating female rats, that Cabergoline and/or its metabolites tend to accumulate in milk.

It is suggested that cabergoline might be the active species that elicits striatal dopamine D_2 receptor activity in the brain. (See p. 6 this review.)

Various toxicity studies including sub-chronic studies in mice, rats and monkeys and studies of up to 52 weeks in rats and monkeys support safety of the drug's use. Although in the chronic rat study adrenal hyperplasia occurred at all doses and erosion of the glandular mucosa of the stomach occurred at the high dose (the drug's pharmacological action also affected pituitary, gonads and uterus), there were no clearly drug or dose related toxicities noted in the chronic monkey study.

In general, due to Cabergoline's specific activity on the endocrine system, reproductive tests could only be performed in rats by using very low dose levels (lower than antiprolactin activity threshold values) or by modifying standard protocols.

Fertility studies (doses expressed as base) in rats showed 3 µg/kg/day to totally inhibit fertility and 2 µg/kg/day to be the maximum dose level which allows implantation in rats on repeated dosing. (Due to species differences in the role of prolactin this might not be a true indicator of effects in humans.) None of the standard reproductive parameters including behavior, general condition, food intake or body weight were impaired either in the treated males up to 320 µg/kg/day or treated females of the F_0 generation or in the untreated F_1 generation in doses up to 2 µg/kg/day.

No teratogenic properties were seen in mice at doses up to 8.0 mg/kg/day, nor in rats at doses up to 25 µg/kg/day although there was a very high increase in early resorptions in rats at this dose.

Four rabbit teratology studies were carried out with FCE 21336 in 2 strains of rabbits at four different locations with three different batches of drug.

The study at doses up to 200 γ/kg/day in New Zealand White rabbits showed no significant embryotoxic or teratogenic effects; however, the number of resportions and the incidence of delayed fetal development were increased.

The study was carried out in White Russian rabbits. No malformed fetuses were found at the highest dose of 500 µg/kg, however there were 3 fetuses with malformations at 5 µg/kg scoliosis, hemicephalus and immobile, stretched hind limb) and 1 a 50 µg/kg (omphalocele) - reported as spontaneous according to laboratory experience.

used New Zealand White rabbits at dose up to 4000 mcg/kg. There was a dose related increase in number of various malformations. (See report p. 11) According to the sponsor the incidences of malformed fetuses in the low and mid-dose are lower than in the high dose (most in two litters) and although there were no malformed fetuses in present controls they are within range and type of historical controls. From this study the suspicion of teratogenic potential cannot actually be ruled out.

Another study using New Zealand White rabbits was conducted by at dose up to 8.0 mg/kg. Although not statistically significant some increases were seen in pre- and postimplantation loss. Total malformations found in 3 (3), 5 (4), 7 (5) and 7 (7) fetuses (litters) showed isolated changes with an apparent lack of dose repsonse.

At doses up to 100 µg/kg maternal toxicity and the duration of gestation and physiology of parturition were not affected in the rat. However, due to the specific activity of Cabergoline on milk secretion, a dose dependent inhibition of postnatal development and a high pup mortality was observed from 6-10 µg/kg onwards.

In order to study the direct effects of higher dosages, cabergoline was given orally to newborn pups from day 7 to day 13 after birth. Neither growth nor behavior was impaired at doses up to 90 µg/kg/day , and at maturity rats showed only minimal hematology or blood chemistry changes.

Prolactin is known to be a luteotropic hormone, able to maintain the functionality of corpora lutea and progesterone secretion for long periods of time. Prolactin exerts a luteotropic activity and maintains progesterone secretion in rodents (rats) but not in women.

Carcinogenicity tests [See attach Statistical Review (including tables).] Carcinogenicity studies were carried out in mice (0, 20, 140, 980 µg/kg/day) and rats (0, 20, 80, 320 µg/kg/day). In the mouse study females showed some decreased body and body weight gains. Food consumption of all treated groups was at times decreased. Findings in the uterus of treated females appeared dose related and included a higher incidence of abnormal size, cyst, masses and abnormal color. Histopathology showed females to have an expected range of findings reflecting a probable alteration in hormone ratios caused by treatment. These included a reduction in mammary gland hyperplasia and secretory activity, increased incidences in epithelial hyperplasia and/or stromal proliferations in the uterus, cervix and vagina, and a small increase in smooth muscle tumors (reported similar to historicals) in the cervix and ovary.

There was a small increase in the incidence (reported as similar to historical data for the strain) of leiomyomas and/or leiomyosarcomas in the mouse uterus and cervix (cervix $p < 0.05$). The incidence of benign tumor hepatocellular adenoma ($p < 0.05$) in the female livers was 0, 0, 1, 2 control through high dose.

Rat body weights and weight gains were decreased in treated females. Food intake was also decreased. Both females and males showed an increase in abdominal masses and testes were enlarged in mid and high dose males. A dose related increase in uterine enlargement, distension and masses was seen in females. Females also showed enlarged spleens, extramedullary hemapoiesis, and lymphoid hyperplasia. The extent of non-neoplastic findings in both sexes reflected the inhibition of prolactin secretion.

Neoplastic changes were also reflective of the pharmacological activity of the drug - pituitary adenomas were decreased in both males and females, mammary fibroadenomas were decreased in females and interstitial cell adenomas (8, 14, 31, 28 control-high dose) were increased ($P < 0.05$) in male testes. There also appeared to be a slight increase ($P < 0.05$) in skin malignant basal cell carcinoma (0, 1, 0, 2 control-high dose) male rats.

Also probably related to a secondary response to the non-neoplastic changes was a slight increase in malignant tumors of the uterus and cervix. The sponsor reports stromal sarcoma (trend with actual dose only: $P<0.05$) and squamous carcinoma (chi-quare value for intergroup differences: $P<0.005$; Test for trend with dose level: $P<0.05$) in the uterus to be statistically significant. [FDA Statistical Review - (According to Haseman's rule!) None of the tested tumor types in female rats showed a statistically significant positive linear trend.]

The life span treatment of rats with the same does as the CA study showed somewhat similar findings. Neoplastic changes included a reduced incidence in pituitary adenoma, a treatment related increase in interstitial cell adenoma of the testes, and mid-dose only, 2 uterine squamous cell carcinomas. Other neoplastic changes were considered generally in the range of spontaneous findings. Hormone levels in general for females showed reductions in prolactin, LH levels (some variable), progesterone and progesterone/estradiol ratio (estradiol was increased). For males prolactin and testosterone (also some increases) were reduced and LH increased.

Vaginal smear patterns showed that cabergoline at all tested doses progressively shifted the estrous cycle picture from the predominant continuous diestrous (acyclicity) observed in controls (specifically after 52 weeks), to that of extended or prolonged estrous. This alteration can be attributed to prolactin secretion inhibition caused by cabergoline.

Pathological effects on Leydig cells observed in the CA study in rats, as well as in the 1 year rat study, have not been seen in either the mouse CA study or in the 1 year Monkey study. Hormonal findings in rat may thus be species-specific.

It is reported that as expected from its specific pharmacological activity, cabergoline dosing resulted in PRL secretion inhibition at all doses employed and at each time evaluated. As already observed in female animals, control male rats showed increased serum PRL levels at the end of the treatment period (104 weeks), probably as a consequence of the spontaneous development of pituitary adenomas (as confirmed by examination), due to an age-related reduction of the dopaminergic tone at the hypothalamic level.

A battery of mutagenicity tests [gene mutation (S. typhimurium, S. pombe P_1, V79 cells), DNA repair, (S. cerevisiae D_4) chromosomal damage (human lymphocytes and mouse bone marrow] all gave negative results.

According to the sponsor, rats in subchronic and chronic studies were adequately exposed to compound, the AUC values observed at 3.2 and 5 mg/kg/day being 36-72 times higher and C_{max} values being 66-148 times higher than those measured in humans (7 mg in Parkinson's). Also, in animals treated with the highest dose used in the rat carcinogenic study (0.32 mg/kg/day) the exposure to the test compound was fairly prolonged, covering the interval between doses, and AUC and C_{max} values in rats were 2-3 times higher than those measured in humans.

Labeling needs revision. Among other revisions, when plasma drug levels are available, human exposure should be expressed in terms of multiples of the AUC observed in preclinical studies. In the absence of plasma drug levels, drug exposure comparisons between preclinical and clinical doses should be based on surface area (mg/m^2) rather than on mg/kg.

Pharmacology recommends approval of Dostinex (cabergoline) for treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas. However, Labeling needs revision.

David H. Hertig
Pharmacologist

cc:
Original NDA 20-664; IND
HFD-24 JDeGeorge
HFD-400 JContrera
HFD-345
HFD-510 NDA 20-664; IND
HFD-510 AJordan
HFD-510 DHertig

A Jordan
6/14

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020664

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEWS

NOV 12 1996

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-664
Dostinex®
Cabergolin

SUBMISSION DATE: October 31, 1996

Pharmacia & Upjohn Company
Kalamazoo, MI

REVIEWER: Hae-Young Ahn, Ph.D.

SUBMISSION TYPE: Labeling Revision

SUBMISSION:
The sponsor has submitted a revised package insert for Dostinex®. It was noted that the changes requested by the Office of Clinical Pharmacology and Biopharmaceutics (reviewers: Drs. Ette and Miller) had been incorporated. Therefore, the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II finds the revision acceptable.

Hae-Young Ahn, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT initialed by J. Hunt, Deputy Director 11/12/96

cc: NDA 20-664, HFD-510(Hedin), HFD-870 (Ahn and M. Chen), HFD-870 (Chron, Drug, Review)

OCT 4 1996

NDA: 20-664 SUBMISSION DATE: DEC. 26, 1995

CABERGOLINE (FCE 21336)
Dostinex ® (0.5 mg tablet) CODE: 1 S

Pharmacia Inc
7001 Post Rd.
Dublin, OH 43107

REVIEWERS: Ene I. Ette, Ph.D & Raymond Miller, Ph.D

TYPE OF SUBMISSION: Original NME

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

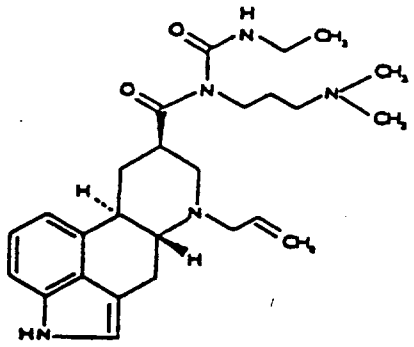

Figure 1

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1. BACKGROUND:

NDA 20-664 was submitted for cabergoline tablet. Cabergoline (N-[3-(Dimethylamino)propyl]-N-[ethylamino)carbonyl]-6-(2-propenyl)-8β-ergoline-8-carboxamide, Fig. 1) is an ergoline derivative which is freely soluble in ethanol, chloroform and N,N-dimethylformamide, slightly soluble in aqueous 0.1 N HCL, and insoluble in water. The pKa of the two basic groups, N-dimethylaminopropyl and N-propenyl, are 9.3 and 6.4, respectively. The pH of a suspension of the substance in twice distilled water at room temperature is 9.2, and the partition coefficient of cabergoline (CAB) in octanol/phosphate buffer (pH 7) is 1.1. The drug substance is stable in light and oxidative conditions. Fifty pg/ml of the drug in human plasma stored at -20°C is stable for up to 18 months, and in urine (2000 pg/ml) is stable for up to 12 months. At a concentration of 1500 pg/ml cabergoline is stable at room temperature or 4°C for 24 h. In the urine at the same concentration, it is stable for 1 h at room temperature and for 23 h at 4°C.

The drug possesses selective, potent, and long lasting D_2 dopamine receptor agonist activity. It is reported to have a long lasting prolactin (PRL) lowering effect in animals and humans. Cabergoline (CAB) is said to have a much higher affinity for D_2 receptors than for D_1 receptors and very low affinity for adrenergic, serotonin, or histamine receptors.

The NDA has been submitted for the use of CAB in the treatment of pathologic hyperprolactinemic disorders of idiopathic origin or due to microprolactinoma (adenoma with a diameter of < 10 mm). The proposed dosage regimen is 0.5 mg once a week administered orally. The Sponsor proposes that the dose may be increased in 0.5 mg increments according to the patient's serum prolactin level to a maximum of 4.5 mg.

1.1 SYNOPSIS:

Sixteen studies have been performed in healthy subjects and patients to characterize the pharmacokinetics of CAB.

Dose Proportionality: Results from single and multiple dose studies indicate that CAB exhibits dose independent pharmacokinetics. In a single dose study involving the administration of 0.5, 1, and 1 mg doses to subjects, no significant difference was found in the AUCs normalized to the 1 mg dose. In a multiple dose study involving the administration of 0.5 mg bid for 15 days, an accumulation ratio of 1.73 with a coefficient of variation of 89% was estimated. Large inter-subject variability and oscilating values of plasma levels within individual kinetic experiments were observed in this study, and in fact all the pharmacokinetic studies. This was attributed to plasma values being frequently near the detection limit of the RIA method, and possible interference by unknown metabolites. CAB exhibits dose independent pharmacokinetics up to a 7 mg dose level that was studied.

Mass Balance: CAB is extensively metabolized. Five healthy volunteers were given a single oral dose of 1 mg ^{14}C-Cabergoline. The mean urine excretion accounted for 22.3±4.1% (mean±S.D.) of the administered radioactivity, while in the two subjects taken into consideration for the excretory balance 56% and 57.8%, respectively, of radioactivity was found in the feces. Fecal excretion only becomes significant after the third day. In these two subjects, therefore, the percentage radioactivity excreted accounted for 80.0% and 78.7% of the administered dose.

After oral administration of 0.6 mg ^{3}H-Cabergoline solution to three subjects, radioactivity was mainly eliminated by the fecal route (72% after 10 days). Urine contained 17% of the dose after the same period. The major metabolite of CAB identified in the urine is 6-allyl-8β-carboxy-ergoline which occurs as a result of the hydrolysis of the acylurea bond of the parent compound. After administration of either ^{14}C-Cabergoline or ^{3}H-Cabergoline, this metabolite accounted for 41% and 38%, respectively, of the radioactivity excreted in 0 - 24 h urine sample.

Distribution and Protein Binding: There was no intravenous administration of drug to permit the estimation of the volume of distribution of the drug. The drug is 40 to 42% protein bound and the

binding is independent of drug concentration.

Elimination Half-Life: The elimination half-life of the drug has been estimated from urinary data to be 63 to 69 h.

Relative Bioavailability: The bioavailability of CAB tablet relative to solution (calculated from the amount of drug excreted unchanged in the urine) was 99% (geometric mean) with a 90% confidence interval of 68 - 144%.

Special Populations: Renal impairment does not affect the pharmacokinetics of CAB. However, the pharmacokinetics of the drug is affected by severe hepatic impairment (Child-Pugh score 11). There were no age effect studies and no pooled data analysis was done to examine age effect.

Drug Interaction: L-dopa and l-deprenyl did not affect CAB pharmacokinetics. Also, CAB was found not to influence the pharmacokinetics of l-deprenyl.

Food Effect: Twelve healthy male volunteers received a single oral dose (1 mg) of cabergoline under fasting conditions and after a standard meal (high-fat breakfast) according to a randomized cross-over design with a 4 week wash-out period. Very low plasma concentrations of cabergoline were found under both fasting and fed conditions for all subjects even though several subjects showed measurable plasma levels of the drug up to 336 h after dosing. The percentage of administered dose excreted in the urine ranged from % (average 1.2±1.1 %) and from % (average 1.3±0.7 %) under fasting and fed conditions, respectively. Food does not appear to affect absorption of cabergoline in man.

Pharmacokinetics/Pharmacodynamic Relationship: The characterization of the pharmacokinetic /pharmacodynamic relationship was not possible because of assay limitations - low levels of the drug could not be measured in the plasma.

Dissolution: Dissolution tests were conducted in 500 ml 0.1 N HCL at 37°C using USP apparatus 2 (paddle) at 50 rpm with serial sampling at 5, 10, 15 and 30 min. More than 80% (range: %) of the drug was dissolved in min. The batches tested were those used for clinical trials (TF/23436 (study HPRL007), TF/23549 (study 21336/ONC/026), TF/23613 (studies APLHKI001, APLHKI004, APLHKI005) and stability studies (N3001, N4001 and N4002)., N3001, N4001 and N4002). Although the Sponsor proposed a dissolution specification of Q - % at min., it would be reasonable to set the dissolution specification at min - Q = %.

2. FORMULATION:

Table 1 summarizes drug formulation history. The Sponsor used three different clinical trial formulations for the 0.5 mg tablet. These clinical trial formulations and the to-be-marketed formulation were slightly different. The clinical trial formulations included an overage which ranged from %. The differences in formulation are presented below:

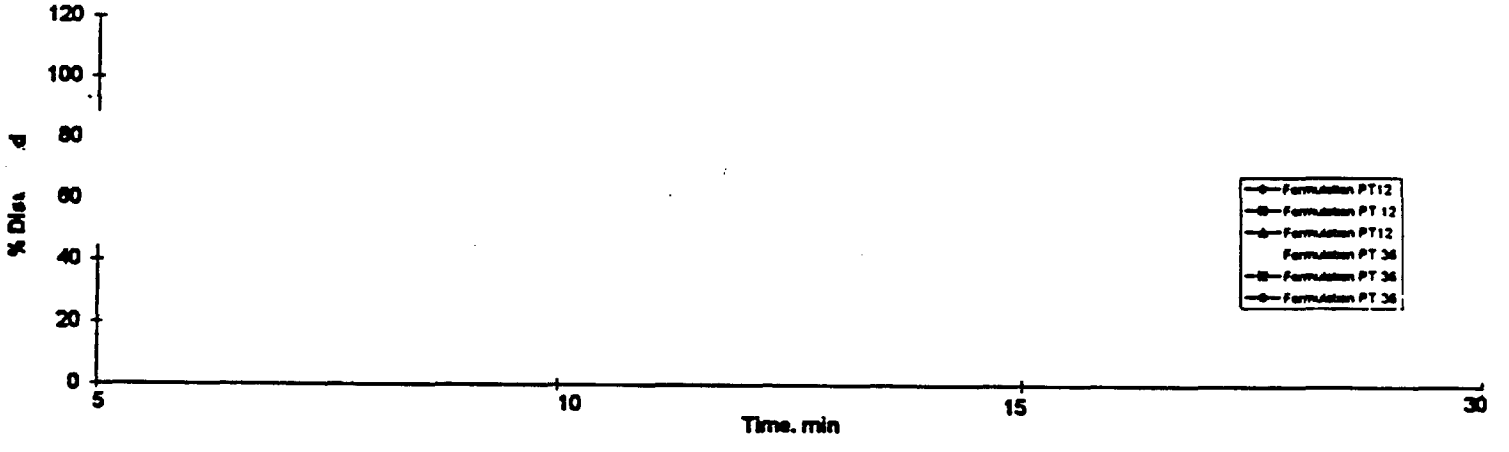
CLINICAL AND TO-BE-MARKETED FORMULATIONS FOR CABERGOLINE (0.5 mg active ingredient per 80 mg tablet)

Ingredient per 80 mg tablet	To-be-marketed Formulation PT 36	Clinical Trial formulation PT 12	Clinical Trial formulation PT 30	Clinical trial formulation PT38
Cabergoline	mg	mg*	mg**	mg***
Leucine, USP	mg	mg	mg	mg
Lactose (anhydrous), NF	mg	mg	mg	mg

* includes a 10% overage and 6 mm round tablet, ** includes a 5% overage and 6 mm round tablet, *** includes a 0% overage and a 6 mm round tablet.

The shape of the to-be-martketed formulation differed from the 6 mm round tablet evaluated in the clinical trials.
The PT 12 formulation was the major formulation used in most of the pharmacokinetic studies. The PT 30 formulation was used in the renal impairment and hepatic insufficiency trials. The PT 38 formulation was used in one of the levodopa drug interaction studies. The to-be-marketed formulation was not evaluated in the clinical / PK studies and no bioequivalence study was performed to assess the bioequivalency of the to-be-marketed formulation when compared with the clinical trial formulations. In lieu of the latter the Sponsor performed dissolution tests on various batches. Three batches used in clinical trials and three batches manufactured on a commercial scale were evaluated, and the results are shown in the figure below.

In Vitro Comparative Dissolution Profiles of Clinical Trial Formulations and to-be-Markted Formulations



3. GENERAL COMMENTS

1. The Sponsor should develop a more specific RIA method for quantifying CAB plasma levels. Alternatively, the sensitivity of the more specific HPLC assay should be significantly improved upon.

