CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-866

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	20-866
AMENDMENT:	29
DATE RECEIVED BY CENTER:	4/15/2008
PRODUCT:	Cycloset
INTENDED CLINICAL POPULATION:	Type 2 diabetes
SPONSOR:	Veroscience LLC (RI)
DOCUMENTS REVIEWED:	Paper and Electronic Submission
REVIEW DIVISION:	DMEP (HFD-510)
PHARM/TOX REVIEWER:	Gemma Kuijpers
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Date of review submission to Division File System (DFS): October 14, 2008

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

Approval (AP), pending acceptance of recommended labeling changes.

B. Recommendation for nonclinical studies

Additional nonclinical studies are not required for approval of the NDA.

C. Recommendations on labeling

Recommended labeling changes have been appended to this Review (see pages 19-21).

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Nonclinical pharmacology, ADME and toxicology studies were reviewed upon submission of the original NDA 20-866 (1997).

Pharmacology

Bromocriptine can affect dopaminergic as well as non-dopaminergic pathways. Interference with a central dopaminergically controlled diurnal pattern of prolactin action and body metabolism may explain the effect of the compound on glycemic control and lipogenesis.

ADME

In rat and monkey there was moderate but rapid absorption, high first-pass metabolism, distribution to various tissues, and mainly biliary excretion of metabolites.

Toxicity

In the rat target organs included CNS, cardiovascular system, skin (hair), adrenal, pituitary, ovary and uterus. In the dog effects were observed in CNS, thymus, liver, kidney, sexual skin, ovaries, pituitary, stomach and adrenal. In the monkey, CNS effects and pituitary lesions wee observed. Genotoxicity tests were negative.

Carcinogenicity

In a 74-week dietary mouse study there was no evidence of tumorigenicity.
In a 100-week dietary rat study there was an increase in malignant uterine tumors (endometrial and myometrial) in the mid and high dose groups. The increase is probably due to the suppression of prolactin-stimulated progesterone secretion from the corpus luteum in the aging rat leading to estrogen dominance and endometrial stimulation. The effect is unlikely to be relevant for humans.

Reproductive toxicology

In rats, there was a decrease in implantation and increase in resorptions in pregnant females probably due to a rat-specific pharmacologic effect. A reduction in offspring viability in a male rat fertility study at 24 to 120-fold human dose multiples (mg/m^2 basis) was also observed. In rabbits, there was a low incidence of fetal abnormalities and embryolethality at maternally toxic doses but there were no fetal abnormalities at up to 140-fold human dose multiples (mg/m^2 basis). No embryolethality or teratogenicity was observed in two small monkeys studies.

Animal data suggest a very low risk to the fetus. Data from human observational studies do not indicate fetal harm. Thus, a Pregnancy Category B is justified. The Parlodel label for bromocriptine mesylate for the indications of hyperprolactinemia, acromegaly and Parkinson's disease also includes a Pregnancy Category B.

Impurities

Impurities in drug stubstance and degradants in drug product were not qualified in nonclinical studies. There were no impurities in the drug substance that exceeded the qualification threshold of 0.15%. For the Cycloset drug product, the specification limit for bromocriptinine (NMT—— exceeded the qualification threshold and was ——than the limit in Bromocriptinine Mesylate Tablets USP (NMT—— This is, however, acceptable since products manufactured in compliance with USP guidelines have been on the market for approximately 30 years at recommended dosages up to 100 mg/day or 20 times the proposed dose of 4.8 mg/day, rendering bromocriptinine essentially qualified. b(4) b(4)

B. Pharmacologic activity

Bromocriptine is a potent dopamine receptor D_2 agonist and a D1 receptor antagonist. The effect of bromocriptine on glycemic control is thought to be mediated by activation of central dopaminergic pathways involved in the diurnal control of prolactin release and regulation of carbohydrate and lipid metabolism. Support for this hypothesis has been derived from studies in various animal species (rodent, swine, hamster).

III. Nonclinical safety issues relevant to clinical use

Cycloset is contraindicated in pregnancy.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

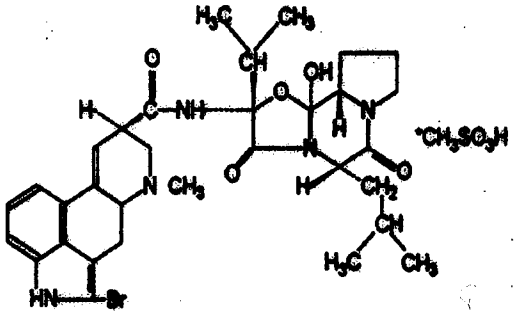
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number:	**20-866**
Submission date:	**April 13, 2008**
Amendment #	**29**
Type of submission:	**N**
Information to Sponsor:	**Yes (x) (Labeling comments)**
Sponsor:	**Veroscience LLC, RI**
Manufacturer for drug substance:	——— b(4)
Manufacturer of drug product:	**Patheon Pharmaceutical Inc.**
Reviewer name:	**Gemma Kuijpers**
Division name:	**Division of Metabolism and Endocrinology Products (DMEP, HFD-510)**
Review completion date:	**Oct 9, 2008**

Drug:

Trade name:	**Cycloset™**
Chemical name:	**Bromocriptine mesylate**
Laboratory Codes:	**CB-154**
CAS registry number:	**22260-51-1**
Molecular formula:	**$C_{32}H_{40}BrN_5O_5.CH_4SO_3$**
Molecular weight:	**750.7**

Structure:



$C_{32}H_{40}BrN_5O_5 \cdot CH_4SO_3$ Mol. wt. 750.72

b(4)

Relevant IND/NDA/DMF:	**IND 34,661/NDA 17-962/DMF———**
Drug category:	**Dopamine D_2 agonist**
Indication:	**Adjunct to diet and exercise, with or without other hypoglycemic agents, to improve glycemic control in patients with type 2 diabetes**
Clinical formulation:	**Tablet**

Route of administration:	Oral
Dosage form:	Tablet
Tablet strengths:	0.8 mg
Proposed clinical dose:	1.6-4.8 mg/day
Proposed use:	Once daily
Clinical study:	165-AD-04-03-US-1 (safety trial)

Clinical Program
As requested by the Division in the approvable letter of October 15, 1999, sponsor conducted a new placebo-controlled cardiovascular safety trial in patients with Type 2 diabetes.