2. The nonspecificity of the RIA assay casts serious doubts on the reliability of CAB levels measured, and renders the results of the PK studies inconclusive. Thus, most of the plasma data which for most of the times were near the limit of detection are to be interpreted with caution. A highly sensitive and specific assay is necessary for the proper characterization of the pharmacokinetics of the drug and of course pharmacokinetic/pharmacodynamic relationships.

3. It is wrong to use historical data (in this case results from a food effect study) as control for comparison with data obtained in the renal impairment study. The cohort of subjects are different,

4. The Sponsor's proposed dissolution method is acceptable. It is, therefore, recommended that the dissolution specification be set at [redacted] min - Q = [redacted]%.

4. LABELING COMMENTS

5. RECOMMENDATION:

The Pharmacokinetics Section of NDA 20-664 is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. However, the above general and labeling comments should be conveyed to the Sponsor.

Ene I. Ette, Ph.D. 9/5/96
Raymond Miller, Ph.D. 9/5/96
Pharmacometrics Staff

FT initialed by H. Y. Ahn, Ph.D. 9/12/96

Biopharm Day Attendees: Lesko, Collins, Chen, Lazor, Malinowski, Gillespie, Shiu, Ette, Miller

cc: NDA 20-664 (Orig.), HFD-510, HFD-855 (Ette, Miller), HFD-870 (Chen ML, Ahn), HFD-850 (Lesko), HFD-340 (Vishwanathan), HFD-205 (FOI), Chron, Division, Drug, Reviewer's Files

6. SUMMARY OF STUDIES

6.1 ASSAY METHOD: A sensitive, precise, accurate and reproducible but non-specific radioimmunoassay method was used for the quantification of CAB and its metabolites in body fluids. A less sensitive but specific HPLC was also developed.

6.2 SINGLE DOSE / MULTIPLE DOSE PROPORTIONALITY STUDIES

PLASMA LEVELS AND URINARY EXCRETION OF CABERGOLINE IN THE HEALTHY VOLUNTEER: APPLICATION OF A NEW DEVELOPED RIA (STUDY 606i)

The purpose of the study was to set up a radio-immunological method for the determination of cabergoline in biological fluids and to evaluate its suitability when the method is applied to the analysis of samples taken from subjects given a single dose of 1 mg.

Cabergoline was made immunogenic by conjugation to bovine serum albumin (BSA) through a methylene bridge. The immunogen given to four rabbits produced an antiserum that could be used in the radioimmunoassay. Six healthy male volunteers received a single oral 1 mg dose of cabergoline. Cabergoline was supplied as white tablets containing 0.5 mg (batch TF/23374), and each subject received two tablets. Blood samples were taken from 0 to 168 h after administration and plasma assayed by RIA for cabergoline and prolactin levels. Urine was collected within the same interval and cabergoline assayed by RIA.

Plasma levels were under the sensitivity limit of 80 pg/ml for the assay in all cases and could not be quantified by direct analysis of plasma. To improve the sensitivity a selective extraction step was applied to some plasma samples of the volunteers before the RIA assay. Values of unchanged drug in the range 15-80 pg/ml were found but should only be considered as indicative because of the lack of suitable controls. Urinary excretion between 0.6 and 2.8% of the dose was determined in the volunteers who received the drug.

The RIA described was successfully used in the determination of the urinary excretion of cabergoline in healthy volunteers. The results were consistent with other data. The sensitivity of 80 pg/ml for the assay was not adequate to measure cabergoline accurately in plasma.

Note: A more sensitive RIA assay with a limit of sensitivity of 12 pg/ml was later developed.

EVALUATION OF CABERGOLINE ELIMINATION HALF-LIFE IN URINE OF HYPERPROLACTINEMIC PATIENTS TREATED WITH A SINGLE ORAL DOSE OF CABERGOLINE(0.5, 0.75 OR 1 MG) (STUDY 608i PK)

The purpose of this study was to obtain urinary data on cabergoline after single oral administration of three different doses (0.5, 0.75, 1.0 mg) to hyperprolactinemic patients, as well as the effect on serum prolactin levels.

Eighteen female patients were divided into three groups of six subjects each and each group was treated with a single oral dose 0.5 mg, 0.7 mg and 1 mg cabergoline, respectively (Batch no. TF/23342). Urine was collected up to 168 h after dosing for cabergoline determination, and blood samples were collected for prolactin determination.

The total urinary excretion of the unchanged drug accounted for 0.2-1.3% of the administered dose (Table 2). The data showed large variations among subjects at all the three doses studied. The profile of the excretion rates vs time was relatively irregular in all the patients so that the half life of 79 to 115 h could only be estimated in 10 of the 18 patients and is very suspect. Serum prolactin levels were inhibited up

to 168 h after dosing but no dose response relationship could be identified.
The irregular excretion rates may be due to incomplete collection of urine and thus spurious results. The half life of 79 to 115 should be confirmed with further studies. Because of the parallel nature of the study one cannot draw any conclusions about dose linearity. The normalized amount excreted does not indicate a difference.

PLASMA LEVELS AND URINARY EXCRETION OF CABERGOLINE AFTER SINGLE ORAL ADMINISTRATION OF THREE DOSES (0.5, 1, 1.5 MG) IN HEALTHY MALE VOLUNTEERS (STUDY 611i PK)

The purpose of this study was to evaluate the urinary excretion and plasma levels of cabergoline after single oral administration of three different doses (0.5, 1, 1.5 mg) in male healthy volunteers.
Volunteers received three different single oral doses of cabergoline (0.5, 1, 1.5 mg). Urine and plasma samples were collected up to 168 hours after dosing. Each administration was separated by a five-week wash-out period. Cabergoline concentration in plasma and urine samples was measured using a previously validated RIA method.
The percentages of the administered doses of cabergoline excreted in urine were 1.1±0.1%, 1.1±0.1%, and 1.2±0.1% for the 0.5, 1, and 1.5 mg doses, respectively (p=ns)(Table 3). Cabergoline $AUC_{0\text{-}186}$ and C_{max} normalized to the 1 mg dose were compared by two-way analysis of variance (Tables 4 & 5); no significant difference was found for AUC; normalized C_{max} after 0.5 mg was significantly higher than after the 1 and 1.5 mg doses. Large inter-subject variability and oscillating values of plasma concentrations inside the individual kinetics, probably caused by the plasma levels frequently near to the detection limit of the method, as well as interference produced by some unknown plasma metabolite were observed.
These results demonstrate that, in the dose range 0.5-1.5 mg, the pharmacokinetics of cabergoline are probably dose independent.

PLASMA AND URINARY EXCRETION OF CABERGOLINE AFTER A SINGLE AND MULTIPLE DOSE REGIMEN (STUDY APL PHKI 004)

This study was performed to investigate the pharmacokinetics of CAB after single and multiple dosing in female subjects in a regimen similar to that used in hyperprolactinemic patients. 12 healthy female volunteers (weight: 63.5 ± 7.19 kg, age: 24.0 ± 3.81 yr , and height: 167.0 ± 5.69 cm) received a 1 mg [two 0.5 mg tablets (batch #: TF/23613)] oral dose of CAB after a high fat breakfast, and 15 days later they were started on 0.5 mg bid regimen for a four-week period. Plasma and urine samples were collected for 14 days at specified times after the first dose, and after the last dose for the determination of CAB levels by RIA. Statistical moments analysis method was used for pharmacokinetic data analysis. Large inter-subject variability and oscilating values of plasma levels within individual kinetic experiments were observed in this study (Table 6), probably caused by plasma values being frequently near the detection limit (12 pg/ml) of the method as well as possible interference by unknown metabolites. Accumulation calculated from the ratio of $AUC^{MD}_{(0\text{-}336\ h)}$: $AUC^{SD}_{(0\text{-}336\ h)}$ was 1.73 with a coefficient of variation (CV) of 89%.

PLASMA LEVELS OF INCREASING DOSES OF CABERGOLINE IN PARKINSONIAN PATIENTS (STUDY CAB TOPD/004)

The study was designed to evaluate the linearity of the pharmacokinetics (PK) of CAB at steady state. Nine idiopathic parkinsonian patients (7 males and 2 females, weight: 75.67±10.06 kg, age: 64.0±7.6 yr) receiving stable levodopa medication two weeks prior to the study were enrolled in the study. No

other medication other than L-dopa was taken by the patients. Three different doses (3, 5, and 7 mg) of CAB requiring tablets of different strengths [0.5 mg (batch # TF/23374), 1 mg (batch # TF/23467), and 2 mg (batch # TF/23477)] were tested at three different experimental sessions. For each session a cabergoline dose (given once daily) was maintained constant for a period of at least 18 days before a further modification of the dose was applied (day 0). CAB administration for 18 days was done in order to reach steady state since CAB urinary elimination half-life was estimated in a previous study to be 63 - 69 h. Each day's dose was administered with breakfast. Blood samples were collected before CAB administration on day -2, -1, and 0. On day 0 (the eighteenth day) blood samples were taken at specified times for up to 24 h after drug administration. Statistical moments analysis method was used for data analysis. To evaluate the linearity of the kinetics, C_{min}, C_{max}, and AUC values obtained from patients (N = 6) who received the same doses (3, 5 and 7 mg) were normalized to the 1 mg dose and compared for differences among doses using a two way ANOVA. No significant differences were detected for any of the parameters (Table 7), but there was significant inter-subject variability.

6.3 MASS BALANCE STUDIES

PHARMACOKINETICS AND EXCRETION BALANCE OF ^{14}C-CABERGOLINE IN MALE HEALTHY VOLUNTEERS (STUDY 610i PK)

Five healthy volunteers were given a single oral dose of 1 mg ^{14}C-Cabergoline (FCE 21336). Immediately before dosing, 17 ml of distilled water were added to the solution of 1 mg ^{14}C-Cabergoline as free base in 3 ml of distilled water containing H_3PO_4. The mean urine excretion accounted for 22.3±4.1% (mean±S.D.) of the administered radioactivity, while in the two subjects taken into consideration for the excretory balance (subjects 2 and 4), 56% and 57.8% of radioactivity was found in the feces, respectively. Fecal excretion only becomes significant after the third day. In these two subjects, therefore, the percentage radioactivity excreted accounted for 80.0% and 78.7% of the administered dose (Table 8). The unchanged drug and metabolites present in urine were identified and quantified by separation through resin columns and comparison with reference compounds. In urine the main radioactive peak detected in 0-24h was the acid derivative FCE 21589 amounting to 41% of urinary radioactivity, whereas unchanged cabergoline accounted for 10%. Less polar metabolites amounted to 20% and radioactivity detected as polar metabolites amounted to 6%. The remaining radioactivity was distributed among metabolites FCE 21590 (7%), FCE 27391 (5%) and FCE 21904 (8%) (see Fig 2). In the 24-72h interval cabergoline increased to 24% of urinary radioactivity, while FCE 21589 decreased to 29%. The relative percentages of the other compounds did not change significantly.
After oral administration of ^{14}C-Cabergoline, radioactivity is mainly excreted in feces. This may indicate biliary elimination because of the delay in appearance of the radioactivity. Cabergoline undergoes extensive metabolism after oral administration giving several metabolites, known and unknown. The major metabolite is the acid derivative of cabergoline FCE 21589 indicating that hydrolysis rather than oxidation is the major metabolic pathway for cabergoline.

PHARMACOKINETICS ^{3}H-CABERGOLINE IN MALE HEALTHY VOLUNTEERS (STUDY 605i PK)

After oral administration of 0.6 mg ^{3}H-Cabergoline solution to three subjects, radioactivity is mainly eliminated by the fecal route (72% after 10 days). Urine contains 17% of the dose after the same period (Table 9). The unchanged drug and metabolites present in urine were identified by comparison with reference compounds and quantified by radio-TLC analysis. Cabergoline is extensively metabolized. Unchanged drug in 0-24 h urine represents less than 14% of total urinary radioactivity, reaching 20%

(~3% of dose) in the 0-96 h urine. The acid derivative FCE 21589 is the main metabolite, amounting to 30% (~5% of dose) of the urinary radioactivity in 0-96 hr.

6.4 RELATIVE BIOAVAILABILITY

URINARY KINETICS AND RELATIVE BIOAVAILABILITY OF CABERGOLINE (1 MG TABLETS VS SOLUTION) AFTER ORAL ADMINISTRATION TO HEALTHY FEMALE VOLUNTEERS (STUDY 609i PK)

The purpose of this study was to obtain urinary pharmacokinetic data on cabergoline after single oral administration of 1 mg to female healthy volunteers and to evaluate the relative bioavailability of 2x0.5 mg cabergoline tablets vs 1 mg cabergoline solution.

Twelve healthy female volunteers, aged 23-35 years, were treated according to an open, randomized, crossover design, with cabergoline (1 mg oral dose) both as tablets and as a solution. Tablets were administered as two 0.5 mg cabergoline (batch TF/23468) tablets and solution as freeze-dried cabergoline (batch SF/1038) reconstituted with tap water. The two administrations were separated by a 4-week wash-out period. Cabergoline and prolactin were measured in urine and plasma, respectively, by RIA. Blood samples were collected before and up to 30 days after dosing. Urine was collected before and up to 8 days after dosing.

For each urinary collection interval, the average excretion rate was calculated and the data plotted against the midpoint of the collection interval on a semilogarithmic scale. Cabergoline elimination half life was estimated by least-squares fitting of data judged to be on the terminal linear part of the curve. Relative bioavailability of cabergoline tablets (T) vs the solution (S) was estimated from the total amount of unchanged cabergoline excreted in urine (Ae) by the ratio: $F_{T/S} = Ae_T/Ae_S$.

Cabergoline elimination half-lives calculated from urinary data were 68 and 63 h after administration of the tablets and the solution, respectively. Urinary excretion of unchanged cabergoline accounted, on average, for 1.92%(range,) and 1.8% (range,) of the dose after administration of the tablets and the aqueous solution, respectively. Relative bioavailability of tablets vs solution was 99% (geometric mean with the 90% confidence intervals of 68-144%)(Table 10). Prolactin levels in 10 out of 12 subjects fell below the detection limit of the assay (1.5 μg/ml) after both treatments. The mean maximum prolactin decrease of about 70% was achieved by 2 or 3 hours after dosing, the effect persisted up to 9 days, being completely exhausted 23-28 days after dosing.

The recovery of unchanged cabergoline in urine was very low and consistent with previous studies. Based on total amount of unchanged cabergoline excreted in urine there is some evidence that the extent of absorption after tablets and solution are similar, albeit highly variable.

6.5 STUDIES IN SPECIAL POPULATIONS

RENAL IMPAIRMENT

PHARMACOKINETICS OF CABERGOLINE (1 MG SINGLE ORAL DOSE) IN PATIENTS WITH RENAL INSUFFICIENCY (STUDY CBA PHKI 022)

This study was performed to assess the pharmacokinetics (PK) of a single 1 mg dose (two 0.5 mg tablets, batch #: TF/23718) of CAB in patients with impaired renal function. This was an open, non-randomized, single dose study lasting for 14 days. Twelve renal impaired patients (6 males and 6 females, age: 53.33 ± 12.24 yr, weight: 62.17 ± 11.26 kg, height: 164.33 ± 6.91 cm) participated in the study. Patients were categorized into two groups: moderate (creatinine clearance (CRCL): 30 to 59 ml/min, 47.0 ± 12.2 ml/min) and severe (CRCL: 10 - 29 ml/min, 16.4 ± 8.0 ml/min) renal impairment. Blood and urine

samples were collected before and after drug administration at specified times for up to 336 h after drug administration.
Oscillating plasma levels precluded the estimation of the elimination of half-life from plasma data. However, Ae and AUC were calculated using moments analysis.
The Sponsor made a comparison of results obtained in this study with those obtained using healthy volunteers in the food effect study. This historical comparison is inappropriate. None of the parameters evaluated differed significantly in the two patient groups (Tables 11 & 12). Compared with data obtained from the food effect study in healthy volunteers (CRCL: 104.1 ± 22.3 ml/min), pharmacokinetics of the drug were similar in both renal impaired and unimpaired patients. The PK parameters (mean ± SD) for the healthy volunteers (from the food effect study) and the two groups of renal impaired patients were as follows: healthy subjects - C_{max}: 69.1 ± 38.3 pg/ml, T_{max}: 2.6 h (median with a range of h), AUC_{0-168h} : 2861 ± 1673 pg.h/ml, Ae: 11.9 ± 11.4 μg; moderate renal impairment- C_{max}: 86.7 ± 34.8 pg/ml, T_{max}: 1.6 h (median with a range of h), AUC_{0-168h}: 3778 ± 2466 pg.h/ml, Ae: 12.6 ± 11.0 μg; severe renal impairment- C_{max}: 66.7 ± 42.1 pg/ml, T_{max}: 2.6 h (median with a range of h), AUC_{0-168h} : 2834 ± 3831 pg.h/ml, Ae: 4.4 ± 2.7 μg.

HEPATIC INSUFFICIENCY

PHARMACOKINETICS OF CAB (1 MG ORAL SINGLE DOSE) IN PATIENTS WITH HEPATIC INSUFFICIENCY*(STUDY CBA PHKI 021)

The objective of this study was to assess the PK of a single 1 mg dose (two 0.5 mg tablets, batch #: TF/23718) of CAB in patients suffering from hepatic insufficiency since the drug is highly metabolized and bile is an important route of elimination. Twelve adult patients (9 males and 3 females, age: 48.58 ± 9.39 yr, weight: 63.08 ± 11.92 kg, and height: 170.08 ± 6.84 cm) who participated in the study fell into three hepatic impairment groups according Child Pugh classification (hepatic insufficiency of grade A (score 5/6), B (score 7/9), C (score 10/11)). No patients were included with a score higher than 11. Blood and urine samples were collected before drug administration and at specified time intervals up to 336 h after drug administration. Pharmacokinetic data analysis was done using the statistical moments analysis method.
Hepatic insufficiency up to grade C (score 10) may not affect CAB PK, but caution is required in cases of severe hepatic insufficiency (score 11) (see Tables 13 & 14, and Fig. 3 - a local regression (loess) fit to the data).

6.6 DRUG INTERACTIONS

EVALUATION OF PHARMACOKINETIC INTERACTION BETWEEN CAB AND L-DOPA IN "DE NOVO" PARKINSONISM PATIENTS (STUDY PHKI 025)

The objective of the study was to evaluate the effect of concomitant administration of l-dopa on CAB PK in patients with Parkinson's disease. This was an open label study in which 10 patients were enrolled. After a wash out period for excluded medications, patients were given CAB in increasing doses up to a daily dose of 2 mg which was maintained for 3 weeks (see Table 15). [The dosage strengths of the tablets used were: 0.25 mg (batch # TF/23882), 0.5 mg (batch # 23881), 1 mg (batch # TF/23856), 2 mg (batch # TF/23860).] At the end of the three week period the PK of CAB was assessed. Thereafter patients were further treated for a week with CAB (2mg/day) and l-dopa (250 mg/day). At the end of this period CAB PK was again assessed.
The results are summarized in Tables 16 to 18. CAB $AUC^{ss}_{(0-24h)}$ and C^{ss}_{max} in the presence and absence of l-dopa were similar. $AUC^{ss}_{(0-24h)}$ and C^{ss}_{max} (mean ± SD) were 4029 ± 3246 pg.h/ml and 234 ± 172

pg/ml, respectively in the absence of l-dopa; and 4038 ± 2515 pg.h/ml and 238 ± 163 pg/ml, respectively, in the presence of l-dopa. The median T_{max} for CAB obtained when l-dopa was coadministered with CAB was 4 h compared to 2 h when CAB alone was administered.

EVALUATION OF PHARMACOKINETIC INTERACTION BETWEEN CABERGOLINE AND L-DEPRENYL (SELEGILINE ®) IN PARKINSONIAN PATIENTS (STUDY FCE 21336/023)

This study was conducted to evaluate reciprocal pharmacokinetic interactions, if any, between cabergoline and l-deprenyl. It was also to examine whether the urinary excretion of selective MAO-B substrate β-phenylethylamine (PEA), taken as an index of MAO-B inhibition, is modified in Parkinsonian patients when CAB is administered concomitantly with l-deprenyl. Six Parkinsonian patients (age: 57.5 ± 7.1 yr, weight: 75.0 ± 12.8 kg, height: 168.6 ± 10.1 cm, duration of disease: 10.8 ±a 7.3 months, Hoehn and Yahr grade 1 - 1.5) were given l-deprenyl (Selegeline®, 10 mg qd) for 8 days, then l-deprenyl and CAB (10 mg and 1 mg (1 mg tablet (batch #-TF/23762), respectively, once a day) for 22 days (up to day 30 after study initiation), and then CAB alone (1 mg, once a day) for 22 days (up to 52 days after study initiation).