Previous Human Experience
Parlodel
Bromocriptine is on the market under the name Parlodel™ (Novartis) for various indications. The dose form is oral (2.5 mg tablets or 5 mg capsules). Therapeutic dosage ranges from 2.5-15 mg/day (hyperprolactinemic indications), 20-30 mg/day (acromegaly), and a 2.5 mg/day multiple (Parkinson's disease). The maximum recommended dose for acromegaly and Parkinson's for which safety has been demonstrated is 100 mg/day. The indication of suppression of postpartum lactation was removed in 1995, due to concerns of an increased risk of hypertension, heart attack, seizures and stroke in the target population. Side effects reported for Parlodel in hyperprolactinemic patients include nausea, headache, dizziness, abdominal cramps, nasal congestion, constipation, drowsiness, hypotension.

Regulatory History
Ergoscience, the original sponsor of IND 34,661 and NDA 20-866, submitted NDA 20-866 on August 18, 1997, for Ergoset (bromocriptine mesylate) for the improvement of glycemic control in patients whose hyperglycemia cannot be managed by diet alone. Proposed dose was 0.8-4.8 mg/day. The NDA was given an "AE". In the approvable letter dated October 15, 1999, DMEP requested additional clinical and biopharmaceutical data. Regarding pharmacology/toxicology, responses were requested to three issues: (1) impurity qualification, (2) labeling, (3) Pregnancy Category.

For the original NDA 20-866 submission, Ergoscience referenced the nonclinical studies that had been conducted previously to support the marketing of Parlodel (NDA 17-962, AP June 28, 1978) with some additional studies. The pharmacology/toxicology review of NDA 20-866 concluded that the nonclinical data were adequate and supported the use of Ergoset tablets at a dose of 0.8-4.8 mg/day for the proposed indication.

In November 2003, ownership of IND 34,661 and NDA 20-866 was transferred from Ergoscience to Pliva d.d. (PLIVA), and PLIVA became the new manufacturer of Cycloset™ for ongoing clinical studies. In May 2006, the ownership of the IND and NDA for Cycloset™ (bromocriptine mesylate) tablets was transferred from PLIVA to VeroScience LLC (VeroScience). A new contract manufacturer, Patheon Pharmaceuticals Inc. (Patheon) is manufacturing the drug product for Veroscience.

On April 13, 2008 Veroscience submitted a complete response (NDA 20-866, Amendment 29) and addressed the issues outlined in the approvable letter. Data from a placebo controlled safety trial were submitted. No new nonclinical studies were performed. New draft labeling was submitted.

Changes to the nonclinical sections of the label included a desription of the nonclinical studies in relevant sections. While the Division requested Sponsor maintained Pregnancy Category B as indicated in the labeling for Parlodel. A justification was provided.

Outstanding Nonclinical Issues

Reprotoxicity

Reproductive toxicity studies in rats and rabbits were reviewed for NDA17-962 and NDA 20-866. At the time of the original submission of NDA 20-866 by Ergoscience, sponsor did not propose a Pregnancy Category for the labeling. For the current NDA submission, sponsor proposes a Category B. Parlodel™ (Novartis) is currently also labeled Pregnancy Category B. Sponsors rely on the same reprotoxicity studies for these two NDA's. NDA 17-962 supplements S-063 and S-064 (Novartis) were approved on Nov 9, 2005 (DRUP). The nonclinical sections of the approved Parlodel labeling are attached to this review. Reprotoxicity study data and Pregnancy Category for Cycloset are discussed in the Toxicology section of this review.

Impurity qualification

In the 1999 approvable letter it was communicated to sponsor that qualifications of impurities should be carried out according to ICH guidances. Qualification of the related substance bromocriptinine in the Cycloset product is discussed in the Toxicology section of this review.

2.6.2. PHARMACOLOGY

The alkaloid bromocriptine is a potent dopamine receptor D_2 agonist and an antagonist at the D_1 receptor. Bromocriptine interacts with dopamine receptors in the CNS, cardiovascular system, hypothalamo-pituitary axis and GI tract. Bromocriptine is well known as an inhibitor of pituitary hormone (prolactin, growth hormone) secretion. Ergot alkaloids have long been known as potent uterine stimulants.

Non-insulin-dependent diabetes mellitus is characterized by hyperglycemia, resulting from both an impaired insulin secretory response to glucose and decreased insulin effectiveness (insulin resistance). Prolactin secretion appears to be shifted in subjects with altered glucose tolerance, body fat stores and insulin sensitivity. Hypothalamic dopamine activities are thought to be linked to pituitary prolactin secretion and lipogenesis. Sponsor contends that timed daily bromocriptine administration resets a dopamine-dependent circadian neurosecretory mechanism, producing an improvement and/or normalization of the diurnal serum prolactin concentrations and a shift in metabolism from the obese, insulin-resistant condition to the lean, insulin-sensitive state, thereby reducing body fat stores and enhancing glycemic control.

2.6.6 TOXICOLOGY

The toxicity data reviewed previously for NDA 20-866 were from published studies. The literature publications did not specify the exact drug formulation.

CARCINOGENICITY

Human dose multiples (mg/m2 basis)

Species	#/sex/dose group	Duration	Route	Dose (mg/kg/day)	Human dose multiple (mg/m^2)
Rat	50	100 weeks	oral (diet)	0, 1.8, 9.9, 44.5	0, 4.4, 24, 106
Mouse	50	74 weeks	oral (diet)	0, 2, 10, 50	0, 2.3, 12, 58

*based on human dose of 4.8 mg, is 0.07 mg/kg (70 kg human)

In a 78-week study in OF1 mice, with oral dietary doses of 0, 2, 10, 50 mg/kg/day, there was no evidence of tumorigenicity in any organ including uterus.

In a 100-week study in rats, at oral dietary doses of 0, 1.8, 9.9, 44.5 mg/kg/day, there was a dose-dependent increase in malignant uterine tumors (endometrial and myometrial) at 4.3, 24, 106x the human dose of 4.8 mg, based on body surface area mg/m2 comparison. There were also endometrial inflammatory and plastic changes in treated groups. The endometrial changes and uterine tumors in the rat are believed to be the result of bromocriptine-induced inhibition of prolactin-stimulated progesterone secretion from the corpus luteum in the aging rat, leading to estrogen dominance and endometrial stimulation. Prolactin plays a critical role in corpus luteum maintenance and progesterone production in rodents (Risk & Gibori 2001), but not in other mammals. Thus, the human relevance of this finding is likely to be low.