Plasma PK of l-deprenyl metabolites was assessed on days 8 and 30. PK of CAB was assessed on days 30 and 52. Determinations of drugs and metabolite levels were done by RIA and HPLC with fluorescence. The possible reciprocal interaction between the two drugs on PEA urinary excretion was assessed by measuring the daily urinary excretion of PEA prior to treatment (day -1) and on days 8, 30 and 52. PEA urinary levels were determined by HPLC with fluorescence detection. Analysis of PK data was by non-compartmental approach.

When l-deprenyl was administered alone, the average peak (mean ± S.D.) levels of its three metabolites (desmethyldeprenyl, methamphetamine and amphetamine) were 11 ±2, 16 ± 7 and 7 ± 3 ng/ml, respectively, and occurred at 1.1 ± 0.6, 2.4 ± 1.3 and 2.7 ± 1 h post-dosing, respectively. $AUC^{SS}_{(0\text{-}24h)}$ (mean ± SD) of desmethyldeprenyl, methamphetamine and amphetamine were 58 ± 37, 243 ± 136 and 123 ± 63 ng.h/ml, respectively. The corresponding parameter values for these metabolites when l-deprenyl was coadministered with CAB are: $AUC^{SS}_{(0\text{-}24h)}$: 83.19 ± 46.21, 263.42 ± 149.91, and 139.92 ± 74.92 ng.h/ml; C^{ss}_{max}: 11.01 ± 2.88, 15.05 ± 6.73, 7.21 ± 3.19 ng/ml; and T_{max}: 1.36 ± 1.48, 3.63 ± 2.72, 3.71 ± 2.61 h. No significant differences in the C^{ss}_{max}, T^{ss}_{max} , and $AUC^{SS}_{(0\text{-}24h)}$ of l-deprenyl metabolites were noted by associating l-deprenyl with CAB administration. Also, l-deprenyl did not affect the PK of CAB. The C_{max}, $AUC^{SS}_{(0\text{-}24h)}$, and T_{max} for CAB in the absence of l-deprenyl are 122 ± 30 pg/ml, 2087 ± 665 pg.h/ml, 1.32 ± 0.62 h, respectively. When CAB was co-administered with l-deprenyl the values for these parameters were: 121 ± 24 pg/ml, 2138 ± 527 pg.h/ml, 1.36 ± 1.49 h.

The daily urinary excretion of PEA was 18 ± 6 μg/24 h prior to initiation of treatment. More than 3-fold increase in mean urinary PEA excretion was found after l-deprenyl administration for 8 days (63 ± 60.4 μg/24 h). Mean PEA urinary excretion was further increased (103 ± 81 μg/24 h) after l-deprenyl and CAB coadministration for 22 days. After the administration of CAB alone for 22 days, the value of PEA urinary excretion returned close to control value (25 ± 9 μg/24 h) (Table 19). It is reported that a single oral dose of 10 mg l-deprenyl is sufficient to inhibit more than 98% of platelet MAO-B activity (Thornton *et al.* 1980; Psychopharmacol 70: 163). In this study, an increase in PEA excretion from day 8 to day 30 seems to indicate the absence of correlation between inhibition of platelet MAO-B and the extent of PEA excretion in urine as already reported by Elsworth *et al* (1993; Psychopharmacol 57: 33). The reason for the cumulative effect of l-deprenyl on PEA is not apparent, and might reflect a progressive MAO-B in other tissues besides platelets. The reason for the increase in PEA excretion during CAB co-administration is not obvious. The Sponsor has suggested that this may be due

to the fact l-deprenyl needs more than 8 days to completely inhibit MAO-B in all tissue compartments.

6.7 EFFECT STUDY FOOD

PLASMA LEVELS AND URINARY EXCRETION OF CABERGOLINE AFTER 1 MG SINGLE ORAL DOSE IN HEALTHY MALE VOLUNTEERS UNDER FED AND FASTING CONDITIONS (STUDY 612i PK).

The purpose of this study was to investigate the influence of food on cabergoline absorption and disposition after administration of a single dose to healthy volunteers both under fasting conditions and after a standard high-fat breakfast.

Twelve healthy male volunteers received a single oral dose (2x0.5 mg tablets) of cabergoline both under fasting conditions and after a standard meal (high-fat breakfast) according to a randomized cross-over design. A 4 week wash-out period separated the two administrations. Plasma and urine samples were collected for 14 and 7 days, respectively, after each drug administration.

Very low plasma concentrations (limit of sensitivity 12 pg/ml) of cabergoline were found under both fasting and fed conditions for all subjects even though several subjects showed measurable plasma levels of the drug up to 336 h after dosing. The percentage of administered dose excreted in the urine ranged from % (average 1.2±1.1 %) and from % (average 1.3±0.7 %) under fasting and fed conditions, respectively (Table 20).

Food does not appear to affect absorption of cabergoline in man.

1 Page deleted

Fig. 3. A Loess Fit of AUC in Hepatic Impaired Patients

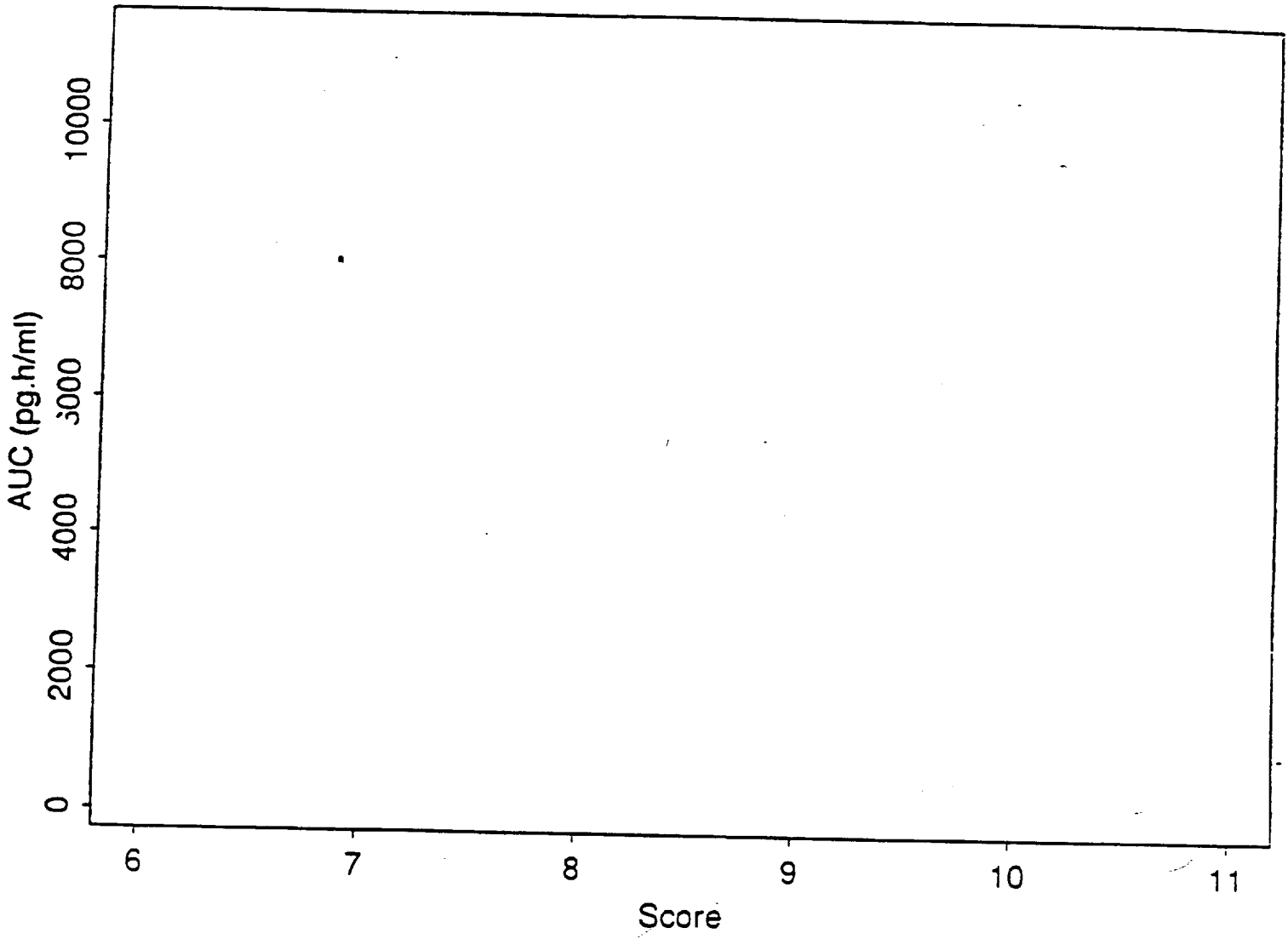


Table 1

Summary Table of Drug Formulation History

Formulation No.	Formulation	
	Ingredient	Per Tablet
FCE 21336/PT 12	Cabergoline Lactose (anhydrous), NF Leucine, USP Total Weight * includes a 10% overage Shape: 6 mm round	mg* mg mg mg
FCE 21336/PT24	Cabergoline Lactose (anhydrous), NF Leucine, USP Total Weight * includes a 10% overage Shape: 4 x 6 mm, capsule shape	mg* mg mg mg
FCE 21336/PT 13	Cabergoline Lactose (anhydrous), NF Leucine, USP Total Weight * includes a 10% overage Shape: 6 mm round	mg* mg mg mg
FCE 21336/PT 18	Cabergoline Lactose (anhydrous), NF Leucine, USP Total Weight * includes a 10% overage Shape: 6 mm round	mg* mg mg mg
FCE 21336/PT 19	Cabergoline Lactose (anhydrous), NF Leucine, USP Total Weight * includes a 10% overage Shape: 5 mm round	mg* mg mg mg

Table 1
(continued)

Summary Table of Drug Formulation History

Formulation No.	Formulation	
	Ingredient	Per Tablet
FCE 21336/PT 20	Cabergoline Lactose (anhydrous), NF Leucine, USP Total Weight * includes a 10% overage Shape: 3 mm round	mg mg mg mg
FCE 21336/PT 21	Cabergoline Lactose (anhydrous), NF Leucine, USP Total Weight * includes a 10% overage Shape: 5x10 mm, capsule shape	mg* mg mg mg
FCE 21336/PT 26	Cabergoline Lactose (anhydrous), NF Leucine, USP Total Weight * includes a 5% overage Shape: 6 mm round	mg* mg mg mg
FCE 21336/PT 28	Cabergoline Lactose (anhydrous), NF Leucine, USP Total Weight * includes a 5% overage Shape: 4 x 8 mm, capsule shape	mg* mg mg mg
FCE 21336/PT 30	Cabergoline Lactose (anhydrous), NF Leucine, USP Total Weight * includes a 5% overage Shape: 6 mm round	mg* mg mg mg

Table 1
(continued)

Summary Table of Drug Formulation History

Formulation No.	Formulation	
	Ingredient	Per Tablet
FCE 21336/PT 33	Cabergoline	mg*
	Lactose (anhydrous), NF	mg
	Leucine, USP	mg
	Total Weight	mg
	* includes a 0% overage	
	Shape: 4.58x7.12 mm, ovoid	
FCE 21336/PT 34	Cabergoline	ıg*
	Lactose (anhydrous), NF	mg
	Leucine, USP	mg
	Total Weight	mg
	* includes a 0% overage	
	Shape: 5x10 mm, capsule shape	
FCE 21336/PT 35	Cabergoline	mg*
	Lactose (anhydrous), NF	mg
	Leucine, USP	mg
	Total Weight	mg
	* includes a 10% overage	
	Shape: 6 mm round	
FCE 21336/PT 36	Cabergoline	mg*
	Lactose (anhydrous), NF	mg
	Leucine, USP	mg
	Total Weight	mg
	* includes a 0% overage	
	Shape: 4x8 mm, capsule shape	
FCE 21336/PT 38	Cabergoline	mg*
	Lactose (anhydrous), NF	mg
	Leucine, USP	mg
	Total Weight	mg
	* includes a 0% overage	
	Shape: 6 mm round	

TABLE 2

Table # - Amount excreted in urine (ng), percent of dose eliminated in urine (%) and elimination half-life (h) of cabergoline, in hyperprolactinemic patients after a single oral administration of 0.5, 0.75 or 1 mg of cabergoline.

Subject No.	Dose (mg)	Amount excreted (ng)	% Dose	t1/2 (h)
	0.50	2379.6	0.48	n.e.
	0.50	5010.5	1.00	95.62
	0.50	1310.0	0.26	n.e.
	0.50	4567.4	0.91	97.90
	0.50	3897.1	0.78	87.47
	0.50	1308.5	0.26	n.e.
	0.75	2587.5	0.35	n.e.
	0.75	9285.0	1.24	95.62
	0.75	1324.2	0.18	78.83
	0.75	7451.4	0.99	n.e.
	0.75	5275.8	0.70	n.e.
	1.00	4775.7	0.48	115.02
	1.00	5878.6	0.59	95.37
	1.00	10531.3	1.05	82.17
	1.00	6710.7	0.68	113.00
	1.00	12464.5	1.25	112.95
	1.00	7349.1	0.73	n.e.

n.e.: not evaluable

TABLE 9

TABLE 3

% DOSE EXCRETED WITH THE URINE UP TO 168 h AFTER DOSING BY THE TWELVE VOLUNTEERS PARTICIPATING IN THE STUDY

Subject N°	% dose excreted		
	Administered dose (mg)		
	0.5 mg	1 mg	1.5 mg
	1.4	1.0	1.6
	0.7	1.4	0.9
	1.1	1.3	1.1
	1.1	1.9	1.4
	2.8	2.2	2.9
	1.0	0.9	0.8
	1.9	2.5	--
	0.8	1.0	0.8
	1.1	0.7	1.2
	1.0	0.7	1.3
	0.7	0.5	0.9
	0.9	0.7	0.7
Mean±S.D. N = 11	1.1±0.6	1.1±0.5	1.2±0.6

-- Volunteer did not participate and was excluded from all calculations

TABLE 7

TABLE 4

AUC$_{(0-168\ h)}$ CALCULATED USING THE TRAPEZOIDAL RULE AND NORMALIZED TO THE 1 mg DOSE, FOR THE TWELVE VOLUNTEERS PARTICIPATING IN THE STUDY

Subject N°	AUC$_{(0-168\ h)}$		
	Administered dose (mg)		
	0.5 mg	1 mg	1.5 mg
	202	3718	815
	192	2675	1477
	3868	1923	101
	2872	792	2024
	6858	2791	2964
	6032	2063	2447
	6014	2575	--
	480	782	439
	356	2997	1953
	1058	1016	1974
	5086	505	3063
	1480	1463	1422
Mean±S.D. N = 11	2589±2500	1884±1064	1698± 965

-- Volunteer did not participate and was excluded from all calculations

TABLE 5

TABLE 5

Cmax NORMALIZED TO THE 1 mg DOSE FOR THE TWELVE VOLUNTEERS PARTICIPATING IN THE STUDY

Subject N°	Cmax (pg/ml)		
	Administered dose (mg)		
	0.5 mg	1 mg	1.5 mg
	40	35	37
	36	44	40
	50	31	21
	46	52	29
	96	47	57
	78	52	23
	84	42	--
	42	29	25
	72	42	67
	78	40	61
	102	30	43
	92	42	90
Mean±S.D. N = 11	66.5±24.5	40.4±8.3	44.8±21.7

-- Volunteer did not participate and was excluded from all calculations

TABLE 6

PHARMACOKINETIC PARAMETERS FOR THE TWELVE VOLUNTEERS PARTICIPATING IN THE STUDY

N°	Cmax (pg/ml)		Tmax (h)		AUC (0-336 h) (pg.h/ml)		µg excreted (0-336 h)		% dose excreted (0-336 h) single dose
	S*	R**	S	R	S	R	S	R	
1	39	60	2	2	8142	14013	10.1	12.3	1.0
2	39	90	1	4	4058	18507	7.5	10.2	0.7
3	50	24	8	3	7574	970	9.6	15.0	1.0
4	31	73	8	2	5768	20317	8.6	10.0	0.9
5	--	--	--	--	--	--	--	--	--
6	39	46	0.5	8	6913	5728	6.0	9.8	0.6
7	50	44	1	8	7633	8921	9.1	11.5	0.9
8	28	70	1	3	2551	9275	7.2	13.4	0.7
9	31	50	6	3	4342	9392	11.6	12.5	1.2
10	35	43	8	3	6587	3422	9.4	11.6	0.9
11	30	29	6	3	5461	2931	10.1	6.0	1.0
12	30	24	1	2	5907	1544	5.5	11.9	0.5
MEAN±SD	3710	50±21	2[a]	3[a]	5903±1720	8638±6641	8.6±1.9	11.3±2.3	0.9±0.2

* : S = Single dose
** : R = Repeated dose
[a] : read median instead of mean

TABLE 7

Values of C_{max} and AUC_{0-24h} for the patients participating in the study

Patient	Session	Dose (mg)	Cmax (pg/ml)	AUC0-24h (pg.h/ml)
	1	3	587	11465
	2	5	1000	15599
	3	4	800	12585
	1	3	950	14280
	2	5	812	12064
	3	7	925	17266
	1	3	700	10060
	2	5	1050	16480
	3	7	2150	30568
	1	3	750	8338
	2	5	650	9321
	3	8	2500	21483
	1	3	420	3598
	2	5	370	5088
	3	7	500	5140
	1	3	230	4380
	2	5	450	6681
	3	7	1100	15012
	1	3	625	4451
	2	5	650	8540
	3	7	725	10982
	1	3	775	14601
	2	5	1000	17780
	3	7	2150	26837
	1	3	320	5021
	2	5	525	7978
	3	6	500	5870

TABLE 8

TABLE 4 - CUMULATIVE PERCENTAGE OF THE DOSE EXCRETED BY HEALTHY VOLUNTEERS GIVEN AN ORAL DOSE OF 1 mg OF ^{14}C-FCE 21336

Excreta	Time	Subjects -
URINE	0-4 h	
	0-8 h	
	0-12 h	
	0-24 h	
	0-2 Day	
	0-3	
	0-4	
	0-5	
	0-6	
	0-7	
	0-8	
	0-9	
	0-10	
	0-11	
	0-12	
	0-13	
	0-14	
	0-15	
	0-20	
FAECES	0-1 Day	
	0-2	
	0-3	
	0-4	
	0-5	
	0-6	
	0-7	
	0-8	
	0-9	
	0-10	
	0-11	
	0-12	
	0-13	
	0-14	
	0-15	
	0-20	

N.D. = not detectable
N.E. = not excreted
N.C. = sample not collected
*see Appendix 1 pages 129 and 167

TABLE 9

Cumulative urinary (non-volatile) and fecal excretion of radioactivity after single oral administration of 0.6 mg ^{3}H-FCE 21336 to 3 healthy volunteers. Results are expressed as per cent of administered dose.

Subject no.	Urinary radioactivity(% of dose)at times (h):												
Mean	3.340	5.414	7.163	9.120	10.939	12.664	13.915	14.065	15.604	16.145	16.594	16.889	17.313
S.D.	0.258	0.138	0.249	0.304	0.307	0.245	0.093	0.022	0.100	0.176	0.100	0.206	0.227
	Fecal radioactivity(% of dose) at times (h):												
Mean				0.058	14.273	25.869	41.079	66.959	70.112	71.831	72.104	72.167	72.241
S.D.				0.040	14.011	12.090	9.499	3.087	2.766	3.415	3.570	3.581	3.514

TABLE 10

Table I - Individual and mean values of urinary excretion of free cabergoline, elimination half-life and relative bioavailability, ($F_{T/S}$) grouped by treatment (T: tablets; S: solution).

Subject	Amount excreted (ng)		% Dose		t1/2 (h)		$F_{T/S}$	
	T	S	T	S	T	S		
MEAN	19233	18020	1.92	1.80	68.54	63.13	1.21	0.99*
S.D.	8509	8590	0.85	0.86	31.76	33.66	0.67	
SEM	2456	2480	0.25	0.25	9.58	10.15	0.19	

*geometric mean
n.e.: not evaluable

Confidence intervals of relative bioavailability ($F_{T/S}$)

calculated using	: arithmetic mean	geometric mean
90% confidence intervals :	0.87 - 1.55	0.68 - 1.45
95% confidence intervals :	0.79 - 1.63	0.62 - 1.58

TABLE 11

Comparison of the pharmacokinetic parameters in renal insufficiency patients (using the data obtained in the present study up to 168h after dosing) with those of healthy volunteers from a previous study (18). Both patients and healthy volunteers received a single oral dose of 1 mg cabergoline under fasting condition.

HEALTHY VOLUNTEERS					MEDIUM RENAL INSUFFICIENCY (Group 3)					SEVERE RENAL INSUFFICIENCY (Group 3)				
N°	creatinine clearance (ml/min)	C_{max} (pg/ml)	T_{max} (h)	$AUC_{0-\infty}$ (pg h/ml)	N°	creatinine clearance (ml/min)	C_{max} (pg/ml)	T_{max} (h)	$AUC_{0-\infty}$ (pg h/ml)	N°	creatinine clearance (ml/min)	C_{max} (pg/ml)	T_{max} (h)	$AUC_{0-\infty}$ (pg h/ml)
1	84.0	27	1	1394	4	40.7	111	1	1612	1	10.2	33	3	2183
3	100.0	29	1	1858	6	31.0	60	4	3727	2	10.5	69	0.5	766
5	80.0	156	0.75	2416	7	50.8	58	0.5	1284	3	25.0	27	3	807
4	99.0	77	3	4599	10	65.9	133	0.5	6360	5	8.0	136	3	10789
6	136.0	40	24	3882	11	37.1	108	2	3118	8	13.0	31	8	1302
8	67.0	90	3	3110	12	58.4	58	2	2674	9	28.0	84	4	1173
7	110.0	46	12	6498										
8	137.0	65	3	4477										
9	102.5	67	1	666										
10	133.0	29	2.5	633										
11	95.0	-	-	-										
12	108.4	36	2	3029										
mean ± S.D.	104.1 ± 23.3	69.1 ± 38.3	2.5*	2861 ± 1673	mean ± SD	47.0 ± 12.2	88.7 ± 34.8	1.5*	3778 ± 2466	mean ± SD	15.4 ± 8.0	55.7 ± 42.1	2.5*	2834 ± 3831

* Read median instead of mean;

- All plasma samples collected from volunteer No 11 contained cabergoline at concentration below the limit of quantitation of the analytical method employed.

TABLE 12

Total amount (Ae), creatinine clearance, cabergoline renal clearance (CL_R, calculated using the data up to the last measurable time point in both plasma and urine), and % dose excreted in the 0-336h urine after a single oral dose of 1 mg of cabergoline in patients with renal insufficiency divided according to the severity of their renal impairment.

MEDIUM RENAL INSUFFICIENCY (Group 2)						SEVERE RENAL INSUFFICIENCY (Group 3)					
PATIENT NUMBER	creatinine clearance (ml/min)	Ae (µg)	Cl_R (ml/min)	time interval chosen to calculate Cl_R (h)	% dose excreted	PATIENT NUMBER	creatinine clearance (ml/min)	Ae (µg)	Cl_R (ml/min)	time interval chosen to calculate Cl_R (h)	% dose excreted
	40.7	7.3	32.7	0.24	0.73		10.2				
	31.0	2.5	20.4	0.72	0.25		10.5				
	58.8	9.7	51.6	0.48	0.97		25.0	9.8	70.1	0.48	0.98
	55.9	42.4	77.1	0.336	4.24		8.0	3.6	9.6	0.336	0.36
	37.1	28.7	42.0	0.336	2.87		13.0	1.6	17.6	0.48	0.16
	58.4	9.5	41.3	0.96	0.95		26.0	7.6	58.0	0.48	0.76
mean ± S.D	47.0 ± 17.2	16.7 ± 15.5	41.7 ± 17.5		1.7 ± 1.5	mean ± S.D	15.4 ± 8.0	5.6 ± 3.7	38.9 ± 29.8		0.56 ± 0.37

- Urine samples collected from these patients contained cabergoline at concentration below the limit of quantitation of the analytical method employed and therefore the pharmacokinetic parameter could not be calculated.

TABLE 13

TOTAL AMOUNT (Ae), ELIMINATION HALF-LIFE ($t_{½}$) AND % DOSE EXCRETED IN THE 0-336 h URINE AFTER A SINGLE 1 mg ORAL DOSE OF CABERGOLINE FOR THE PATIENTS ENROLLED IN THE STUDY DIVIDED ACCORDING TO THE CHILD-PUGH CLASSIFICATION.

CHILD PUGH CLASSIFICATION															
A					B					C					
Patient No	Score	Ae (µg)	% dose excreted	$t_{½}$ (h)	Patient No.	Score	Ae (µg)	% dose excreted	$t_{½}$ (h)	Patient No.	Score	Ae (µg)	% dose excreted	$t_{½}$ (h)	
Mean ± S.D.	5.7 ± 0.5	23.2 ± 10.1	2.3 ± 1.0	108.4 ± 22.0	Mean ± S.D.	7.5 ± 0.8	49.2 ± 18.7	4.9 ± 1.8	187.7 ± 86.7	Mean ± S.D.	10.8 ± 0.8	40.7 ± 18.1	4.1 ± 1.8	321.3 ± 37.1	

TABLE 14

PHARMACOKINETIC PARAMETERS AFTER A SINGLE 1 mg ORAL DOSE OF CABERGOLINE FOR THE TWELVE PATIENTS ENROLLED IN THE STUDY DIVIDED ACCORDING TO THE CHILD-PUGH CLASSIFICATION

CHILD PUGH CLASSIFICATION														
A					B					C				
Patient No.	Score	C_{max} (pg/ml)	T_{max} (h)	AUC_{0-336h} (pg h/ml)	Patient No.	Score	C_{max} (pg/ml)	T_{max} (h)	AUC_{0-336h} (pg h/ml)	Patient No.	Score	C_{max} (pg/ml)	T_{max} (h)	AUC_{0-336h} (pg h/ml)
Mean ± S.D.	5.7 ± 0.5	73.2 ± 86.1	1**	957 ± 1483	Mean ± S.D.	7.5 ± 0.8	71.2 ± 38.2	2.6**	1394 ± 1278	Mean ± S.D.	10.6 ± 0.8	120.7 ± 74.8	0.76**	5838 ± 5045

* Cabergoline plasma levels for this patient were always below the quantitation limit of the assay. The C_{max} and $AUC_{(0-336h)}$ values for this patient were considered equal to 0 in the calculation of mean C_{max} and $AUC_{(0-336h)}$ values for group A.

** Median instead of mean; T_{max} value of patient No. [redacted] was not included in the calculation.

Table 15 Treatment schedule

Week 1	Day 1-3	0.25 mg cabergoline
Week 1	Day 4-7	0.5 mg cabergoline
Week 2	Day 8-14	1 mg cabergoline
Week 3-4	Day 15-28	1.5 mg cabergoline
Week 5-6-7	Day 28-49	2 mg cabergoline
Week 8	Day 50-56	2 mg cabergoline + sinemet (250 mg levodopa and 25 mg carbidopa

Blood samples for the pharmacokinetic study sessions were collected at week 7, day 49 (cabergoline alone) and at week 8, day 56 (cabergoline + sinemet), see text for details.

Table 16 $AUC_{(0-24h)}$, at steady state, in parkinsonian patients receiving cabergoline (2 mg/day p.o.) alone or in combination with levodopa (250 mg/day).

Patient N°	Cabergoline $AUC_{(0-24h)}$ (pg·h/ml)	Cabergoline $AUC_{(0-24h)}$ (pg·h/ml) concomitant treatment (Sinemet®)
	12594	8698
	2801	2740
	2509	2321
	2102	2246
	3522	3333
	2737	3570
	1598	1769
	2480	3325
	3993	3769
	5951	8614
mean ± S.D.	4029 ± 3246	4038 ± 2515

The data were compared using Student's t-test for paired data; no statistically significant difference was found.

Table 17 C_{max}, at steady state, in parkinsonian patients receiving cabergoline (2 mg/day p.o.) alone or in combination with levodopa (250 mg/day).

Patient N°	Cabergoline C_{max} (pg/ml)	Cabergoline C_{max} (pg/ml) concomitant treatment (Sinemet®)
	626	499
	173	144
	138	135
	118	145
	175	169
	156	232
	84	94
	164	160
	250	230
	457	571
mean ± S.D.	234 ± 172	238 ± 163

The data were compared using Student's t-test for paired data; no statistically significant difference was found.

Table 12 T_{max}, at steady state, in parkinsonian patients receiving cabergoline (2 mg/day p.o.) alone or in combination with with levodopa (250 mg/day).

Patient N°	Cabergoline t_{max} (h)	Cabergoline t_{max} (h) concomitant treatment (Sinemet®)
	2	4
	1	4
	2	0.5
	1	4
	2	4
	2	4
	4	8
	2	4
	1	0.5
	0.5	0.5
median	2	4

When T_{max} values obtained in the two sessions were compared for difference using the Wilcoxon signed-rank test, a statistically significant difference was found ($p < 0.05$).

Table 19 Urinary excretion of free PEA (μg/24 h) in parkinsonian patients before all treatments (D-1/D1), after administration with l-deprenyl (10 mg/day) (D8/D9), l-deprenyl (10 mg/day) plus cabergoline (1 mg/day) (D30/D31) and cabergoline alone (1 mg/day) (D52/D53).

Subject	Control D-1/D1	l-deprenyl D8/D9	Deprenyl + cabergoline D30/D31	Cabergoline D52/D53
	16.2	26.0	75.5	30.7
	14.1	57.6	85.9	15.1
	20.1	32.4	47.1	33.9
	26.3	184.1	265.5	34.3
	10.2	31.9	68.2	15.7
	20.4	45.4	73.1	22.3
mean ± S.D. All subjects	17.9 ± 5.6	62.9 ± 60.4	102.6 ± 80.9	25.3 ± 8.8
mean ± S.D. Except patient 4	16.2 ± 4.3	38.7 ± 12.7**	70.0 ± 14.3***	23.5 ± 8.6

[a] patient 4 was not considered in the statistical analysis

The data are compared using 2-WAY ANOVA followed by Tukey-test
** $p < 0.05$ vs D-1/D1 group
*** $p < 0.01$ vs D-1/D1, D8/D9 and D52/D53 groups

TABLE 20

TABLE 1

PHARMACOKINETIC PARAMETERS OF THE TWELVE VOLUNTEERS PARTICIPATING IN THE STUDY

N°	Cmax (pg/ml)		AUC 0-168 h		% dose excreted in 0-168h urine		Tmax (h)	
	Fasting	Fed	Fasting	Fed	Fasting	Fed	Fasting	Fed
1	27	30	1394	2683	0.5	0.4	1	1.5
2	29	85	1858	8154	0.8	1.4	1	1.5
3	156	42	2416	3964	0.8	1.0	0.75	2.5
4	77	60	4599	6916	1.4	1.4	3	4
5	40	60	3992	6016	4.7	3.1	24	2
6	90	36	3110	3007	1.0	1.2	3	4
7	45	32	5499	2291	0.7	1.6	12	6
8	65	55	4472	4528	1.3	1.1	3	12
9	57	26	565	2812	0.8	0.7	1	6
10	29	33	533	1124	0.6	0.6	2.5	0.75
11	0	25	0	143	1.0	1.8	--	0.5
12	35	43	3029	656	0.7	0.9	2	2.5
Mean ± SD	54±40	44±18	2622±1796	3591±2496	1.2±1.1	1.3±0.7	2.5*[a]	2.5*[a]
p	N.S.		N.S.		N.S.		--	

* : N = 11

a : read median instead of mean

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020664

CHEMISTRY REVIEWS

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS HFD-510

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-664 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 18-NOV-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	26-DEC-96	27-DEC-96	
BC	25-OCT-96	28-OCT-96	30-OCT-96
BC	31-OCT-96	04-NOV-96	07-NOV-96

NAME & ADDRESS OF APPLICANT:

Pharmacia & Upjohn.
7000 Portage Road
Kalamazoo, MI 49001-0199

DRUG PRODUCT NAME

Proprietary: Dostinex®

Nonproprietary/USAN: Cabergoline tablets (INN; USAN submitted)

Code Name/#: 3030900

Chem.Type/Ther.Class: 1S

PATENT STATUS: US Patent 4,526,892 exp. 02-JUL-2002

PHARMACOL.CATEGORY/INDICATION:

Treatment of hyperprolactinemic disorders, either idiopathic or due to primary adenomas

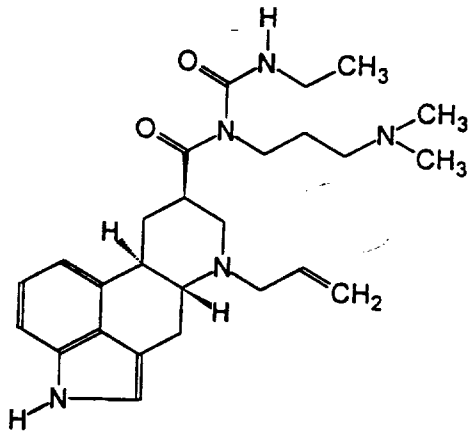
DOSAGE FORM: tablet

STRENGTHS: 0.5 mg

ROUTE OF ADMINISTRATION: oral

DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:



CAS Name: N-[3-(Dimethylamino)propyl]-N-[(ethylamino) carbonyl]-6-(2-propenyl)-8β-ergoline-carboxamide

IUPAC Name: 1-[(6aR,9R,10aR)-7-Alllyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]-quinoline-9-carbonyl]-1-(3-dimethylaminopropyl)-3-ethylurea

CAS Registry Number: 81409-90-7 $C_{26}H_{37}N_5O_2$ M.W. 451.61

SUPPORTING DOCUMENTS: None

CONSULTS:

The firm's response to Environmental Assessment issues was submitted to Nancy Sager, Team Leader of the EA group, on 10/31/96. A Methods Validation Package was submitted to the Cincinnati District Office on 6/26/96. Due to the closure of the Cincinnati office and the change of ownership of the NDA from Pharmacia with administrative offices in Ohio, to Pharmacia & Upjohn with administrative offices in Michigan, the MV request was forwarded to the Detroit District Office on 7/17/96. The MV samples requested from the firm were received intact by the Division of Drug Analysis on 10/17/96. An EER was sent to Compliance on 2/13/95 and an Acceptable report returned on 9/23/96.

REMARKS/COMMENTS:

This review is of correspondence from the sponsor responding to an information request for CMC and EA issues; the environmental issues will be reviewed by the EA team. The second item to be reviewed is the firm's revised package insert.

CONCLUSIONS & RECOMMENDATIONS:

This new drug application is approvable from a chemistry standpoint subject to receipt of an acceptable review of the firm's response to the deficiencies in the Environmental Assessment.

cc:
Orig. NDA 20-664
HFD-510/Division File
HFD-510/Chemist/Seevers/Moore
HFD-510/DNDCII/~~Chiu~~ Gibbs
HFD-510/CSO/Hedin
R/D Init by: Moore

Robert H. Seevers, Chemist

Stephen K. Moore
11/20/96

ORIGINAL

JUN 11 1996

DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS HFD-510

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-664 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 03-MAY-96 **REVISED:** 11-JUN-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	26-DEC-95	27-DEC-95	02-JAN-96

NAME & ADDRESS OF APPLICANT:

Pharmacia, Inc.
P.O. Box 16529
Columbus, OH 43216-6529

DRUG PRODUCT NAME

Proprietary:	Dostinex®
Nonproprietary/USAN:	Cabergoline tablets (INN; USAN submitted)
Code Name/#:	3030900
Chem.Type/Ther.Class:	1S

PATENT STATUS: US Patent 4,526,892 exp. 02-JUL-2002

PHARMACOL.CATEGORY/INDICATION:

Treatment of hyperprolactinemic disorders, either idiopathic or due to primary adenomas

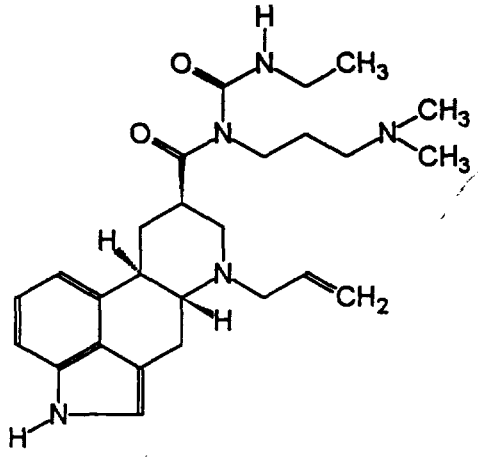
DOSAGE FORM: tablet

STRENGTHS: 0.5 mg

ROUTE OF ADMINISTRATION: oral

DISPENSED: X Rx _ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:



CAS Name: N-[3-(Dimethylamino)propyl]-N-[(ethylamino) carbonyl]-6-(2-propenyl)-8β-ergoline-carboxamide

IUPAC Name: 1-[(6aR,9R,10aR)-7-Alllyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]-quinoline-9-carbonyl]-1-(3-dimethyl aminopropyl)-3-ethylurea

CAS Registry Number: 81409-90-7

$C_{26}H_{37}N_5O_2$

M.W. 451.61

SUPPORTING DOCUMENTS: None

CONSULTS:

EER submitted 2/13/96 for three Italian sites. Inspection performed mid-April. Waiting on report. Environmental Assessment submitted to Nancy Sager, Team Leader of EA group on 1/16/95. Trademark submitted to Labeling and Nomenclature Committee on 2/13/96 and found acceptable on 4/4/96.

REMARKS/COMMENTS:

This review is of an original NDA for Dostinex® (Cabergoline) 0.5 mg tablets. The drug product a dopamine agonist and is indicated for the treatment of hyperprolactinemia.

CONCLUSIONS & RECOMMENDATIONS:

This new drug application is approvable from a chemistry standpoint subject to the following provisions:

Drug Substance

1. The sponsor needs to provide specificity evidence for the identification tests for the lysergic acid monohydrate starting material in the drug substance synthesis and add a specific ID test if necessary.

2. The sponsor needs to indicate whether or not solvents are reused in the drug substance synthesis.

3. The rationale and acceptable criteria for replacing the current drug substance reference standard must be provided.

4. The sponsor needs to commit to the determination of residual methylene chloride in the drug substance.

5. Additional information on the components of the drug substance container/closure system must be provided.

Drug Product

1. An more detailed sampling plan for the finished drug product must be submitted.

2. Additional information on some of the components of the drug product container/closure system must be provided.

3. A revised immediate container label must be submitted with space for an expiration date, a lot number and a storage statement.

Consults

1. An acceptable review of the Environmental Assessment must be received.

2. An acceptable inspection report must be received for the drug's manufacturing sites.

cc:
Orig. NDA 20-664
HFD-510/Division File
HFD-510/Chemist/Seevers
HFD-510/DNDCII/Chiu
HFD-510/CSO/Hedin
R/D Init by: Davies

H.W. Davies
6/11/96

Robert H. Seevers 6/11/96
Robert H. Seevers, Chemist

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020664

ENVIRONMENTAL ASSESSMENT AND FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

DOSTINEX®

(cabergoline)

0.5 mg Tablets

NDA 20-664

Division of Metabolism and Endocrine Drug Products (HFD-510)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

Dostinex®

(cabergoline)

0.5 mg Tablets

NDA 20-664

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 DOSTINEX®, Pharmacia & Upjohn Company has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) in the Tier 0 format which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Cabergoline is a chemically synthesized drug which is administered as a 0.5 mg tablet in the treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas. The drug substance is manufactured by the Pharmacia S.p.A., Rodano (Milan) Italy. The drug product is manufactured by Pharmacia S.p.A., Nerviano, Milan, Italy. The finished drug product will be used in hospitals, clinical settings, and consumer dwellings throughout the United States.

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 in the firm's on-site permitted incinerator. 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.

11/15/96
DATE

Prepared by
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

11/15/96
DATE

Concurred
Nancy Sager
Acting Supervisor/Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

ENVIRONMENTAL ASSESSMENT REPORT (EA)

This Environmental Assessment is being submitted in accordance with the requirements of 21 CFR 25.31a to accompany Pharmacia & Upjohn Company's (P&U) New Drug Application (NDA) for DOSTINEX® (cabergoline) Tablets.