GENOTOXICITY

In Vitro Assays

Bromocriptine tested negative in the Ames bacterial mutation assay with or without metabolic activation. Compound A and B, two impurities in the drug substance (— ⟹), respectively, did not have mutagenic activity in the mouse lymphoma assay with or without metabolic activation. b(4)

In Vivo Assays

Bromocriptine was not mutagenic in the bone marrow micronucleus test in CD-1 mice and Chinese hamsters, or in a bone marrow chromosomal aberration test in Chinese hamsters. Negative results from the dominant lethal test in male CD-1 mice indicated that bromocriptine had no effect on male germ cells of CD-1 mice. Bromocriptine also tested negative in a reproductive capacity test in female mice, indicating no effect on female germ cells.

REPRODUCTIVE TOXICITY

Species	Study Type	Route	Duration	Dose (mg/kg/day)	Human dose multiple (HDM) (mg/m^2 basis)*
Rat	Fertility (♀)	oral (gavage)	d14 ac-GD13/LD21	0, 1, 3	0, 2.4, 7.2
Rat	Fertility (♂)	oral (gavage)	d70 ac-GD13	0, 2, 10, 50	0, 4.8, 24, 120
Rat	Teratology	oral (gavage)	GD6-GD15; or single 10 mk dose GD5	0, 3, 10, 30; 10	0, 7.2, 24, 72; 24
Rat	Teratology	oral (gavage)	GD6-GD15, GD8-GD15	0, 3, 10, 30	0, 7.2, 24, 72
Rat	Reprotox	s.c. single; multiple	GD5,6,7,8,9 or 10; GD10-GD15	0, 2; 0, 50, 100	?
Rat	Peri- and postnatal	oral (gavage)	GD15-GD20	0, 3, 10, 30	0, 7.2, 24, 72
Rabbit (YS)	Teratology	oral (gavage)	GD6-GD18	0, 3, 10, 30, 100; 300, 1000	0, 14, 48, 140, 480; 1400, 4800
Rabbit (YS and NZW)	Teratology	oral (gavage)	GD6-GD18	0, 100, 300	0, 480, 1400
Rabbit (YS and NZW)	Preimplantation	oral (gavage)	GD1-GD6	0, 100, 300	0, 480, 1400
Monkey	Reprotox	oral	up to GD30/GD80	0, 0.3	0, 1.4
Monkey	Teratology	oral (gelatin capsule)	GD20/24-GD39	2	10

*based on human dose of 4.8 mg, ie 0.07 mg/kg (65 kg human)

Segment I/Fertility

Rat

In female rats treated with 0, 1, 3 mg/kg/day, there was no effect on fertility. NOAEL was 3 mkd (HDM = 7x)

In male rats treated with 0, 2, 10, 50 mg/kg/day, there was a significant decrease in body weight gain in the 50 mkd male group. Fertility (copulation or fertility indices) was not statistically significantly affected.
Pre- and perinatal mortality was increased significantly (3x control) in dams mated with 50 mg/kg/d males and litter size was reduced although not significantly in the high dose group.
Postnatal mortality (pup loss PPD 0-21) was increased (9-11% vs. control of 4.3%) in all three treatment groups in non-dose-dependent manner. The effect was statistically significant at 10 and 50 mkd (NDA 17-962 review). Pup loss in the female rat fertility study was 4.3%-12.7% (range in control and dosed groups) and was not increased in dose-dependent manner. There was no effect on F1 pup weight gain. NOAEL is 2-10 mg/kg/day (HDM 5-24x)

Sponsors (Parodel NDA 17-962, Ergoset NDA 20-866) have argued that in view of the toxicity in the 50 mkd males the moderate increase in pre- and perinatal mortality (3x control) in this group is not considered relevant. In a publication describing these findings the effects in the 50 mkd group were attributed to a LH and prolactin inhibition in the treated males affecting fertility and offspring viability. However, this is speculative. Paternal toxicity may have contributed to decreased offspring viability (pre/peri/postnatal mortality) in the 50 mkd group (HDM=120x). The cause and significance of postnatal pup loss in the 10 and 50 mkd groups (HDM=24x-120x) is unclear. Postnatal pup loss was increased vs control but in non-dose-dependent manner in all dose group and was within the range observed in another female rat fertility study.

Current sponsor commented that in the groups that tolerated bromocriptine well (2, 10 mg/kg) there were no adverse effects on fertility or pre- and postnatal fetal development.

Monkey

In female monkeys dosed with 0.3 mg/kg/day, fertility (cycle length, ovulation, conception) was not affected. NOAEL = 0.3 mkd (HDM 1.4x)

Segment II/Teratology

Rat

In the first study (albino rats; oral doses 0, 3, 10, 30 mg/kg GD6-15, or single 10 mg/kg dose GD5), implantation was inhibited in dams treated with 10 mkd (single dose GD5) and 30 mkd (doses GD6-15) (reflected by reduction in % pregnant dams). An increase in the incidence of fused sternebrae was seen in the GD5 single dose 10 mg/kg group only. NOAEL = 3 mkd (HDM 7.2x)

In a second study (OFA rats; oral doses 0, 3, 10, 30 mg/kg GD6-15, or 0, 3, 10, 30 mg/kg GD8-15), body weight gain in dams was reduced at 30 mg/kg/day partly due to reduced litters. Implantation was markedly inhibited (% pregnant reduced) in dams treated with 10 and 30 mkd from GD6-15, but not in dams treated from GD8-15. An increase in prenatal mortality (resorptions) was observed at 10 mg/kg (GD6-15) (NDA 17-962) and 30 mkd (GD8-15) (NDA 17,962 and Parlodel™ label). The Parlodel label also mentions the finding of one anomaly i.e. aplasia of spinal vertebrae and ribs, in the group of 262 fetuses derived from dams treated with 30 mg/kg/day. However, according to NDA 17-962 review, abnormalities were within normal limits. NOAEL = 3mkd (HDM 7.2x)

In a third study (single sc doses of 2 mg/kg on GD 5,6,7,8,9 or 10; or repeat sc doses of 0, 50, 100 mg/kg/day on GD10-15) rats dosed with a single 2 mg/kg sc dose on GD5, 6, 7, or 8 had abortions and reduced numbers of implantations. This confirms the finding in the above two studies on implantation inhibition. Multiple sc doses of 50 or 100 mkd on GD10-15 had no effect on implantation, fetal viability, postimplantation loss or fetal weight. Teratogenicity was not evaluated.

Comment:
The inhibition of implantation when rats were dosed on or from GD5 or GD6 was probably due to the effect of bromocriptine on prolactin secretion resulting in dysfunction of the corpora lutea. In the rat, implantation which takes place on GD6-8, is dependent on prolactin maintaining the function of the corpora lutea preparing the endometrium for implantation. In humans, implantation is dependent on pituitary LH and the effect in rats is unlikely to be relevant.

Rabbit
In a first study in female Yellow Silver rabbits (oral doses 0, 3, 10, 30, 100 mg/kg/day GD 6-18; or 300-1000 mg/kg/day GD6-18), there was maternal toxicity (body weight reduction at ≥10 mkd, mortality at ≥300 mkd) and increased prenatal mortality (postimplantation loss/early resorptions) at ≥10 mg/kg/day. Cleft palate was observed in 1 control fetus and in 3 fetuses from the 100 mkd group, portions of vertebral segments were missing in 1 each of 30 and 100 mg/kg fetuses. Hydrocephalus was seen in 1 control, one (1) 3mkd and two (2) 100mkd fetuses, skeletal retardations in three (3) 300 mkd fetuses. NOAEL = 3 mkd (HDM 14x)

In a second study in Yellow Silver and New Zealand rabbits (oral doses 0, 100, 300 mg/kg/day, GD6-18) there was materal toxicity (reduced body weight) at 100-300 mkd, reduced implantations and increased preimplantation loss at 300 mkd (NZW), increased postimplantation loss at 100-300 mkd (NZW) and 300mkd (YS). There were 2 fetuses from one litter with cleft palate in the 300 mkd Yellow Silver group, and a fetus with missing caudal vertebral column in the 100 mkd group (Review NDA 17-962). In New Zealand white rabbits cleft palate did not occur. NOAEL < 100 mkd (HDM 480x)

In a third study in Yellow Silver and New Zealand white rabbits (oral doses 0, 100, 300 mg/kg/day, GD 1-6), there was maternal toxicity (reduced body weight) in both strains at 100-300 mkd, and increased postimplantation loss in the NZ 300 mkd group. The latter was possibly due to maternal toxicity. Implantation was not affected. There were no

obvious treatment-related fetal abnormalities. NOAEL < 100 mkd (HDM 480x)

Monkey
In stumptailed macaque monkeys given oral doses of 2 mg/kg/day (GD20-24 through GD39) (N=6) no embryolethality or teratogenicity was observed. NOAEL = 2 mkd (HDM 10x).

Doses of 0.3 mkd (oral, given during one or more cycles before pregnancy and through GD30 or GD80) had no teratogenic effects. NOAEL = 0.3 mkd (HDM 1.4x)

Segment III/Peri- and postnatal toxicity
Rat
In female rats (doses 0, 3, 10, 30 mg/kg/day, GD 15-GD 20), there was a decrease in maternal body weight gain during pregnancy and increased weight gain during lactation at 30 mg/kg/day. Increased postnatal pup mortality (2x control; Day 0-21) (stat sign) and slightly decreased pup body weight gain (not stat sign) were seen at 30 mg/kg/day. The decrease in pup BW gain latter may have been due to impairment of lactation. There were no developmental or behavioral effects in F1 or F2. NOAEL = 10 mkd (HDM 24x)

The Parlodel label states that no fetotoxic effects were found in offspring of dams treated during the peri- and postnatal period.

Dominant Lethal Test in male CD-1 mice
CD-1 mice (40 males/group) were treated with single doses of 100, 300 mg/kg. Males were mated with untreated females. Fertility of males was determined by successful mating frequency, and by pre- or post-implantation losses in females mates.
There was no effect on male fertility. Pre- or post-implantation losses were not affected as indicated by number of total implants/pregnant female. Sponsor concluded that there was no effect of bromocriptine on the male germ cells of CD-1 mouse under the test conditions.

Total Reproductive Capacity Test in Female Mice
Female mice were treated orally with a single dose of 350 mg/kg before mating with untreated males. Reproductive performance was monitored for 1 year.
The treatment had no effect on female fertility during the 1-year test period. Conclusion by Sponsor is that there was no fertility-reducing effect of bromocriptine on female germ cells under the test conditions.

Reprotoxicity Summary
- Reduction in offspring viability in male rat fertility study
- Decrease in implantation and increase in resorptions in pregnant rats in absence of maternal toxicity, possibly related to a rat-specific pharmacologic effect
- Low incidence of fetal abnormalities in pregnant YS and NZ rabbits at maternally toxic doses
- No obvious treatment-related fetal abnormalities in rabbits at doses up to 140-fold human dose (mg/m2 basis).

- Postnatal pup mortality in pregnant rats dosed in late pregnancy at a maternally toxic dose
- No embryolethality or teratogenicity in monkeys (small number of animals)
- NOAEL levels in most studies at multiples of human dose (mg/m^2 basis)

Evaluation of Pregnancy Category

Upon review of the label submitted for NDA 20-866 in 1998, DMEP requested that Ergoset be labeled as Pregnancy Category C instead of Category B which the sponsor had proposed. This was mainly based on the finding of fetal and pup death in a male rat fertility study. The request was communicated to the sponsor in the approvable letter of October 15, 1999. Parlodel, which was originally approved in 1978, is assigned a Pregnancy Category B. Category C communicates an unknown risk to the fetus based on positive animal data, while Category B indicates a low risk based on a lack of animal findings or animal findings in combination with safety shown in well controlled human studies.