1. DATE

December 1995
Revised: September 1996

2. NAME OF APPLICANT

Pharmacia & Upjohn Company

3. ADDRESS

7000 Portage Road
Kalamazoo, Mi 49001

4. DESCRIPTION OF THE PROPOSED ACTION

4.1. Requested Approval

The former Pharmacia Inc. filed NDA 20-664 pursuant to Section 505(b) of the Food, Drug and Cosmetic Act for DOSTINEX® (cabergoline) 0.5 mg Tablets.

The drug substance is packaged in amber glass bottles with a plastic stopper and seal.

The drug product will be marketed in the U.S. in Type I amber glass bottles with a polyethylene-lined tamper-evident screw cap and a child-proof cover cap with a silica gel insert.

4.2 Need for Action

4.2.1 Indication

Treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas.

4.2.2 Action Mode

The secretion of prolactin by the anterior pituitary is mainly under hypothalamic control, likely exerted through release of dopamine by tuberoinfundibular neurons. Cabergoline is a potent agonist with high affinity for D_2 receptors.

4.3 Production Locations

4.3.1 Drug Substance: Pharmacia S.p.A
(Bulk Process Development)

, together with three other factories belonging to different chemical companies form the area surrounding the towns of to the east of Milan.

This area is near the residential suburbs of (less than 100 metres distance), Limito (300-500 metres),) (about 1000 metres), (about 1000 metres) and a large park (Villa Invernizzi), close to the factory.

4.3.2 Drug Product: Pharmacia S.p.A.
Via per Pogliano
Nerviano, Milan, Italy

The Nerviano plant is owned by Pharmacia S.p.A. This plant was established in 1971 and is located in the neighborhood of Nerviano, a small town not far from Milan. The area includes Pharmacia R & D Centre, Laboratories and facilities for other subsidiary activities. It is located 20 km from Milan, on the "Sempione" national road, 1 km from the Town of Nerviano, and 5 Km from the North-West Milan expressway.

The neighboring installations are:

- North — factory for the production of optical and electronic instruments for the aeronautical and space industry
- South — Pharmacia R & D Centre
- East — small carpenter's shop
- West — small lake

4.4 Locations of Use

The ultimate use and disposal of the finished product will be mainly at hospitals, clinic settings, and consumer dwellings. Finished products will be stored in distribution centers throughout the U.S. prior to transportation for sale at drugstores and pharmacies.

4.5 Disposal Sites

Disposal of drug product may result in the form of rejected, expired, or 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 site provides for the following recovery and/or ultimate disposal mechanism.

4.5.1 Rejected, Expired or Returned Drug Product

Rejected, expired, or returned drug product will be disposed in the on-site permitted incinerator at the P&U Kalamazoo, MI site. This incinerator is being operated as a Resource Conservation and Recovery Act (RCA) 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 RCA 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.

A hazardous waste RCA 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 P&U 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 MDEQ Air Quality Division air permit issued on July 15, 1980 (#242-80), revised to incorporate the Act 451, Part 111 requirements, was approved on May 26, 1993.

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.

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.

4.5.1.1. Hazardous Waste Landfill Sites. Ash generated as a result of the incineration process will be sent to a permitted hazardous waste landfill. At the present time, P&U uses the following facilities:

- operating license listed under Indiana Dept. of Environmental Management (IDEM) Permit No. IND 078911146;
- (treatment) operating license listed under EPA ID No. MID 000 724 831; (disposal) operating license listed under EPA ID No. MID 048 090 633;
- P&U may use other facilities for such disposal which are suitable for that purpose and are properly permitted.

P&U has contracts with each of these facilities that require the facility to be in compliance with all applicable laws and regulations. The waste stream profile support documentation established with the hazardous waste landfill sites affirm compliance status. All facilities are audited and approved for use by a P&U environmental auditor prior to the first shipment of waste from P&U to the site. In addition P&U personnel conduct periodic environmental audits of off-site disposal facilities during use of the facilities.

4.5.2 Discarded Product in Hospital or Clinical Setting

At U.S. hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy or clinic procedures. In homes, 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, although minimal quantities of unused drug may be disposed of in the sewer system.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THIS PROPOSED ACTION

Cabergoline Drug Substance

The material safety data sheet (MSDS) for the drug substance, cabergoline, is enclosed as non-confidential Attachment A3.

The ingredients used in formulating the drug product, DOSTINEX (cabergoline) Tablets, including Chemical Abstracts Service (CAS) No., molecular weight (M.W.), empirical formula, and a brief physical description, are included below:

Ingredient	CAS No.	M.W.	Formula	Physical Appearance
Cabergoline	81409-90-7	451.6	$C_{26}H_{37}N_5O_2$	White crystalline powder
Leucine, USP	61-90-5	131.17	$C_6H_{13}NO_2$	White powder
Lactose (anhydrous), NF	63-42-3	343.3	$C_{12}H_{22}O_{11}$	Fine white powder

A chemical summary and physical characteristics of cabergoline are included below:

International
Non-Proprietary Name: Cabergoline

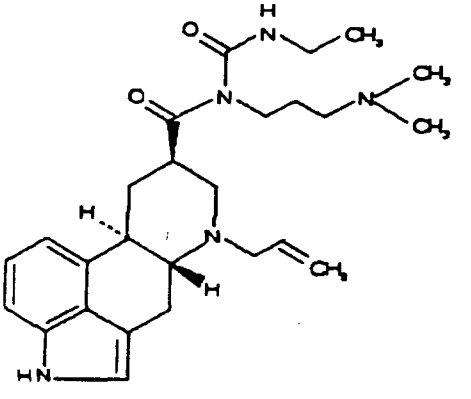
Chemical Name: 1-[(6aR,9R,10aR)-7-allyl-4,6,6a,7,8,9,10,10a-octahydroindole[4,3-fg]-quinoline-9-carbonyl]-1-(3-dimethyl-amino-propyl)-3-ethylurea.

Other Names:

1. 1-[(6-allylergolin-8β-yl)-carbonyl]-1-[3-(dimethylamino)propyl]-3-ethylurea
2. N-[3-(dimethylamino)propyl]-N-[(ethylamino)carbonyl]-6-(2-propenyl)-8β-ergoline-8-carboxamide

CAS Number: 81409-90-7

Chemical Structure:



Molecular Formula: $C_{26}H_{37}N_5O_2$

Molecular Weight: 451.6

Physical - Chemical Characteristics

Physical Description: White, crystalline powder

Density: 1.2 g/mL

Specific Rotation: $[\alpha]_D^{20}$ = -77.0° to -83.0°
(c = 1% in 95% ethanol)

Melting Range: 94°-112°C

Solubility: Semi-quantitative solubility data, expressed according to the solubility categories defined in the USP are as follows:

- Freely soluble in ethanol, chloroform and dimethylformamide
- Slightly soluble in aqueous 0.1 N HCl
- Very slightly soluble in n-hexane
- Insoluble in water

Quantitative solubility data determined in aqueous buffers at 25°C follow:

pH	Solubility (g/L)
5	8.1
7	4.6
9	2.9*

* Degradation noted at pH 9

Partition Coefficient: The partition coefficients of Cabergoline between n-octanol and buffers follow:

System	Partition Coefficient (K_{ow})
Octanol/pH 5 Buffer	0.77
Octanol/pH 7 Buffer	17.2
Octanol/pH 9 Buffer	- 1500.00

Dissociation Constant: The dissociation constants of cabergoline in water at 25°C follow:

pKa_1	6.5 (N-propenyl group)
pKa_2	8.8 (N-Dimethylaminopropyl group)

UV-VIS Spectra: The UV-VIS spectra of cabergoline in buffer solutions (pH 5.7 and 9) were determined. The spectra were also determined in cyclohexane and methanol. Copies of the spectra are shown in Attachment A1. Absorbance maxima are seen at approximately 220 and 280 nm.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Substances Expected to be Emitted

Lists of substances that may be emitted during the synthesis of the drug substance and the formulation of the drug product are provided in Confidential Attachment B1. The drug product ingredients list is also provided in Section 5.

6.2 Controls Exercised

In Italy, although there are a number of stringent laws and regulations controlling environmental protection, there exists no single, central governmental agency responsible for granting approval of compliance with these regulations. Instead, the function is delegated to local authorities who issue the various permits or to whom applications and data are submitted which may then be approved by "silent

consent" (ie, the company asks for a permit to the specific local authority; if this authority does not reply in writing to the company during the time period foreseen for obtaining the specific permit, the implication is that approval is automatically granted).

Certifications from responsible company officials that the drug substance synthesis plant and drug product manufacturing plant are in compliance with, or on an enforceable schedule to be in compliance with all national, regional, provincial and local environmental laws and regulations and all emission limits, permits and consent decrees are provided in non-confidential Attachment A2.

6.2.1 Chemical Process

For the plant at Rodano outside Milan, at which the cabergoline drug substance is produced, the Unità Socio Sanitaria Locale (USSL) [the local Department of Health] has responsibility for authorization of the start-up of new pharmaceutical production processes, for major modifications to existing plants, for new chemical syntheses, for environmental health concepts, and for water discharge (if, as is the case at Rodano, there is discharge into a stream). The USSL is the department which issues authorizations for all water discharges from the plant.

The Region of Lombardy applies the State laws for waste destruction, and the Region is empowered by the State to issue authorizations for the construction and functioning of treatment plants. Disposal of hazardous and industrial waste is, on the other hand, controlled by the Province of Milan to which notification must be made of both of the wastes sent for destruction by external contractors.

The Comitato Regionale contro L'Inquinamento Atmosferico Lombardia (CRIAL) [Regional Committee Controlling Atmospheric Pollution] is empowered by the Region of Lombardy to control atmospheric emissions and the scrubbers used for reducing emissions. In 1988, a national law (Presidential Decree 203) was promulgated which placed controls on existing scrubbers. Existing scrubbers are to be upgraded to comply with limits imposed by Decree 203, at which time CRIAL must be notified. New scrubbers must be authorized before installation. The project submitted for upgrading is considered authorized by "silent consent".

6.2.2. Pharmaceutical Formulation

For the Pharmaceutical Development Department and the QC Laboratories at Nerviano where the tablets (finished dosage form) are manufactured and tested for release, the Unità Socio Sanitaria Locale (USSL) [the local Department of Health] has

the responsibility for the authorization of pharmaceutical processes, for environmental health concepts, and for water discharge. The USSL is the department which issues authorizations for all water discharge from the plant.

The Lombardy Region applies the State laws for waste destruction so the region is empowered by the State to issue authorizations for the construction and functioning of treatment plants. Disposal of hazardous and industrial waste is controlled by the Province of Milan to which notification must be made of the wastes sent for destruction by outside contractors.

On the other hand, Settore Ambiente ed Ecologia [Environment and Ecology Section] for the Lombardy Region is empowered to control atmospheric emissions used to prevent pollution. According to a national law (Presidential Decree 203) promulgated in 1988, the Company sent to the competent authorities a technical report including, among other things, data and technology adopted for atmospheric pollution prevention. The petition submitted is considered authorized by "silent consent".

A full description of the permit and silent approval system for compliance with the laws and regulations controlling environmental protection at the sites in Italy is given in Confidential Attachments C1, C2 and C3.

6.2.3. Rejected, Expired or Returned Drug Product

Section 4.5.1. includes a discussion of any rejected, expired or returned drug product that would be disposed through the P&U Kalamazoo, MI site.

6.3 Citation of and Statement of Compliance with Applicable Emission Requirements

6.3.1. Production Sites - Italy

Applicable regulations at the chemical processing and pharmaceutical manufacturing sites are discussed in Section 6.2, above.

6.3.2. Disposal Site - Kalamazoo, MI

The following regulations or standards are cited as applicable to the proposed action:

1. Federal Food, Drug and Cosmetic Act, PL 75-717, as amended, including subsections 306(a) and (b) [debarment].
2. Clean Air Act PL 91-604, as amended.
3. Clean Water Act PL 95-217, as amended.
4. Safe Drinking Water Act PL 93-523.
5. Resources Conservation and Recovery Act of 1976 PL 94-580, as amended.
6. Occupational Safety and Health Act of 1970, as amended.
7. Hazardous Materials Transportation Act of 1975, as amended.
8. Standards from the American National Standards Institute.
9. National Fire Protection Agency Standards.
   a. National Electrical Code Standards
   b. Life Safety Requirements
10. Act # 451 of 1994, Michigan Natural Resources and Environmental Protection Act, as amended including:
    - Part 31, Water Resources Protection
    - Part 55, Air Pollution Control
    - Part 111, Hazardous Waste Management
    - Part 115, Solid Waste Management
    - Part 121, Liquid Industrial Waste
    - Part 625, Mineral Wells
11. Act #399 of 1976, Michigan Safe Drinking Water Act, as amended.
12. Act #368 of 1978, Public Health Code.
13. Chapter 28 of the Kalamazoo City Code (Services and Wastewater) as amended by ordinance No. 1190.
14. Michigan Occupational Safety and Health Act of 1970, as amended. (Local regulation applicable to the State of Michigan.)

6.3.2.1. *Emission Requirements.* P&U 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 or administrative orders applicable to the disposal of cabergoline at its facilities in Kalamazoo, Michigan, as well as emission requirements set forth in applicable Federal, State, and local statutes and regulations applicable to the disposal of cabergoline at its facilities in Kalamazoo, Michigan.

6.3.2.2. *OSHA Requirements.* P&U certifies that it has comprehensive programs and practices in place addressing all applicable OSHA requirements.

6.4. Discussion of the Effect of Approval on Compliance with Current Emissions

The approval of the cabergoline NDA will have no effect on the ability of Pharmacia S.p.A. to meet its current emission requirements.

6.5 Maximum Expected Environmental Concentrations (MEEC)

A conservative (maximum) estimate of the amount of the annual production of cabergoline drug substance if 50% of all patients in the U.S. with hyperprolactinemia received treatment and 70% of these were treated with cabergoline is provided in Attachment B2. Using the larger estimate as the anticipated amount of cabergoline to be produced, and assuming an even distribution throughout the U.S. per day, and no metabolism of depletion mechanisms, the maximum Expected Introduction Concentration (EIC) can be calculated using the following equation given in the FDA 1995 Guidance for Industry for the Submission of Environmental Assessments as less than 1 part per billion (ppb) (see Confidential Attachment B2).

$$\text{EIC-Aquatic (ppm)} = A \times B \times C \times D$$

where:

A = kg/year production
B = $1/1.115 \times 10^{11}$ liters per day entering POTW's
C = year/365 days
D = 10^6 mg/kg (conversion factor)

The Center for Drug Evaluation and Research (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 EA format items 7, 8, 9, 10, and 11 will normally not be needed whose expected introduction concentration (EIC) is less than 1 ppb. Since the calculated EIC for cabergoline is less than 1 ppb, the format items mentioned above have not been included.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section 14.) wherein cabergoline meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section 14.) wherein cabergoline meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

9. USE OF RESOURCES AND ENERGY

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section14.) wherein cabergoline meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

10. MITIGATION MEASURES

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section 14.) wherein cabergoline meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

11. ALTERNATIVES TO THE PROPOSED ACTION

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section 14.) wherein cabergoline meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

12. LIST OF PREPARERS

The following persons prepared this environmental assessment.

Martin Williamson	Assistant Director, Regulatory Submissions Regulatory Affairs for the former Pharmacia, Inc. Ph.D. in Chemistry Professional experience: 28 years
Donald E. Hagman	Vice-President, Development/Quality Assurance Ph.D. in Industrial Pharmacy for the former Pharmacia, Inc. Professional experience: 24 years
Angelo Ferrari	Head of Prevention and Protection Service Pharmacia S.p.A. Technical High School Certificate Professional experience: 25 years

Franco Montoli	Industrial Safety, Environmental Protection and Ecology Manager Pharmacia S.p.A. Technical High School Certificate Professional experience: 30 years
Enzo Murador	Bulk Process Development Director Pharmacia S.p.A. Industrial Chemistry University Degree Professional experience: 28 years
Jeffrey S. Mehring	Manager, Science & Information Environment & Safety Pharmacia & Upjohn Company Ph.D., Agriculture Professional experience: 25 years
Susan I. Shedore	Environment & Safety Environmental Technician Pharmacia & Upjohn Company A.A. Corporate experience: 25 years

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 and non-confidential Appendices contain non-confidential information and acknowledge that this information will be made available to the public in accordance with 40 CFR § 1506.6.

Randal S. Senger, Associate Director
Environment and Safety
(telephone 616/833-5341)

Sept. 18, 1996
Date

Jeffrey S. Mehring, Manager
Science and Information
Environment and Safety
(telephone 616/833-4746)

18 SEPT 96
Date

14. REFERENCES

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.

15. APPENDICES

Non-Confidential Attachments

Attachment A1:	UV Spectra of Cabergoline
Attachment A2:	Certification of Compliance for Foreign Manufacturing Sites
Attachment A3:	MSDS for Cabergoline Drug Substance

Confidential Attachments

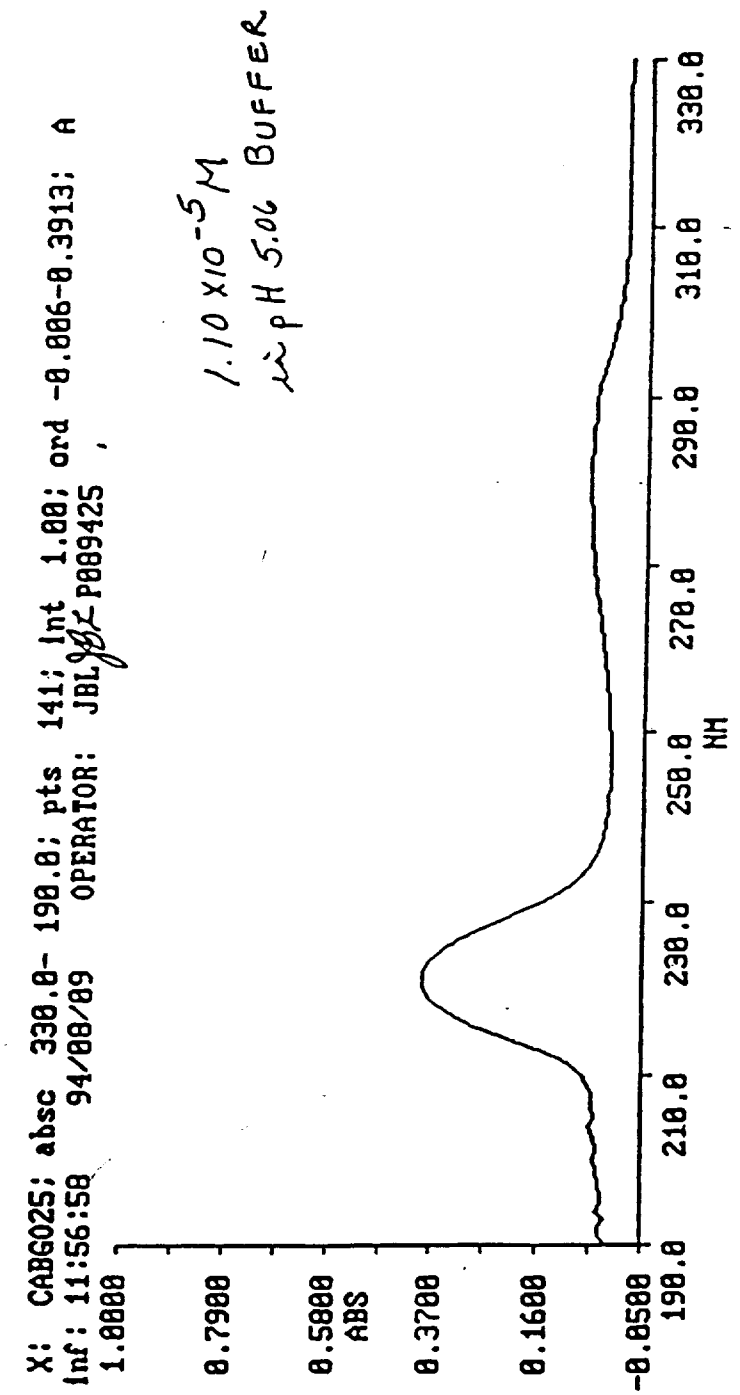
Attachment B1:	List of Substances used in the Manufacture of Cabergoline Drug Substance
Attachment B2:	Estimate of Cabergoline Production
Attachment C1:	Confidential Supportive Information for the Environmental Assessment for Rodano Plant
Attachment C2:	Confidential Supportive Information for the Environmental Assessment for Nerviano Pharmaceutical Development Facilities
Attachment C3:	Confidential Supportive Information for the Environmental Assessment for Nerviano Plant