Pregnancy Category B

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies which have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

Pregnancy Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

In the submission of April 13, 2008, sponsor (Veroscience), sponsor argued that animal and human data on bromocriptine during pregnancy support a Category B. Sponsor noted that the same animal studies regarding fertility and pregnancy are referenced in the Cycloset label as in the Parlodel label which has a Pregnancy category B. As requested in the AE letter, the finding of fetal/pup death, which is also included in the Parlodel package insert, was included in the Cycloset label. Sponsor also included in the label information on human pregnancy outcomes part of which is also mentioned in the Parlodel label. The human data are observational data rather than data from placebo-controlled studies. Incidence of birth defects in 1109 live births from patients receiving bromocriptine during pregnancy (mainly in first 8 weeks) is 3.3%. This falls within the range in the population at large of 2-4.5%. The clinical data do not indicate bromocriptine causes birth defects. Data on paternity of men on bromocriptine therapy were not included in the label. A case report of paternity with normal offspring upon bromocriptine therapy has been published in the literature (Seigel and Federman, NEJM 311, 859, 1984).

In reprotoxicity studies with bromocriptine there were some adverse animal findings while human studies did not show adverse effects. However, human studies were not well controlled. This would warrant a Category B or C according to US regulatory guidelines and a Category B1 or B3 according to Australian regulatory guidelines. Category B was

originally introduced in the Parlodel label probably because the reviewer of NDA 17-962 (April 21, 1977) concluded that dose levels that were above clinical dosage had no teratogenic effects in animals.

Conclusion

Reviewer concludes that a category B is acceptable because animal data indicate a low risk to the fetus (NOAELs at multiples of human dose) and there has been no indication of fetal harm in human observational studies.

APPEARS THIS WAY
ON ORIGINAL

IMPURITIES

The original sponsor's (Ergoscience) drug substance for Ergoset tablets was manufactured by [redacted] and contained two impurities, Compounds A and B at [redacted] These two compounds tested negative for genotoxicity. The nature of the compounds is not clear [redacted] b(4)

[redacted] b(4)

Formulations of bromocriptine tested in toxicity studies and submitted to the Parlodel NDA 17-962 (1977) were not documented.

In the review of NDA 20-866 (1998) it was recommended that sponsor conduct a bridging toxicity study, e.g., a 3-month toxicity study in rats with a formulation containing these two impurities. However, this recommendation was later considered not necessary because bromocrypine mesylate products with USP specifications limits up to 5% of total product related substances and 1% of individual related substances have been marketed for a considerable amount of time and holding the sponsor to other standards was not considered appropriate.

Drug substance and product specifications for Cycloset (April 13 2008 submission) are shown below. Compounds A and B are not included in the Cycloset drug substance specifications.

Drug Substance

Table S-1. Patheon' Specifications for Bromocriptine Mesylate

Test	*Method* [a]	*Acceptance Criterion*
Description	70015051	White to off-white crystalline powder.
Identification A (IR)	USP <197M>	IR absorption spectrum matches standard.
Identification B (UV)	USP <197U>	UV absorption spectrum matches standard.
Color of solution	USP <631>	The solution is clear and not darker in color than matching solutions A, B, and C.
Loss on drying	USP <891>	NMT [redacted]
Heavy metals	USP <231>, Method II	NMT [redacted]
Residue on ignition	USP <281>	NMT [redacted]
Specific rotation	USP <781S>	[redacted]
Limit of methanesulfonic acid content	USP	[redacted]
Assay (titrimetric)	USP	[redacted] (dried basis)
Assay (HPLC)	[redacted]	[redacted]
Chromatographic Purity	USP/[redacted]	[redacted]
Bromocriptinine[b]		[redacted]
Each individual impurity		NMT [redacted]
Total Impurities		NMT [redacted]
Residual Solvents	C837500	
[redacted]		NMT [redacted]
[redacted]		NMT [redacted]
[redacted]		NMT [redacted]
[redacted]		NMT [redacted]
Organic volatile Impurities	USP <467>	Meet requirements

b(4)

b(4)

b(4)

[a] Patheon has developed and validated method number [redacted] using HPLC techniques which are based on the USP test for chromatographic purities. A specification of [redacted] is used for this assay method. Patheon has developed validated method number [redacted] for the determination of chromatographic purity. Residual Solvents are determined by Patheon developed and validated method number [redacted] Each of the four specified class 2 and class 3 solvents meet the established limits specified by USP.

[b] Bromocriptinine is the main degradation product of bromocriptine, and its degradation pathway, epimerization at C-8, is well established.

Drug Product Specification(s)

From CMC review (X. Ysern, 2008)

The proposed specifications for Cycloset™ 0.8 mg tablets include testing for appearance, identification (two orthogonal methods), assay, purity, dosage uniformity and dissolution. Specifications' acceptance criteria are given in Table P.5-1. The acceptance criterion for the content of the bromocriptinine impurity (NMT ——— differs from that of USP Bromocriptine Mesylate Tablets (NMT 3.0 %). For clarity, the specifications of Bromocriptine mesylate tablet USP are shown in Table P.5-2.

Table P.5-1. Bromocriptine Mesylate 0.8 mg Tablets Specifications

Test	*Method*	*Specification*
Description/ appearance	P14100	White round shaped tablet (flat faced beveled edge) with one side debossed "C" and the other debossed "9".
Identification (UV)	836500	The sample solution UV absorption spectrum matches the standard
Identification (HPLC)	836400 [a]	The retention time of the main peak in the sample solution chromatogram must match to that of the standard solution chromatogram
Assay	836400 [a]	——— [Bromocriptine] ——— b(4)
Related Compounds	836400 [a]	Bromocriptinine [c] ———
		Other Individuals ———
		Sum related substances —— %
Dosage Uniformity	836600	Meets USP <905> requirements b(4)
Dissolution	836700 [b]	——— (Q) in 30 minutes (USP <711>)

[a] Reverse phase HPLC system (column ——— mobile phase: phosphate buffer (0.1 M, pH

b(4)

[b] Meets USP *Dissolution Test 2*. The conditions of the *dissolution test 2* are: Medium, 0.1 N HCl at 37 °C, volume 500 ml. USP Apparatus 2 (paddles), 50 rpm.

[c] The chemical structure of Bromocriptinine (C8 epimer of bromocriptine) is shown in Figure P.5.1-1.

b(4)

Figure P.5-1. Relationship between bromocriptine and bromocriptinine.

Table P.5-2. Bromocriptine Mesylate Tablets USP Specifications

Test	*Method*	*Specification*
Identification	TLC	R_f value correspondence
Dissolution[a]	<711>	≥ 80 % (Q) in 60 minutes
Uniformity of Dosage Units	<905>	Current USP 23
Related Compounds	TLC	Maximum Individual ——— b(4)
		Other Individuals ———
		Sum related substances ≤ 5.0 %
Assay	HPLC	——— [Bromocriptine] ———

* The conditions of the USP *dissolution test 1* are: Medium, 0.1 N HCl at 37 °C, volume 500 ml. USP Apparatus I (baskets), 120 rpm.

Qualification thresholds

The qualification threshold for impurities in a new drug substance is 0.15% (dose <2 g/day). The qualification threshold for related substances (degradants) in a new drug product is 1% (dose <10 mg/day) (ICH Guidances Q3A and Q3B).

Drug substance .

The threshold of 0.15% for impurities in the drug substance used for Cycloset is exceeded for bromocriptinine (NMT ——). Qualification of this impurity is not a significant issue since the Cycloset and Parlodel marketed products indicate higher limits (NMT —— and NMT —— for this related substance (see below). b(4)

Drug product

Drug product specifications comply with the USP monograph for Bromocriptine Mesylate Tables with the—— b(4)

Bromocriptinine is the epimer of bromocriptine at C-8 and the main degradation product of bromocriptine. The specification for bromocriptinine is NMT—— instead of NMT 3.0 % by USP. Other individual substances are specified at NMT —— and sum of related substances at NMT —— USP specifications for marketed product list bromocriptinine at NMT 3%, individual substances NMT—— and sum related substances NMT ——. The NMT—— limit for bromocriptine in Cycloset tablets was proposed using the more specific HPLC methodology—— the maximum dose of bromocriptinine would be—— b(4)

Sponsor noted that the qualification threshold for bromocriptinine is exceeded (>1%). Sponsor argues that qualification is not needed since two previously approved bromocriptine mesylate products (Parlodel oral tablets and caplets) have been in world-wide clinical use for approximately 30 years —— person years of exposure to drug) and there is a long history of safety with these products. Parlodel 2.5mg tablets and 5mg capsules are for chronic use in the treatment of Parkinson's disease and acromegaly and the recommended dosages are 20-30 mg/day with a maximum dose not to exceed 100 mg/day. A specification of 3% for bromocriptinine translates to ca. 750 ug/day for the dose range of 20-30 mg/day and 3000 ug/day for the dose of 100 mg/day. This is 3-12 times more than the maximum administered amount at the 4.8 mg daily dose of Cycloset with the NMT —— impurity limit. b(4) b(4)

Conclusion

Reviewer concludes that qualification of bromocriptinine in nonclinical studies to support the specification of NMT—— in the drug product is not needed. ICH guidances Q3A and Q3B are applicable to new drug substances and new drug products not previously registered for marketing (Q3A p.1, Q3B p.1). As pointed out by sponsor, approved bromocriptine mesylate products with a limit of NMT 3% for other indications at —— higher doses (up to —— mg/day) than the dose proposed in the current NDA amendment (≤ 4.8 mg) have been on the market for a considerable amount of time. Thus, Reviewer believes that qualification of bromocriptinine in nonclinical safety studies is not needed b(4)

as such studies are unlikely to provide useful additional information. Bromocriptinine has essentially been qualified by clinical use.

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NDA 20,866
Ergoset™ (Bromocriptine mesylate)

PHARMACOLOGY AND TOXICOLOGY REVIEW

SUMMARY AND EVALUATION

ADVISORY COMMITTEE REPORT

SUMMARY AND EVALUATION

Pharmacology

Bromocriptine inhibits prolactin secretion and lactation in various species. It is a strong emetic in dogs, and has an effect on various dopaminergic as well as non-dopaminergic pathways in the rodent CNS. It can cause a decrease in blood pressure and heart rate in various species. It can interact in an inhibitory manner with various neurotransmitter or hormone receptor-mediated events, and can interfere with the release of several pituitary hormones. However, it is not a uterine stimulant in the rabbit. It affects ovarian, testicular and adrenal steroidogenesis in the rat. The effect of bromocriptine on glycemic control may be mediated by activation of central dopaminergic pathways involved in the diurnal control of prolactin release and regulation of carbohydrate and lipid metabolism.

ADME

Rat, Monkey

In the rat, absorption of oral dose is rapid, and amounts to 30-40% of dose. Thus, 60-70% of dose is not absorbed and excreted in feces.

Absolute bioavailability of radioactive dose is 40%. Absolute bioavailability of parent drug is ca. 6%, and has large variability among animals. Thus, of the absorbed drug, 80-85% is first-pass metabolized.

Biotransformation takes place for a large part (100%>x>50-60%) in the liver.

Tissue distribution studies after radioactive oral dose show high levels of activity in liver and bile, in both rat and monkey.

In rats, most tissue radioactivity is removed within 24h. Data from Study 1 suggest slower elimination from brain then from other tissues.

Major route of elimination is biliary (fecal), and minor route is renal.

Plasma elimination half-life of unchanged drug is 1-2 h in rat, in monkey unknown. In rat, accumulation of parent is therefore unlikely.

Blood elimination half-life of radioactivity is up to 2 days in rat, and several days in monkey. This indicates possible accumulation of metabolites.

Metabolites in rat have been identified and are mostly proline-oxidated forms and their glucuronide conjugates of the uncleaved molecule.

Because of the uncertainty in AUC/exposure in animals vs. humans, expression of animal doses in terms of human dose multiples for the toxicity studies will be based on surface area comparison.