NON-CONFIDENTIAL ATTACHMENTS

Attachment A1
Page No: 1

Figure 1

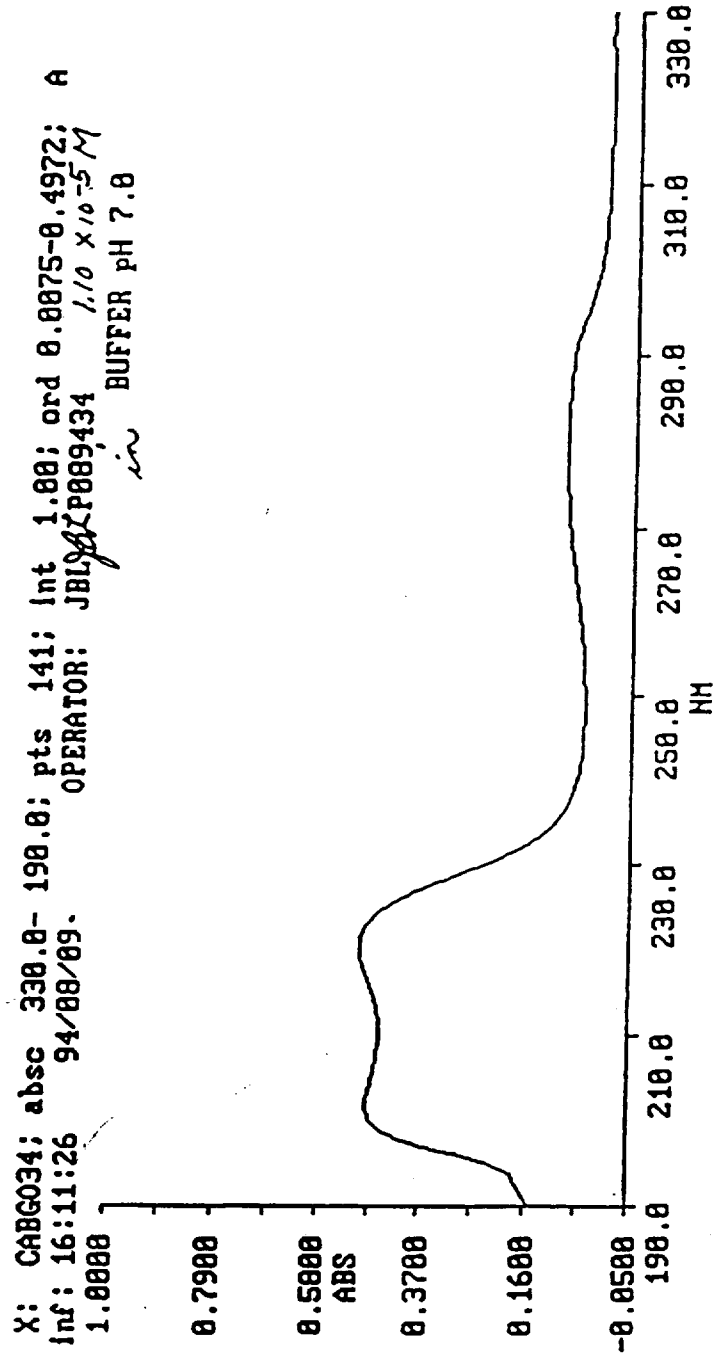
UV - VIS spectrum of Cabergoline in pH 5 buffer



Attachment A1
Page No: 2

Figure 2

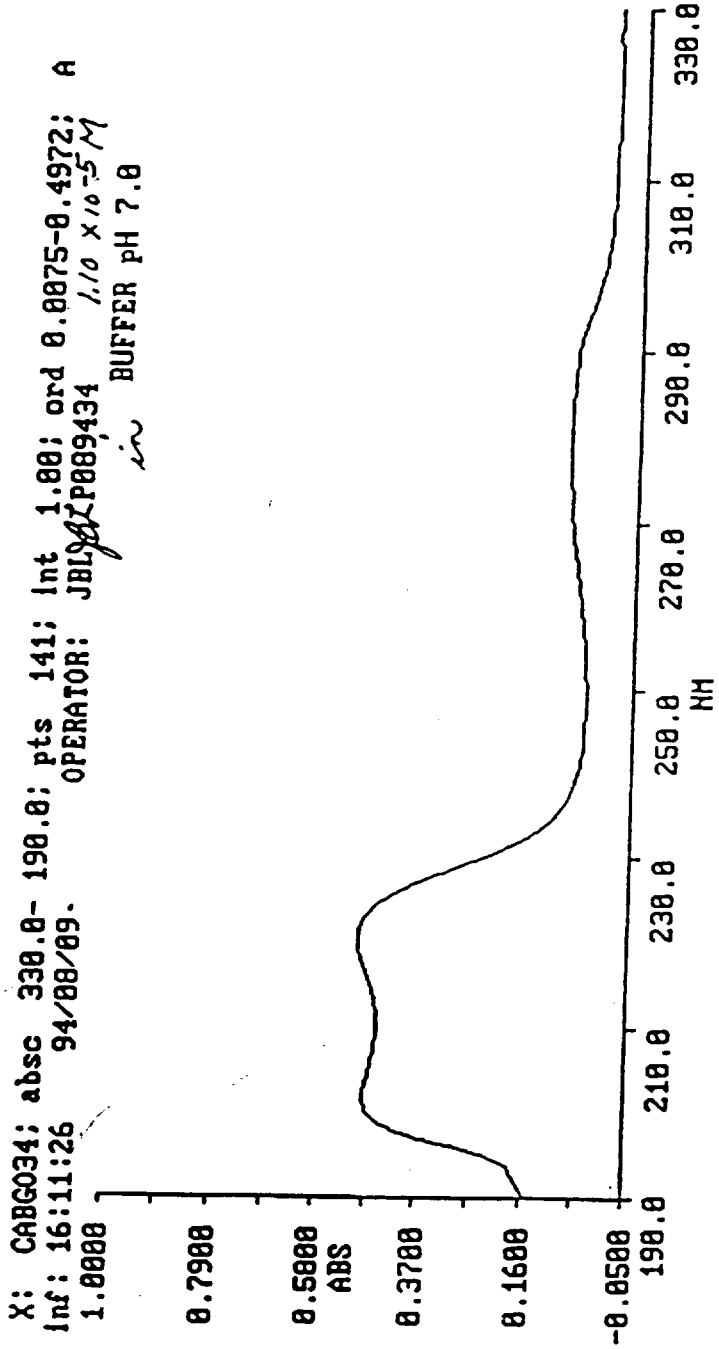
UV - VIS spectrum of Cabergoline in pH 7 buffer



Attachment A1
Page No: 2

Figure 2

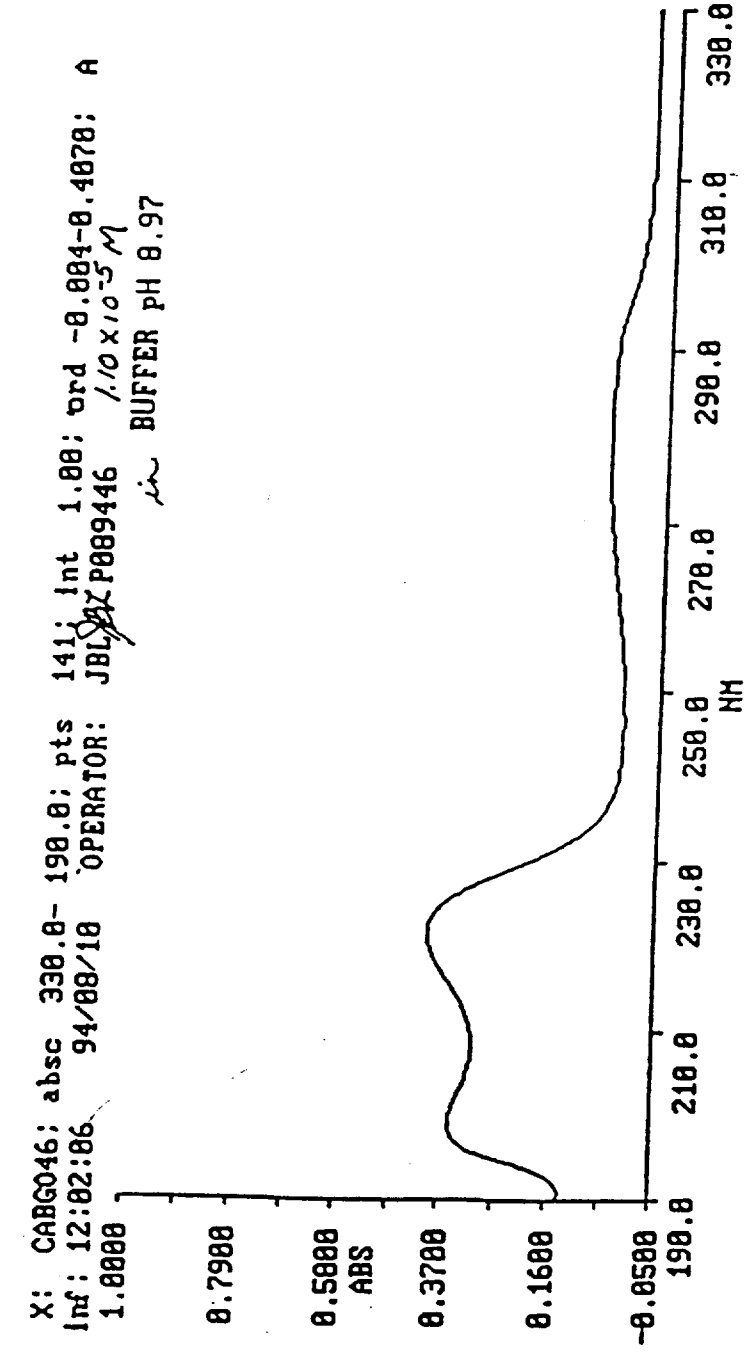
UV - VIS spectrum of Cabergoline in pH 7 buffer



Attachment A1
Page No: 3

Figure 3

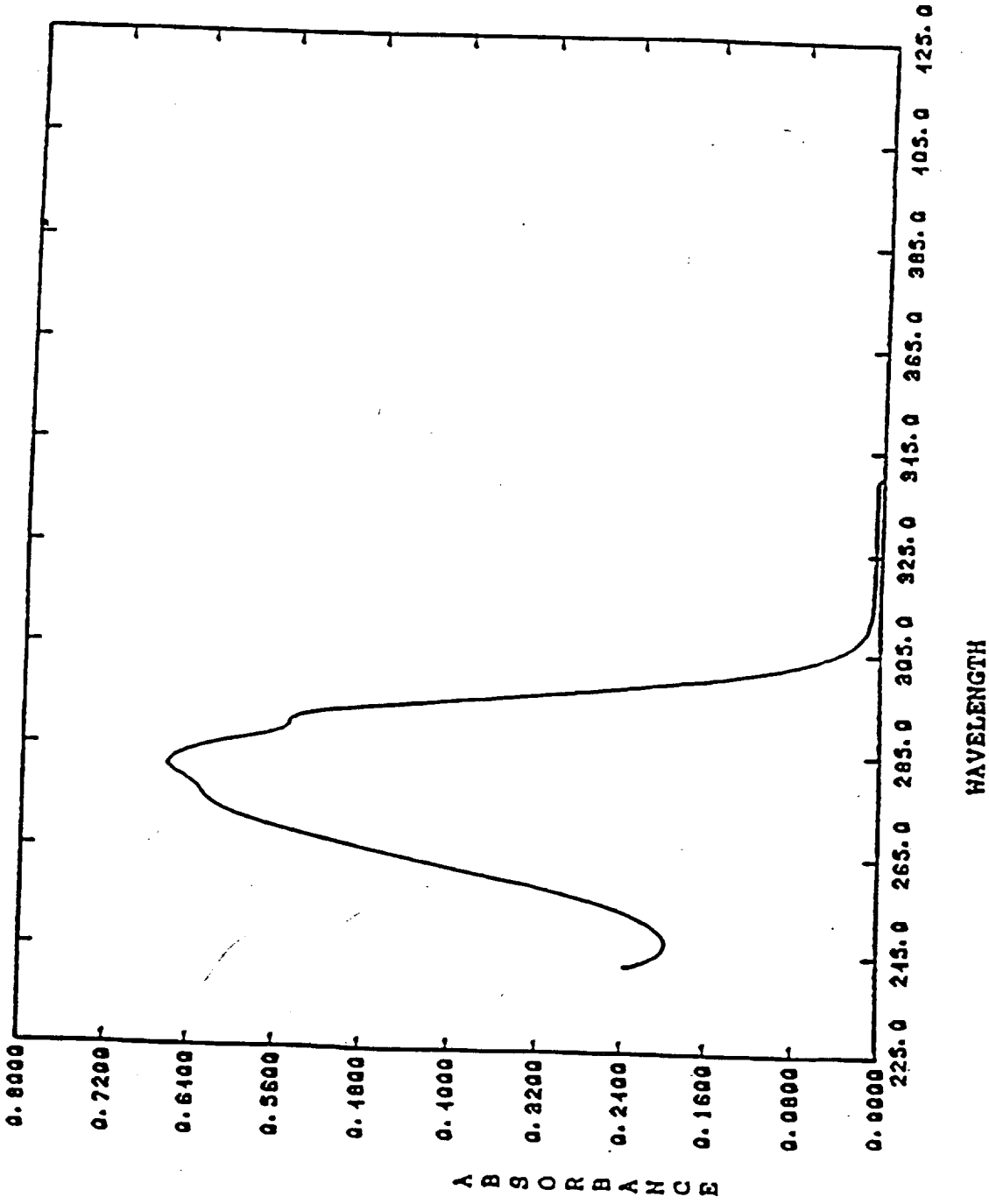
UV - VIS spectrum of Cabergoline in pH 9 buffer



Attachment A1
Page No: 4

Figure 4

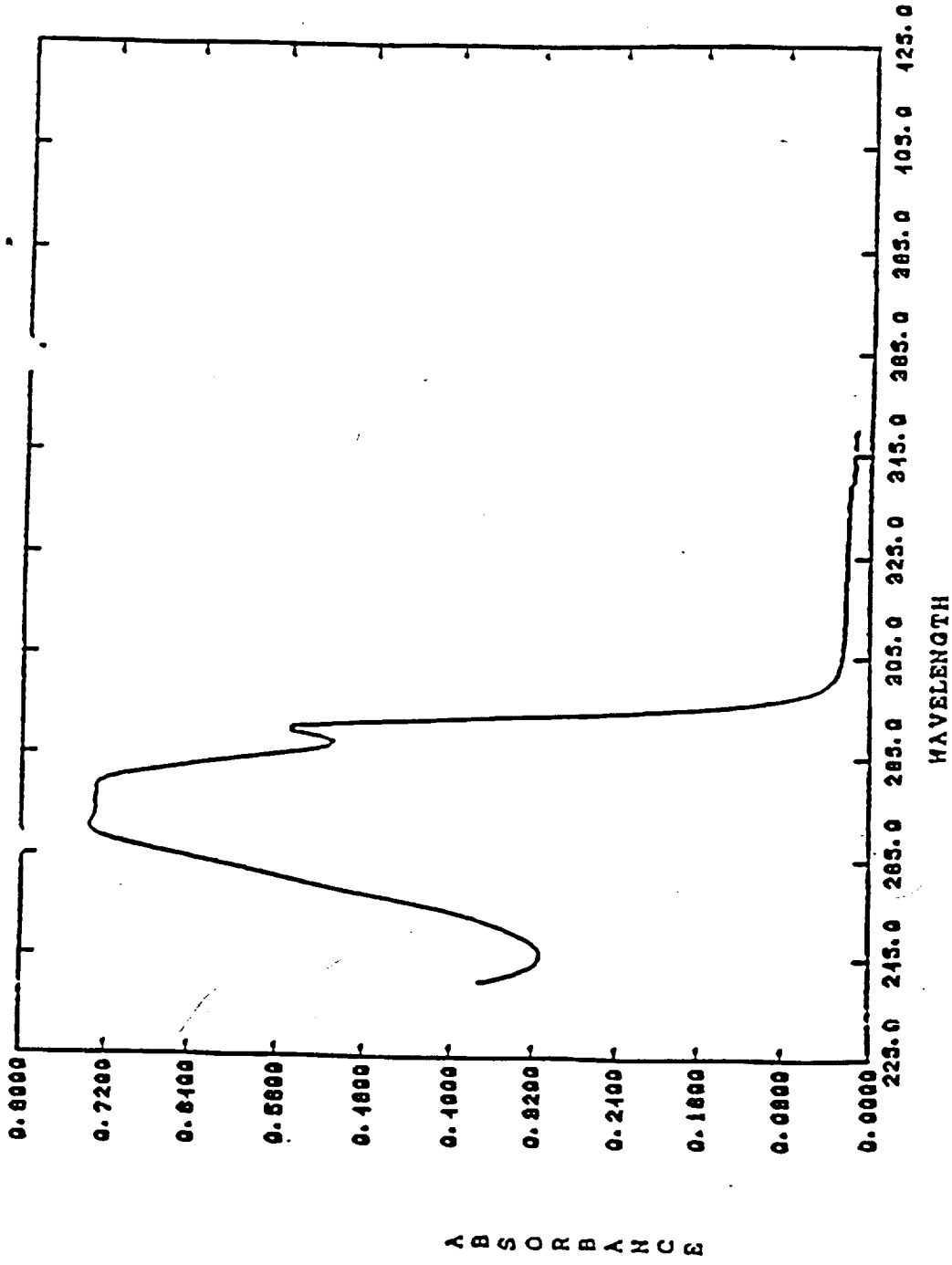
UV - VIS spectrum of Cabergoline in methanol



Attachment A1
Page No: 5

Figure 5

UV - VIS spectrum of Cabergoline in cylohexane



Pharmacia

Attachment A2
Page No: 1

Data December 11th

Vs. Rif.

Ns. Rif.

Tel. Diretto

Pharmacia S.p.A. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all national, regional, provincial and local environmental laws and regulations, and all emission limits, permits, and consent decrees applicable to the synthesis of cabergoline drug substance at its facilities in Rodano, near Milan, Italy.

Dr. Ambrogio Rossetti
Head of Quality Assurance
Bulk Products

Pharmacia Spa
Via Robert Koch, 1.2
20152 Milano
Italia

Telef. (02) 4838.1
Telefax (02) 4838.2734
Telex 326268 Pharm - I
C. Post. 14380 - C.C. Post. 29891207

Sede Legale Milano
Cap. Soc. L. 463.691.602.000 I.V.
Trib. Milano R.S. N. 332132
Vol. 8219 - Fasc. 32

C.C.I.A.A. N. 1135613
Cod. Fiscale N. 07089990159
Partita IVA N. 10887780152

Pharmacia

Attachment A2
Page No: 2

Data November 29th, 1995

Vs. Rif.

Ns. Rif.

Tel. Diretto

Pharmacia S.P.A. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all national, regional, provincial and local environmental laws and regulations, and all emission limits, permits, and consent decrees applicable to the manufacture of cabergoline 0.5 mg tablets at its facilities in Nerviano, near Milan, Italy.

(Angelo Ferrari)
Head of Prevention and
Protection Services

Pharmacia Spa
Via Robert Koch, 1.2
20152 Milano
Italia

Telef. (02) 4838.1
Telefax (02) 4838.2734
Telex 326268 Pharit - I
C. Post. 14380 - C.C. Post. 29891207

Sede Legale Milano
Cap. Soc. L. 463.691.602.000 I.V.
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C.C.I.A.A. N. 1135613
Cod. Fiscale N. 07089990159
Partita IVA N. 10887780152

Material Safety Data Sheet
Cabergoline

Page 1

SAFETY DATA SHEET No.: 190 DATE: 12-01-95

C A B E R G O L I N E

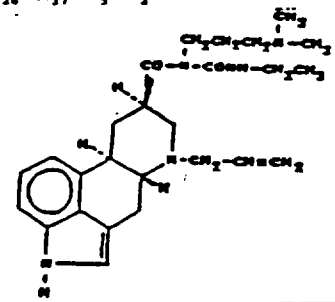
IDENTIFICATION

Chemical name: 1-Ethyl-3-(3'-dimethylaminopropyl)3-(6'-allyl-ergoline-8'-beta-carbonyl)-urea

Synonyms: FCE 21336; Galastop; Dostinex

Company code: 604416000 CAS number: 81409-90-7

Empiric formula: C_{26} H_{37} N_5 O_2 ONU number:

Structural formula:  Molecular weight: 451.6

CHEMICAL-PHYSICAL PROPERTIES

Physical state: Crystalline powder Odor: Odourless

Color: White

Solubility: Insoluble in water; soluble in diluted mineral acids; soluble in acetone, ethyl acetate, ether

Density (water=1): Weight density of vapours(air=1):

Vapour pressure:

Melting point: 100-105°C Spontaneous ignition temperature:

Boiling point:

Flash point:

Reactivity:
May give off toxic fumes of NOx when heated to decomposition temperature.