Toxicology

General Toxicity

Rat, Monkey, Dog

Species	#/sex/dose group	Duration	Route	Dose (mg/kg/day)	Human dose multiple (mg/m^2 basis)
Rat	5	4 weeks	oral (diet)	0, 10, 30, 100	0, 24, 72, 240
Rat	15	13 weeks	oral (diet, micronized)	0, 19	0, 46
Rat	15	53 weeks	oral (diet)	0, 5, 20, 82	0, 12, 48, 197
Monkey	2	13 weeks	oral (suspension)	0, 2, 8, 32	0, 9.5, 38, 152
Dog	1	4 weeks	oral (gelatin capsules)	0, 1, 4, 16	0, 7.1, 29, 114
Dog	3	62 weeks	oral (diet)	0, 1, 3, 10	0, 7.1, 21, 71

Rat: In the 4-week rat study, NOAEL was 10 mkd, disregarding body weight effect. At doses of 30 and 100 mkd toxicities were excitability, hair loss, diuresis, erection, and impaired spermiogenesis.
In the 13-weeks study with 19 mkd, most changes were similar to the ones seen in the 53-week study with 20 mkd.
In the 53-week study, NOAEL was <5mkd. At all doses, there were sex-dependent effects on body weight and food consumption in males and females. At 20 and 82 mkd, excitability and convulsions, and cardiovascular effects were seen. At all doses, there were adrenal and pituitary weight changes and ovario-uterine effects in females, and improvement of nephropathy in males. Morphological changes at 20 and 82 mkd were reversed in 5 weeks.
Dog:
NOAEL in the dog was <1mkd for both 4- and 62-week studies. Early toxicity in both 4-week and 62-week study at at all doses included emesis and excessive salivation, sedation, mydriasis (dilation of pupil), prolapse of nictitating membrane, and ECG changes. In the 4-week study there were thymus, liver and kidney abnormalities at 1, 4 and 16 mkd. In the 62-weeks study, there was alopecia, thyroid hyperactivity, melanosis of sexual skin, ear margin necrosis, and ovarian changes at 1, 3, and 10 mkd. Anterior pituitary, liver, stomach and adrenal abnormalities were seen at 10 mkd. Histopathology findings at 3 and 10 mkd were generally reversible within 8 weeks.
Monkey:
NOAEL in the monkey was <2 mkd for the 13-week study. Excitability and weight loss was seen at all doses. Anemia was seen at 32 mkd. Spleen, prostate and testis weight were decreased at 8 and 32 mkd. Pituitary cysts occurred at 32 mkd.

Carcinogenicity

Rat, Mouse

Species	#/sex/dose group	Duration	Route	Dose (mg/kg/day)	Human dose multiple (mg/m²)
Rat	50	100 weeks	oral (diet)	0, 1.8, 9.9, 44.5	0, 4.3, 24, 106
Mouse	50	74 weeks	oral (diet)	0, 2, 10, 50	0, 2.9, 14, 71

Rat

In the 100-week study in rats, findings at all doses included decrease of body weight, excitability, decrease of plasma cholesterol and triglyceride and increased urinary cations. Incidence of nephropathy and polyateritis nodosa was reduced dose-dependently. In all female dose groups there was a similar, markedly increased incidence of endometrial inflammatory and plastic changes and reduced luteal tissue.

Tumor findings included a dose-dependent increase in incidence of malignant uterine tumors (0,2,7,9). However, incidences of adrenal tumors in males, and of pituitary and mammary tumors in females were clearly and dose-dependently reduced.

The increased uterine tumor incidence occurred at 3.6, 20 and 90 times the human dose multiple, on basis of surface area.

The rat endometrial changes and uterine tumors are thought to be the result of bromocriptine-induced inhibition of prolactin-stimulated progesterone secretion from the corpus luteum in the aging rat, leading to prolonged estrogen dominance and endometrial stimulation. The absence of prolactin control of the corpus luteum in humans makes clinical relevance of this tumor finding unlikely.

Mouse

In the 74-week study in mice, findings at 10 and 50 mkd included decrease of body weight, piloerection, excitability and decreased leukocytes.

Tumor incidences were unaffected in lung, lymphoreticular, liver, uterine, vaginal or other sites.

Reproductive Toxicity

Mouse, Rat, Rabbit, Monkey

Species	Duration	Route	Study Type	Dose (mg/kg/day)	Human dose multiple (mg/m²)
Rat	d14 ao-GD13/LD21	oral (gavage)	fertility (f)	0, 1, 3	0, 2.4, 7.2
Rat	d70 ao-GD13	oral (gavage)	fertility (m)	0, 2, 10, 50	0, 4.8, 24, 120
Rat	GD6-GD15; or single 10 mk dose GD8	oral (gavage)	teratology	0, 3, 10, 30; 10	0, 7.2, 24, 72; 24
Rat	GD6-GD15, GD8-GD15	oral (gavage)	teratology	0, 3, 10, 30	0, 7.2, 24, 72
Rat	GD15-GD20	oral (gavage)	peri- and postnatal	0, 3, 10, 30	0, 7.2, 24, 72

Rat	GD5,6,7,8,9,or 10; GD10-GD15	s.c. single; multiple	reprotoxicity	0, 2; 0, 50, 100	0, 4.8; 0, 120, 240
Rabbit (YS)	GD6-GD18	oral (gavage)	teratology	0, 3, 10, 30, 100; 300, 1000	0, 14, 48, 140, 480; 1400, 4800
Rabbit (YS and NZW)	GD6-GD18	oral (gavage)	teratology	0, 100, 300	0, 480, 1400
Rabbit (YS and NZW)	GD1-GD6	oral (gavage)	preimplantation	0, 100, 300	0, 480, 1400
Monkey	GD20/24-GD39	oral (gelatin capsule)	teratology	2	0, 10
Monkey	up to GD30/GD80	oral	reprotoxicity	0, 0.3	0, 1.4
Mouse	single dose (ac)	oral	reproductive capacity	350	500

Fertility

Rat

In the female rat, there was no effect on fertility at 1-3 mkd. In the male rat, fertility was unaffected at 2-50 mkd. However, dams mated with 50 mkd males had increased pre-, peri- and postnatal mortality.

Monkey

Fertility in monkeys was not affected at 0.3 mkd.

Teratology

Rat

In the female rat implantation was inhibited at 10 mkd (single dose GD5) and 30 mkd (GD6-15). Fused sternebrae were seen at 10 mkd (single dose GD5). In a second study in female rats implantation was inhibited at 10 and 30 mkd (GD6-15). No embryolethal or teratogenic effects were reported in the submission. However, review of NDA 17,962 and the label for Parlodel™ mention increased prenatal mortality (resorption) at 10 mkd (GD6-15) and 30 mkd (GD8-15). Also, NDA review mentions fetal ossification delay at doses ≥3 mkd, and label mentions aplasia of vertebrae and ribs at 30 mkd (GD8-15). Rats dosed with a single 2 mkd sc dose on GD5, 6, 7, or 8 had abortions and reduced numbers of implantations. Multiple 50 or 100 mkd s.c. doses on GD10-15 had no effect on implantation, fetal viability, postimplantation loss or fetal weight. Teratogenicity was not documented.