Keep away from highly oxidizing substances.

Attachment A3
Page No: 2

EXPLOSURE LIMITS

LEL:	% in volume	ppm	mg/cu.m
UEL:	% in volume	ppm	mg/cu.m

EXPOSURE LIMITS

TLV/TWA: n.i. mg/cu.m n.i. ppm TLV/STEL: n.i. mg/cu.m ppm
ACGIH note: Ed. 1993-94

CLASSIFICATION - LABELLING

Type of labelling: Provisional labelling Remarks:

Classification: Xn Harmful

Risk phrases:
R20/21/22 Harmful by inhalation, in contact with skin and if swallowed.

Precautionary advice:
S7 Keep container tightly closed

S22 Do not breathe dust.

S24/25 Avoid contact with eyes and skin.

S36/37 Wear suitable protective clothing and gloves.

TRANSPORTATION

Road/railway -RID/ADR Class: Non hazardous Marginal:

Carriage by sea; IMDG code: Non hazardous RINA Class:

Air transportation - IATA Class: Non hazardous Packing group:

Page 3 CABERGOLINE 12-01-95

TOXICOLOGICAL INFORMATION

Route of entry: Ingestion X Inhalation X Contact X

Acute toxicity:

oral LD50	- rat	M	420 mg/kg	F	383 mg/kg
oral LD50	- mouse	M	362 mg/kg	F	202 mg/kg
intravenous LD50	- rat	M	22 mg/kg	F	22 mg/kg
intravenous LD50	- mouse	M	21 mg/kg	F	24 mg/kg

Chronic toxicity:
Medium and long-term studies conducted on rats and monkeys treated orally with doses of up to 5000 mcg/kg revealed effects, especially on the endocrine and central nervous system, which however must be considered as a response proportional to the high dose and prolonged duration of the treatment.

Corrosive/Irritating power/Skin:
No information is available. Slight irritating power may be hypothesized.

Corrosive/Irritating power/Eyes:
No information is available. Slight irritating power may be hypothesized.

Sensitizing power:
Studies conducted on guinea-pigs did not reveal any sensitizing powers of the substance.

Mutagenesis:
Several in vivo and in vitro studies carried out on different microorganisms and cell lines revealed that the substance was not mutagenic.

Carcinogenesis:
In two studies conducted on rats and mice treated orally respectively for 24 months at doses up to 320 mcg/kg/day and for at least 21 months at doses up to 980 mcg/kg/day, significant evidence of carcinogenicity has not been observed, except for the suppression of prolactine secretion due to the specific pharmacological activity of the product.

Teratogenesis:
In studies conducted on rats, mice and rabbits treated orally during the period of organogenesis, skeletal anomalies but no teratogenic effects were observed only in the rats and at high doses. Peri- and post-natal fertility and toxicity studies on rats revealed a specific anti-prolactine effect. It is advisable for pregnant or lactating women to avoid exposure to the substance.

HEALTH CONTROL REGULATIONS

Preventive and periodic medical check-ups:
//

Compulsory insurance:
//

FIRST AID

In the event of contact with the eyes:
Rinse immediately with plenty of water or saline solution for at least 10-15 minutes. In case disturbance still persists, consult an ophthalmologist.

In the event of contact with the skin:
Wash immediately with plenty of water.
Remove any contaminated clothing.

If swallowed:
Consult a doctor.

If inhaled:
Consult a doctor.

MEASURES TO BE TAKEN IN THE EVENT OF ACCIDENTS

In the event of spillage:
Collect the spilled product in suitable containers, for possible re-use or dispatch to the disposal unit according to the regulations. After having removed the product, wash the area of the spill thoroughly with water.
Begin the operations only after wearing suitable individual protective clothing.

In case of fire:
Use chemical powder

Use carbon anhydride

Use nebulized water.

STORAGE CRITERIA

Store in tightly closed containers.

HANDLING CRITERIA

Whenever no collective protective equipment is available, operate in installations provided with efficient dust-collection systems.

Use anti-dust mask.

Use safety gloves.

Use safety goggles.

REFERENCES

Farmitalia Carlo Erba: Basic Information

REMARKS

ECL (air) 0.002 mg/cu.m..

NDA 20,664
Dostinex™ (cabergoline) 0.5 mg Tablets
Pharmacia & Upjohn

This section not applicable at this time.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020664

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

NDA 20-664
Dostinex (cabergoline) 0.5 mg Tablets
Pharmacia and Upjohn Company

Date:
11/25/96

CONTACT:
Dr. Lisa Rarick
HFD-580

MEMORANDUM OF CONVERSATION

I spoke with Dr. Lisa Rarick, concerning the draft labeling submitted by Pharmacia and Upjohn on November 20, 1996. She stated that Linda Golden will be the reviewer for this NDA when it is transferred to HFD-580. Dr. Rarick further stated that if changes in the labeling are deemed necessary by HFD-580 they will be forwarded in a timely manner to HFD-510; if no changes are needed no further communication will be initiated.

Randy Hedin, CSO

cc:NDA Arch
HFD-580/LRarick
HFD-510
HFD-510/JGuiriguian/AFleming/SSobel/EGalliers
HFD-511/RHedin/11.26.96/N20664.ph1

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 2, 1996

FROM: Robert H. Seevers, Reviewing Chemist, HFD-580
Through Helen W. Davies, Acting Supervisory Chemist H Davies 7/3/96
Division of Reproductive and Urologic Drug Products, CDER

SUBJECT: Laboratory Assignment(s) for NDA Methods Validation (MV) and NDA Sample Collection for MV

TO: John Marzilli, District Director
Cincinnati District Office (HFR-MA400)

NDA No.: 20-664 Product: Dostinex® (Cabergoline) tablets

Applicant: Pharmacia Inc.
7001 Post Rd.
Dublin, OH 43107

Mailing Address: Pharmacia Inc.
P.O. Box 16529
Columbus, OH 43216

Enclosed you will find an MV package with MV request forms (FD 2871 & 2871a) attached.

As a part of the NDA review, one or more FDA laboratories are required to validate the analytical methods submitted by the applicant. To help accomplish this, you are requested to assign one laboratory. Please insert the laboratory identity on the appropriate line of Form FD 2871, and send with a copy of Form 2871a and a copy of the MV package to the laboratory. An MV Package and Forms 2871 and 2871a have been sent directly to the Division of Drug Analysis.

When you have assigned the laboratory, please advise the undersigned reviewing chemist of the identity of the field laboratory that will perform the validation.

In addition, you are requested to assign an investigator/analyst team to collect from the applicant the needed items, consisting of the following:

1. Two identical sets of samples, consisting of the following:

   a) 20 g of cabergoline drug substance; two bottles of 10 g
   b) Dostinex® (cabergoline) 0.5 mg tablets, a total of 480 tablets in 60 bottles
   c) Cabergoline working standard, a total of 2.0 g
   d) Cabergoline acid (Impurity I), a total of 200 mg

2. Two copies of the analytical reports representing the applicant's analyses of the drug product lot providing the above samples, using the proposed NDA methods.

When the samples and analytical reports have been collected, please forward them to the field laboratory and the Division of Drug Analysis, HFH-300, Drug Monitoring Branch, 1114 Market Street, St. Louis, MO 63101. District Laboratories are expected to submit a monthly summary of the status of all MV samples in their laboratories. Copies of this log will be sent to the Offices of Drug Evaluation (ODE's I through V).

All investigational and analytical work conducted under this assignment should be charged to PAC 46832.

Robert H. Seevers, Ph.D.
Reviewing Chemist, HFD-580

Enclosures: MV package and the MV request forms (FD 2871 & 2871a)

cc: Original NDA 20-664
HFD-580/Division File
Division of Drug Analysis, HFH-300
Compliance Evaluation Staff, HFD-320
Division of Field Sciences, HFC-140

NDA 20-664

MAR 28 1996

Pharmacia Inc.
Attention: Mr. Dean Waters
P.0. Box 16529
Columbus, OH 43216

Dear Mr Waters:

Please refer to your pending December 26, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dostinex (cabergoline) 0.5 mg Tablets.

To complete our review of the environmental assessment section of your submission, we have this advice and request the following information:

> We have determined that the information for the environmental assessment format items 7, 8 ,9 ,10, 11, and 15 will not normally be necessary for environmental assessment's submitted pursuant to 25.31a (a) under certain circumstances. These circumstances are identified as Tier 0 (section III.D.7.c) in the Center for Drug Evaluation and Research's (CDER) "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements" which was issued in November of 1995. During the filing review it was determined that your environmental assessment may qualify for Tier 0.
>
> If you determine that your environmental assessment does qualify for Tier 0, format items 7, 8, 9, 10 ,11, and 15 may be withdrawn. You should submit an amendment, preferably within 30 days, requesting that the information provided in those format items be deleted. Because CDER is required to make the environmental assessment (EA), and the finding of no significant impact (FONSI) publicly available you should provide, along with the letter, a revised environmental assessment with the information in those format items deleted. If you choose not to withdraw the information, all information will be reviewed and deficiencies, if any, will be communicated to you in accordance with standard procedures. For additional information regarding withdrawing this information please refer to Notice of Availability, published January 11, 1996, FR Doc. 96-420.

We would appreciate your prompt written response as we continue our evaluation of your NDA.

If you have any questions, please contact:

Randy Hedin, R.Ph.
Consumer Safety Officer
(301) 443-3520

Sincerely yours,

3/23/96

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

RH 3/14/96

cc:
Original NDA 20-664
HFD-643/NSager
HFD-510/Div. Files
HFD-510/CSO/R.Hedin
HFD-510/RSeevers/HDavies
DISTRICT OFFICE

Concurrences: RSeevers, HDavies 03-15, EGalliers 03-18-96\ft/nm 03.26.96

drafted: RH/March 14, 1996/N20664IR.LT1
r/d Initials:
final:

INFORMATION REQUEST (IR)

NDA 20-664

JAN 18 1996

Pharmacia Inc.
Attention: Mr. Dean M. Waters
Manager, Regulatory Affairs
7001 Post Road
DUBLIN OH 43107

Dear Mr. Waters:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Dostinex (cabergoline) Tablet, 0.5 mg
Therapeutic Classification:	Standard
Date of Application:	December 26, 1995
Date of Receipt:	December 27, 1995
Our Reference Number:	20-664

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 25, 1996, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Mr. Randy Hedin at (301) 443-3520.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

EMGalliers 1/18/96

Ms. Enid Galliers
Supervisory Consumer Safety Officer
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

RH 1/16/96

cc:
Original NDA 20-664
HFD-510/Div. Files
HFD-80
HFD-510/CSO/R.Hedin
Concurrence: EGalliers 1.2.96/ft/nm/ 1.11.96

drafted: RH/January 2, 1996/N20664AC.LT1
Final:

ACKNOWLEDGEMENT (AC)

OCT 18 1996

Meeting Date: June 11, 1996 Time: 8:00 - 8:30 pm Location: 14-56

NDA 20-664 Dostinex (cabergoline) Tablets

Type of Meeting: Status Meeting

External participant: None

Meeting Chair: Dr. Troendle

External participant lead: None

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Solomon Sobel, Division Director, DMEDP
Dr. Gloria Troendle, Deputy Division Director, DMEDP
Mr. Dave Hertig, Pharmacology Reviewer, DMEDP
Dr. Robert Severs, Chemistry Reviewer, Division of New Drug Chemistry II
Dr. Gubbi, Reviewer, Division of Biostatistics
Mr. Dan Marticello, Team Leader, Division of Biostatistics
Dr. Hae-Young Ahn Team Leader, Division of Pharmaceutical Evaluation II
Mr. Randy Hedin, CSO, DMEDP

External participant Attendees and titles:

None

Meeting Objectives:

This meeting was an internal meeting to discuss the status of the reviews, and any problems encountered to date.

Discussion Points:

- Pharmacology: The review is finished and with supervisor. Labeling issues need to be resolved with firm.
- Biostatistics: The draft review will be finished by the end of the month and submitted supervisory concurrence.
- Biopharm: The review will be finished by the end of next week. A new reviewer, Dr. Ene Ette, is assigned to the application.

- Chemistry: The review is finished and with supervisor. An IR letter will need to be sent to the sponsor. Also, the nomenclature committee approved the trade name Dostinex. Labeling issues remain. The EER inspection has taken place and the report should be forthcoming.

- Clinical: The review is finished. Labeling issues remain to be resolved. (The reviewer was not at the meeting)

Decisions (agreements) reached:

- An internal labeling meeting will tentatively be scheduled for mid July.

Unresolved or issues requiring further discussion:

- None

Action Items:

- None

Signature, minutes preparer: _____

Concurrence Chair: _____

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers
HFD-511/RHedin/6.11.96/N20664.MN2

Concurrences: DHertig/AGubbi/DMarticello 6.12/RSevers/GTroendle/HAhn 6.13/ SSobel 6.17

ORIGINAL

NDA 20-664
Dostinex (cabergoline) Tablets

February 13, 1996
Pharmacia

Memorandum of Internal Meeting

FDA Staff:

Dr. Sobel
Dr. Troendle
Dr. Gueriguian
Dr. Fleming
Dr. Jordan
Dr. Hertig
Dr. Davies
Dr. Seevers
Dr. Jones HFD-427
Mr. Marticello HFD-713
Mr. Hedin, CSO

Purpose:

To discuss filing and planning the review of Dostinex (cabergoline) Tablets for a hyperprolactinemic disorders indication, either idiopathic or due to pituitary adenomas.

Discussion:

Medical:	Acceptable to file
Chemistry:	Acceptable to file
Pharmacology:	Acceptable to file
Biopharmaceutics:	Acceptable to file
Biostatistics:	Acceptable to file

It was stated that Mr. Hedin would contact Dr. Gus Turner concerning the studies that need to be audited by the Division of Scientific Investigations.

October 18, 1996 was agreed upon as the goal date for completing the reviews. Kathleen Reedy will be contacted concerning tentative dates for an Advisory Committee meeting.

Conclusion: File the application.

Randy Hedin, CSO

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers/SSobel
HFD-511/RHedin/02.13.96/N20664.MN1
Concurrences: JGueriguian 02-20/AFleming 02-22/GTroendle 02-23/DHertig, AJordan, RSeevers, MMcNerney for HDavies 02-26/EGalliers 02-27\ft/nm 05.06.96

12/10/96

Pharmacia & Upjohn

Office of:

Susan M. Mondabaugh, Ph.D.
Director, Regulatory Affairs

Telephone: 616/833-4070
Fax: 616/833-8237

December 10, 1996

Solomon Sobel, M.D., Director
Food and Drug Administration
Division of Metabolism & Endocrine Drug Products, HFD-510
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-664
DOSTINEX® (cabergoline)

NDA Amendment
Non-Insert Labeling

Dear Dr. Sobel,

Enclosed for review are final drafts of non-insert labeling for the above referenced NDA which incorporates the new company tradedress. For ease of review, the following attachments are included:

Attachment 1	Bottle Label	Actual size and 200%
Attachment 2	Carton Label	Actual size
Attachment 3	Sample Bottle Label	Actual size and 200%
Attachment 4	Sample Carton Label	Actual size

The sample labeling has not previously been submitted to the Division.

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

If you have any questions regarding the contents of this submission, please contact me at (616) 833-4070. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Susan M Mondabaugh

Susan M. Mondabaugh, Ph.D.
Director, Regulatory Affairs

SMM:law:Attachments

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: 12/31/95
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT
Pharmacia & Upjohn Company

DATE OF SUBMISSION
December 10, 1996

ADDRESS *(Number, Street, City, State and Zip Code)*
7000 Portage Road
Kalamazoo, Michigan 49001

TELEPHONE NO. *(Include Area Code)*
(616) 833-4070

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (if previously issued)
20-664

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
cabergoline

PROPRIETARY NAME *(if any)*
Dostinex™

CODE NAME *(if any)*
FCE 21336

CHEMICAL NAME
N-[3-(Dimethylamino)propyl]N-[(ethylamino)carbonyl]-6-(2-propenyl)-8β-ergoline-8-carboxamide

DOSAGE FORM
Tablet

ROUTE OF ADMINISTRATION
Oral

STRENGTH(S)
0.5mg

PROPOSED INDICATIONS FOR USE

Treatment of hyperprolactinemic disorders, either idiopathic or due to pituatary adenomas.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

DMF IND
DMF IND
DMF IND
DMF

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))*_____

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

Pharmacia & Upjohn

Office of:

Susan M. Mondabaugh, Ph.D.
Director, Regulatory Affairs

Telephone: 616/833-4070
Fax: 616/833-8237

November 20, 1996

Solomon Sobel, MD, Director
Food and Drug Administration
Division of Metabolism and Endocrine
Drug Products, HFD-510
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-664
DOSTINEX® (cabergoline)

NDA Amendment
Biopharmaceutics Response

Dear Dr. Sobel,

In response to the facsimiles dated August 2, 1996 (received September 20, 1996) and September 25, 1996 from the Division containing biopharmaceutics comments, we are submitting the following responses to Point 3. GENERAL COMMENTS. To aid you in your review of our responses, the August 2,1996 comments will be reiterated in bold and our response will be provided in italics.

1. **The Sponsor should develop a more specific RIA method for quantifying CAB plasma levels. Alternatively, the sensitivity of the more specific HPLC assay should be significantly improved upon.**

   Pharmacia & Upjohn accepts the comment that the specificity of the cabergoline RIA assay reported in DOSTINEX NDA 20-664 is not optimum. We also accept the recommended changes in the labeling to eliminate statements that would require a more specific assay.

2. **The nonspecificity of the RIA assay casts serious doubts on the reliability of CAB levels measured, and renders the results of the PK studies inconclusive. Thus, most of the plasma data which for most of the times were near the limit of detection are to be interpreted with caution. A highly sensitive and specific assay is necessary for the proper characterization of the pharmacokinetics of the drug and of course pharmacokinetic/pharmacodynamis relationships.**

   The revised statements on cabergoline pharmacokinetics in the DOSTINEX labeling are based on plasma concentration data that were not suspect as a result of low values relative to the RIA assay limit of quantitation.

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

3. **It is wrong to use historical data (in this case results from a food effect study) as control for comparison with data obtained in the renal impairment study. The cohort of subjects are different.**

When the historical control data are not considered in the interpretation of the pharmacokinetic data from the moderate and severe renal impairment patients in study CBAPHKI022, the conclusions are the same. There were no differences in the pharmacokinetics between these two groups of renal impairment patients as would be expected when less than 4% of the cabergoline dose is eliminated unchanged in the urine.

4. **The Sponsor's proposed dissolution method is acceptable. It is, therefore, recommended that the dissolution specification be set at [redacted] min - Q = [redacted]%.**

The actual batch size regarded as "semi-industrial" can be considered as "transitional", considering the scale up from [redacted] units scheduled next year. Additionally, our specifications undergo periodic review according to the manufacturing experience gained. Because of these points, the Sponsor proposes to keep the current specifications (i.e. Dissolution NLT [redacted]% (Q) after [redacted] minutes) and provide a committment based upon Company policy to review and tighten specifications as appropriate after periodic review of batch analysis results.

If you have any questions regarding the contents of this submission, please contact me at (616) 833-4070. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Susan M. Mondabaugh, Ph.D.
Director, Regulatory Affairs

SMM:law
Attachments

Pharmacia & Upjohn

Office of:

Susan M. Mondabaugh, Ph.D.
Director, Regulatory Affairs

Telephone: 616/833-4070
Fax: 616/833-8237

November 20, 1996

Solomon Sobel, MD, Director
Food and Drug Administration
Division of Metabolism and Endocrine
Drug Products, HFD-510
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

RE:NDA 20-664
DOSTINEX® (cabergoline)

NDA Amendment
Revised Package Insert

Dear Dr. Sobel,

In response to the facsimile dated October 19, 1996 from the Division containing labeling comments, we are submitting a revised, proposed package insert (dated November 19, 1996).