Rabbit

In female Yellow Silver rabbits, maternal toxicity, prenatal mortality and increased incidences of fetal abnormalities were seen at doses ≥30 mkd (GD6-18). Cleft palate was

observed in 1 control fetus and in 3 fetuses at 100 mkd. In another study with the same breed of rabbits cleft palate was also seen at 100 mkd (GD6-18). In New Zealand white rabbits cleft palate did not occur at these doses. Treatment of New Zealand white rabbits, but not of Yellow Silver rabbits, with 300 mkd (GD 1-6) caused embryolethality and maternal toxicity.

Monkey

No mortality or teratogenicity was observed in monkeys at 2 mkd (GD 20-39). Doses of 0.3 mkd (one or more cycles) also did not cause teratogenic effects.

Peri- and postnatal events

Rat

In the female rat, increased pre-, peri- and postnatal mortality was seen at 30 mkd (GD15-delivery).

Genotoxicity

In Vitro Assays

Bromocriptine tested negative in the Ames bacterial mutation assay with ot without metabolic activation. Compound A and B, two impurities in the Ergoset™ drug substance at ———— concentrations, respectively, did not have mutagenic activity in the mouse lymphoma assay with or without metabolic activation. b(4)

In Vivo Assays

Bromocriptine was not mutagenic in the bone marrow micronucleus test in CD-1 mice and Chinese hamsters, or in a bone marrow chromosomal aberration test in Chinese hamsters. Negative results from the dominant lethal test in male CD-1 mice indicated that bromocriptine had no effect on male germ cells of CD-1 mice. Bromocriptine also tested negative in a reproductive capacity test in female mice, indicating no effect on female germ cells.

Conclusions

Pharmacology studies have shown that bromocriptine can affect dopaminergic as well as non-dopaminergic pathways. Interference with a central dopaminergically controlled diurnal pattern of prolactin action and body metabolism may explain the effect of the compound on glycemic control and lipogenesis.

ADME studies in rat and monkey indicated moderate but rapid absorption, high first-pass metabolism by the liver, distribution to various tissues, and primarily biliary ie fecal excretion of mainly metabolites. Elimination of metabolites is slower than of parent drug. The effect of the metabolites are unknown.

General toxicity studies in the rat showed that the main effects (CNS and cardiovascular effects, hair loss, diuresis, endocrine effects) were seen at doses ≥20 mkd (48x the human dose multiple based on body surface area, HDM). Endocrine effects in females on adrenal, pituitary and ovary-uterus occurred at doses ≥5 mkd (12x HDM).
In the dog various CNS toxicities were evident at doses ≥1mkd (7x HDM). Histological changes in thymus, liver, kidney, sexual skin, ears, and ovaries were seen at doses of 1-16 mkd (7-114x HDM). Pituitary, stomach and adrenal abnormalities were seen at 10 mkd

(71x HDM). In the monkey, CNS effects occurred at ≥2mkd (9.5x HDM), organ weight changes at ≥8 mkd (38x HDM), and pituitary lesions at 32 mkd (152x HDM).

Carcinogenicity studies in rat and mouse, except for the rat malignant uterine tumors at doses ≥ 1.8 mkd (4.3x HDM), were negative. However, the uterine tumors in the rat were probably caused by the inhibition of bromocriptine of prolactin-induced activation of the corpus luteum, resulting in prolonged estrogen dominance in the aging rat. This is unlikely to occur in humans since the corpus luteum is not under the influence of bromocriptine.

Reproductive toxicity studies in the rat indicated reduced viability of the offspring of male rats treated with 50 mkd (120x HDM). Implantation was inhibited upon dosing at GD6-15 at 10,30 mkd (24,72x HDM), and skeletal abnormalities were observed at ≥3 mkd (7.2 x HDM), and upon single dosing on GD5 at 10 mkd (24x HDM). Prenatal mortality was increased at 10 mkd (GD6-15) and 30 mkd (GD8-15).
In the rabbit, treated on GD6-18, maternal toxicity and prenatal mortality were observed at doses ≥30 mkd (140x HDM). Fetal abnormalities were seen at doses ≥30 mkd , and cleft palate was seen specifically in Yellow Silver rabbits at 100 mkd (480x HDM). In New Zealand white rabbits, treated on GD1-6, maternal toxicity and embryolethality was seen at 300 mkd (1400 x HDM).
In the monkey, 2 mkd (10x HDM) on GD20-39 was not embryotoxic or teratogenic.

Genotoxicity findings were negative.

In conclusion, the general and reproductive animal toxic and/or pharmacologic effects that were observed appeared to occur at fairly to very high multiples (7-1400x) of the intended human dose of 4.8 mg. Experience with the marketed drug (Parlodel) indicates that in humans, the most common side effects are nausea, headache, dizziness, fatigue, and hypotension. Thus, some animal CNS toxicity findings (eg emesis) that occurred at a relatively low HDM (human dose multiple on basis of body surface area) were predictive, but not all toxicities seen in the animals have been observed in man, not even at the marketed multiples of the currently proposed 4.8 mg dose. Animal histopathology changes that occurred at relatively low HDM's (adrenal, pituitary, ovary, liver, kidney) should however be kept in mind when using this drug, since they may be predictive of long-term adverse events.
The positive carcinogenicity findings should be mentioned in the label, but are likely to be irrelevant for the clinical situation. Use of Parlodel during early pregnancy in women has not revealed abortions or birth defects. This is in agreement with the generally high HDM's for positive animal reprotoxicity findings. Nevertheless, since the safety of bromocriptine has not been established in pregnant and postpartum women, and since in these women serious CNS and cardiovascular toxicities have been observed, use of bromocriptine should be avoided during pregnancy and lactation. Taken together, the studies support the safety of bromocriptine at the intended 4.8 mg dose for the proposed indication.

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