All of the changes requested by FDA are acceptable to us and they have been incorporated in the revised text.

If you have any questions regarding the contents of this submission, please contact me at (616) 833-4070. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Karen J Bruzinski for

Susan M. Mondabaugh, Ph.D.
Director, Regulatory Affairs

SMM:law
Attachments

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

Pharmacia & Upjohn

Office of:

Susan M. Mondabaugh, Ph.D.
Director, Regulatory Affairs

Telephone: 616/833-4070
Fax: 616/833-8237

November 13, 1996

Solomon Sobel, MD, Director
Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-664
DOSTINEX®
(cabergoline)

NDA Amendment
Safety Update

Dear Dr. Sobel,

In response to the request from the Division, submitted herewith is the safety update for the above referenced NDA. The safety update covers the period from August 1, 1995 to July 31, 1996. During this time interval, there have been no newly completed studies in the U.S. or Europe.

The update consists of serious spontaneous reports from two indications: hyperprolactinemic disorders and Also included are serious adverse events from clinical studies in hyperprolactinemic disorders. Appendix 1 contains spontaneous AEs up to July 31, 1995. Appendix 2 contains serious AEs reported in studies in Parkinson's disease from August 1, 1995 to July 31, 1996.

Additional information provided is a publication on pregnancy outcome after treatment with Dostinex and reports of studies conducted in Japan (English summaries, tables and figures).

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

If you have any questions regarding the contents of this submission, please contact me at (616) 833-4070. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Susan M Mondabaugh

Susan M. Mondabaugh, Ph.D.
Director, Regulatory Affairs

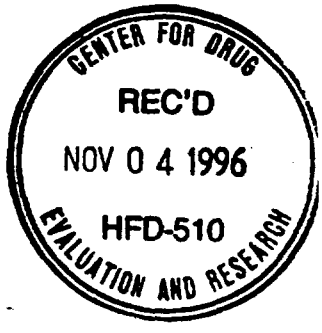
SMM:law
Attachments

Pharmacia & Upjohn

Office of:

Susan M. Mondabaugh, Ph.D.
Director, Regulatory Affairs

Telephone: 616/833-4070
Fax: 616/833-8237



October 31, 1996

Solomon Sobel, MD, Director
Food and Drug Administration
Division of Metabolism and Endocrine
Drug Products, HFD-510
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

RE:NDA 20-664
DOSTINEX® (cabergoline)

NDA Amendment
Revised Package Insert

Dear Dr. Sobel,

In response to the facsimiles dated August 2, 1996 (received September 20, 1996) and September 25, 1996 from the Division containing labeling comments, we are submitting a revised package insert in this amendment. The revised package insert contains the FDA requested changes as well some changes we wish to make in content. In addition, there have been minor changes in format and editorial style.

The revised package insert may be found in Attachment 1. To aid in the review of the revised insert, Attachment 2 contains a comment document detailing the changes that have been made to the insert.

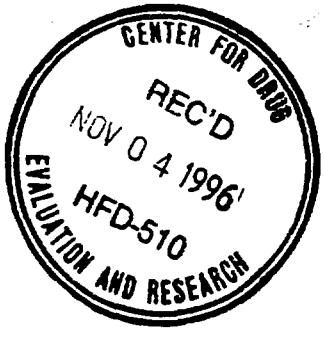
If you have any questions regarding the contents of this submission, please contact me at (616) 833-4070. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

K J Brzezinski for

Susan M. Mondabaugh, Ph.D.
Director, Regulatory Affairs



SMM:law
Attachments

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo MI 49001-0199
USA

Telephone (616) 833-4000

Pharmacia & Upjohn

Office of:

Susan M. Mondabaugh, Ph.D.
Director, Regulatory Affairs

Telephone: 616/833-4070
Fax: 616/833-8237

October 25, 1996

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine
Drug Products, HFD-510
Center for Drug Evaluation and Research
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-664
DOSTINEX® (cabergoline)

General Correspondence
Chemistry, Manufacturing and Control

Dear Dr. Sobel,

Reference is made to the July 12, 1996 facsimile received from the Division which contained questions relating to the Chemistry, Manufacturing, and Controls section of the above referenced NDA. This amendment contains our responses to those questions. For ease of review, each question is repeated on the following pages in italics, followed by our response.

If you have any questions regarding the contents of this submission, please contact me at (616) 833-4070. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Susan M Mondabaugh

Susan M. Mondabaugh, Ph.D.
Director, Regulatory Affairs

SMM:law

Attachments

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

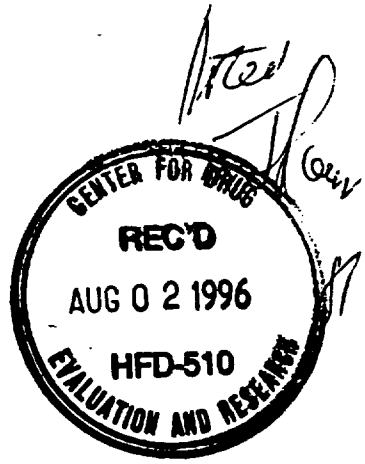
Telephone (616) 833-4000

Pharmacia

ORIGINAL NEW COPY

Office of:
Kenneth F. King
Vice President
Regulatory Affairs

Telephone No. (616) 833-0856
Facsimile No. (616) 833-0409



July 31, 1996

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room #14B-19
5600 Fishers Lane
Rockville MD 20857

Re: Transfer of Ownership

Sir/Madam:

We are transferring ownership rights for the applications listed in the attached table from Pharmacia Inc. to Pharmacia & Upjohn Company. The letter dated June 26, 1996 notified you of the new company name.

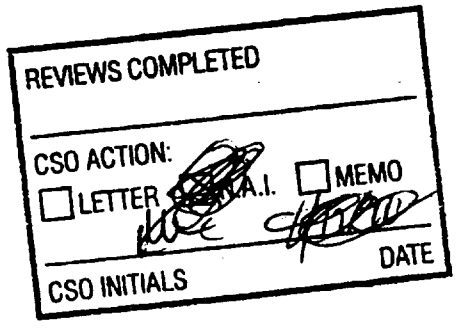
Please contact Robert A. Paarlberg at (616) 833-0646 if you have any questions regarding this notification.

Sincerely,

PHARMACIA INC.

Kenneth F. King
Vice President
Regulatory Affairs

KFK:KMW:met.le



Pharmacia & Upjohn

Office of:
Kenneth F. King, Ph.D.
Vice President
Regulatory Affairs

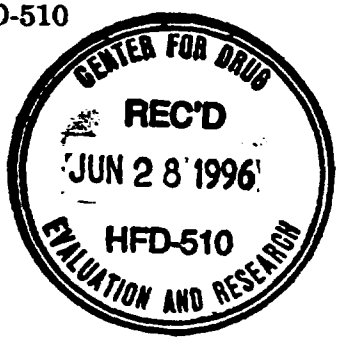
Telephone No. (616) 833-0856
Facsimile No. (616) 833-8237

ORIGINAL

SUPPL NEW CORI

June 26, 1996

Division of Metabolism & Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Noted
7/11/96

Re: NDA 20-664
DOSTINEX®
(cabergoline)

COMPANY NAME CHANGE

Sir/Madam:

This is to notify you that, effective June 11, 1996, Pharmacia & Upjohn Company, Kalamazoo, Michigan, became the holder of the application cited above. Pharmacia & Upjohn Company is a new company formed as a result of the merger of the former Upjohn Company, Kalamazoo, Michigan and the former Pharmacia Inc, Dublin, Ohio. All applications at the Food and Drug Administration held by the two former companies are now held by the new company.

Noted RL
7/11/96

Consistent with 21 CFR §314.72, we wish to advise you that Pharmacia & Upjohn Company commits to any agreements, promises and conditions contained in the application cited above and is in possession of a complete copy of the approved application including supplements and records that are required to be kept under §314.81.

A copy of a completed form 356h, reflecting the new name, is provided for the file.

Please contact Robert A. Paarlberg at (616) 833-0646 if you have any questions about this notification.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Kenneth F. King, Ph.D.
Vice President
Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

Pharmacia

Date May 15, 1996

Reference NDA 20-664

ORIGINAL

[illegible]

AIRBORNE

CSO:-
Please find the Reviewer who requested these Case Report Form copies - and deliver same.
[signature]
5/23/96

Solomon Sobel, M.D., Director
Division of Metabolism &
Endocrine Drug Products (HFD-510)
ATTN: Document Control Room 14B-19
Food and Drug Administration
5600 Rockville Pike
Rockville, MD 20857

RE: DOSTINEX™ (cabergoline)
NDA 20-664
AMENDMENT TO PENDING APPLICATION

Dear Dr. Sobel:

As requested by your Division, enclosed are copies of Case Report Forms for all patients enrolled in Dostinex™ (cabergoline) pivotal studies HPRL007 and ONC/026.

Please contact me at (614) 764-8235 if there are questions concerning this information.

Sincerely,

[signature]

Dean M. Waters
Manager, Regulatory Affairs

DMW/wld

enclosure

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Noted
[initials]
23 May 96

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 17 1996
HFD-510

Postal address
Pharmacia Inc.
Post Office Box 16529
Columbus, Ohio 43216-6529
USA

Visiting address
7001 Post Road
Dublin, Ohio 43017
USA

Telephone
614-764-8100

Telex
246-620

Telefax
614-761-8102

ORIGINAL

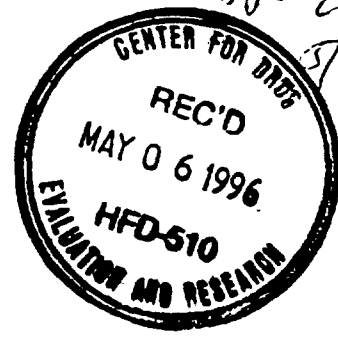
Pharmacia

Date May 2, 1996

Reference NDA 20-664

AIRBORNE

Solomon Sobel, M.D., Director
Division of Metabolism &
Endocrine Drug Products (HFD-510)
ATTN: Document Control Room 14B-19
Food and Drug Administration
5600 Rockville Pike
Rockville, MD 20857



RE: DOSTINEX™ (cabergoline)
NDA 20-664
AMENDMENT TO PENDING APPLICATION

Dear Dr. Sobel:

The enclosed information is being submitted in response to a fax dated April 12, 1996 from Dr. Ananda Gubbi. Enclosed are two (2) diskettes. The first diskette (labeled "SAS") contains two SAS datasets created under PC SAS for Windows, Version 6.08. The datasets are named FDA_007.SD2 and FDA_026.SD2 which corresponds to studies HPRL007 and ONC026, respectively. Also enclosed are hard copy printouts of the SAS CONTENTS PROCEDURE for those two datasets.

The second enclosed diskette (labeled "LOTUS") contains two (2) Lotus spreadsheet files created under Version 2.3 with corresponding format overlays. The spreadsheets are named FDA_007.WK1 and FDA_026.WK1 with applicable formats named FDA_007.FMT and FDA_026.FMT. As in the case of the SAS datasets, the FDA_007 file is Cabergoline HPRL007 and FDA_026 is ONC026. As you know, SAS allows for multiple reasons for "missing" data values. In converting the data in the SAS datasets to the Lotus spreadsheet files, we have translated all SAS missing values to the Lotus "NA" state.

As per your instructions, these files are in their "UNZIPPED" format. Also included are hard copy printouts of these two (2) Lotus spreadsheet files (FDA_007 and FDA_026).

Lastly, as you know, the majority of these data are, in fact, serum prolactin values. In Study HPRL007, 14 investigative sites accrued a total of 188 subjects and utilized a total of 17 laboratories for prolactin determinations. One investigative site (Number 001) utilized 3 laboratories; and, another investigative site (Number 012) used 2 laboratories. A total of 13 of these laboratories reported the prolactin values in nanoGrams/ML, while 4 laboratories reported the prolactin values in microUnits/ML.

Postal address	Visiting address	Telephone	Telex	Telefax
Pharmacia Inc. Post Office Box 16529 Columbus, Ohio 43216-6529 USA	7001 Post Road Dublin, Ohio 43017 USA	614-764-8100	246-620	614-761-8102

Pharmacia

In Study ONC/26, 67 investigative sites accrued a total of 459 subjects and utilized a total of 67 laboratories for prolactin determinations. A total of 39 of these laboratories reported the prolactin values in nanoGrams/ML, while 27 laboratories reported the prolactin values in microUnits/ML and one laboratory reported the prolactin values in Units/Liter.

Universally, if a laboratory reported prolactin values in nanoGrams/ML, the values were reported to one decimal place of accuracy. If a laboratory reported prolactin values in microUnits/ML or Units/Liter, the reported values were transformed by use of an investigative-site/laboratory specified Conversion Factor to nanoGrams/ML. In the enclosed SAS datasets and the Lotus files, the prolactin values are all represented in the nanoGrams/ML. If the value was the result of conversion to nanoGrams/ML, then it most likely will have a value with more than its first decimal place non-zero. Obviously, given the "right" values of prolactin and conversion factor, a value could appear as all zeros after its first decimal place of accuracy even though it was the result of a conversion. For simplicity, on the hard copy Lotus spreadsheet printouts, the prolactin values have been rounded to one decimal place of accuracy on output from the spreadsheet file.

Also included is a listing of sites participating in cabergoline studies HPRL007 and ONC/026 that did not accrue any patients. The sites that Dr. Gubbi has requested treatment outcome information on did not accrue any patients.

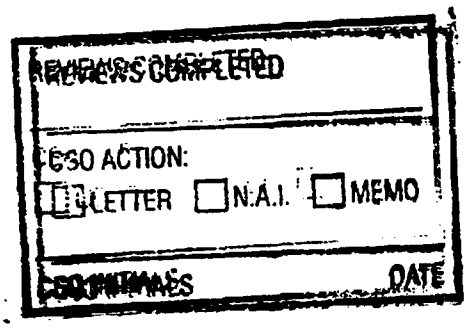
If you have any questions or problems, please feel free to contact me at 614-764-8235.

Sincerely,

Dean M. Waters
Manager, Regulatory Affairs

DMW/wld

enclosure



Pharmacia

Date April 16, 1996

Reference NDA 20-664

AIRBORNE

Solomon Sobel, M.D., Director
Division of Metabolism &
Endocrine Drug Products (HFD-510)
ATTN: Document Control Room 14B-19
Food and Drug Administration
5600 Rockville Pike
Rockville, MD 20857

RE: DOSTINEX™ (cabergoline)
NDA 20-664
AMENDMENT TO PENDING APPLICATION

Dear Dr. Sobel:

In response to your correspondence of March 28, 1996, enclosed is a revised environmental assessment section of the Dostinex™ (cabergoline) NDA.

We have determined that the Dostinex™ NDA environmental assessment qualifies for tier 0 as identified in the Center for Drug Evaluation and Research's document "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements." As such, we are requesting that information provided in format items 7, 8, 9, 10, 11 and 15 be deleted. Attached is a revised Dostinex™ NDA environmental assessment with the format items deleted.

If you have any questions or comments concerning this submission, please contact me at 614-764-8235.

Sincerely,

Dean M Waters

Dean M. Waters
Manager, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

DMW/wld

enclosure

Postal address
Pharmacia Inc.
Post Office Box 16529
Columbus, Ohio 43216-6529
USA

Visiting address
7001 Post Road
Dublin, Ohio 43017
USA

Telephone
614-764-8100

Telex
246-620

Telefax
614-764-8102

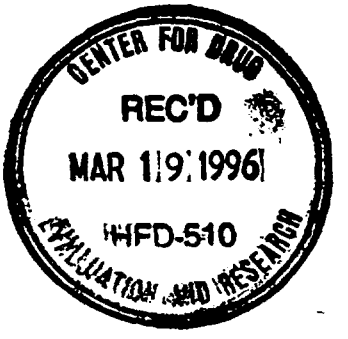
Pharmacia

Date March 18, 1996

Reference NDA 20-664

ORIGINAL

AIRBORNE



Solomon Sobel, M.D., Director
Division of Metabolism &
Endocrine Drug Products (HFD-510)
ATTN: Document Control Room 14B-19
Food and Drug Administration
5600 Rockville Pike
Rockville, MD 20857

Filed
3/25/96

RE: DOSTINEX™ (cabergoline)
NDA 20-664
AMENDMENT TO PENDING APPLICATION

Dear Dr. Sobel:

Enclosed in duplicate is an amendment to Dostinex™ (cabergoline) NDA 20-664. The enclosed information is submitted in response to a request from Dan Marticello, the Statistician reviewing the NDA. The amendment provides site-specific summary statistics for selected efficacy variables from the two NDA pivotal trials.

If you have any questions or comments concerning this submission, please contact me at 614-764-8235.

Sincerely,

Dean M. Waters
Manager, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ [illegible] ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

DMW/wld

enclosure

Postal address
Pharmacia Inc.
Post Office Box 16529
Columbus, Ohio 43216-6529
USA

Visiting address
7001 Post Road
Dublin, Ohio 43017
USA

Telephone
614-764-8100

Telex
246-620

Telefax
614-761-8102

Pharmacia

Date March 4, 1996

Reference NDA 20-664

AIRBORNE

Solomon Sobel, M.D., Director
Division of Metabolism &
Endocrine Drug Products (HFD-510)
ATTN: Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: DOSTINEX (cabergoline)
NDA 20-664
AMENDMENT TO PENDING APPLICATION

Dear Dr. Sobel:

Enclosed is information requested by the cabergoline Medical Reviewer that was previously faxed to the Division.

The following is included:

1) Summary of clinical studies completed with cabergoline.

2) Information summarizing the baseline comparability of treatment groups in the NDA pivotal studies.

If you require any additional information, please contact me at (614) 764-8235.

Sincerely,

Daniel G Waters for

Dean M. Waters
Manager, Regulatory Affairs

DMW/wld
enclosure

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I.
CSO INITIALS DATE

Postal address
Pharmacia Inc.
Post Office Box 16529
Columbus, Ohio 43216-6529
USA

Visiting address
7001 Post Road
Dublin, Ohio 43017
USA

Telephone
614-764-8100

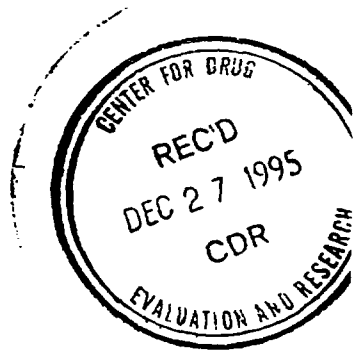
Telex
246-620

Telefax
614-761-8102

Pharmacia

Date December 26, 1995

Reference NDA 20-664



AIRBORNE

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
ATTN: DOCUMENT CONTROL ROOM 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: DOSTINEX®
NDA 20-664

Dear Dr. Sobel:

Pursuant to 21 CFR 314.50, Pharmacia Inc., is submitting herewith a new drug application for Dostinex (cabergoline). Dostinex is a long-acting dopamine receptor agonist. It is indicated for the treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas.

The content and format of this NDA reflects the agreements reached between Pharmacia and your Division at our February 7, 1995 and July 26, 1995 pre-NDA meetings.

The clinical trials providing evidence of the safety and efficacy of Dostinex were reviewed in our meeting of February 7, 1995.

The archival copy of the NDA consists of 211 volumes and is divided into sections 1-15 as listed on the form FDA 356H. As agreed with the Division during our July 26, 1995 meeting no patient CRFs are included in the NDA. A waiver request to not include CRFs in the NDA was also submitted to cabergoline IND on December 12, 1995.

SAS data sets for primary and secondary efficacy and safety variables are not included at this time but will be provided on request.

Postal address
Pharmacia Inc.
Post Office Box 16529
Columbus, Ohio 43216-6529
USA

Visiting address
7001 Post Road
Dublin, Ohio 43017
USA

Telephone
614-764-8100

Telex
246-620

Telefax
614-764-8102

Pharmacia

I look forward to working with you and your staff in the review of this NDA. Please contact me at (614) 764-8235 or fax (614) 764-8125 with any questions or comments concerning the application.

Sincerely,

Dean M. Waters

Dean M. Waters
Manager, Regulatory Affairs

DMW/wld
enclosure