CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 78-035

Name: Cabergoline Tablets, 0.5 mg

Sponsor: Cobalt Laboratories, Inc.

Approval Date: April 21, 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-035

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-035

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-035

Cobalt Laboratories, Inc.
Attention: Richard Sanzen, R.Ph.
Director, Regulatory Affairs
24840 S. Tamiami Trail, Suite 1
Bonita Springs, FL 34134

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 8, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Cabergoline Tablets, 0.5 mg.

Reference is also made to your amendments dated August 28, and October 13, 2006; April 25, June 11, August 8, and August 9, 2007; and March 20, April 4, and April 14, 2008.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Cabergoline Tablets, 0.5 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Dostinex® Tablets, 0.5 mg, of Pharmacia and Upjohn Company. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert L. West
4/21/2008 03:13:53 PM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-035

LABELING

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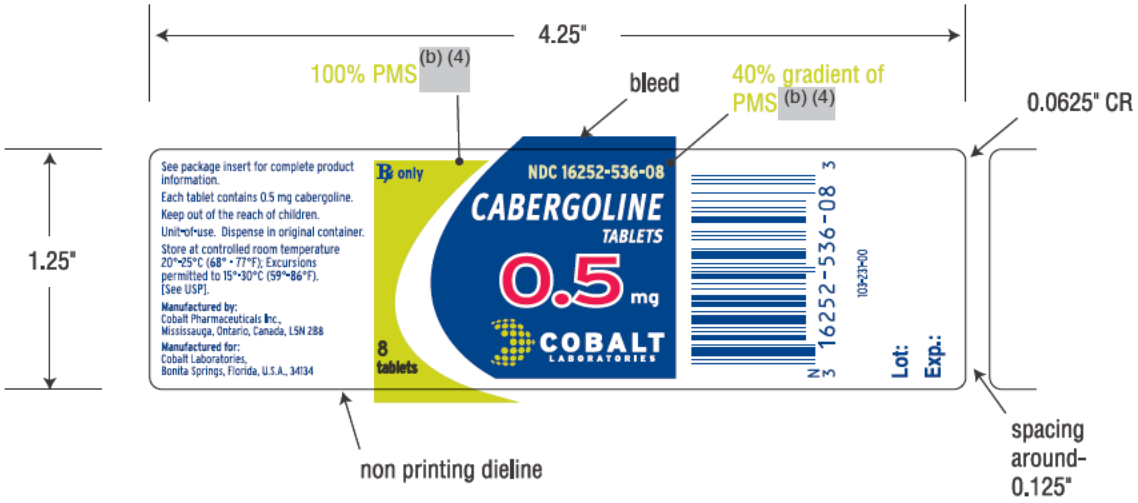

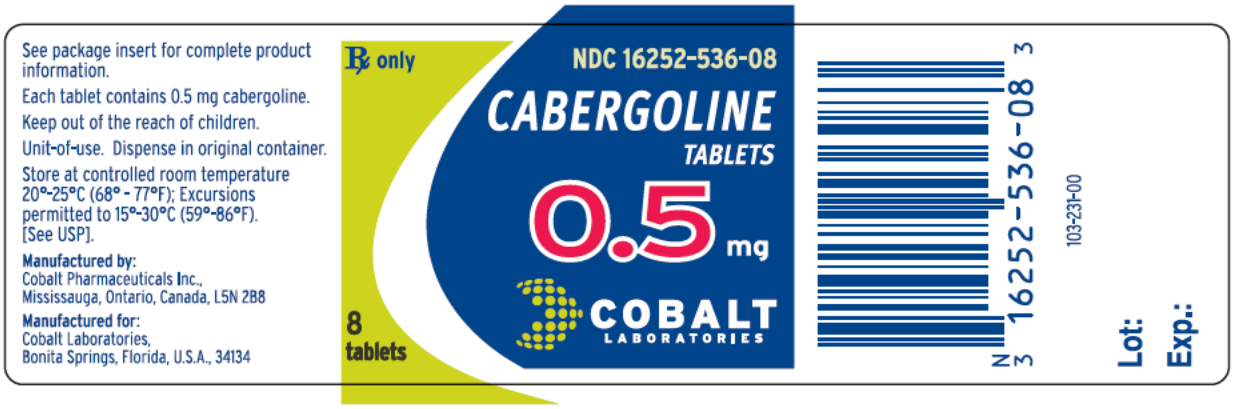

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Revision.5:Sept 11, 2007 Mac Op: (b) (6)
Description: Change "for" to "by": manufactured by Cobalt Canada, arrow on logo (back panel) changed to blue

Revision.4:Sept 11, 2007 Mac Op: (b) (6)
Description: Modify graphics.

Revision.3:Sept 11, 2007 Mac Op:
Description: re-design graphics.

PROOF APPROVAL

(b) (4)

MAC OP: (b) (6)

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773

Cabergoline Tablets

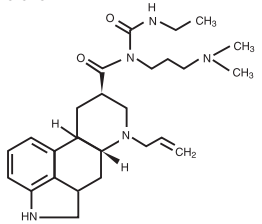
103-773-01

Cabergoline Tablets

Rx Only

DESCRIPTION

Cabergoline Tablets contain cabergoline, a dopamine receptor agonist. The chemical name for cabergoline is 1-[(6-allylergolin-8ß-yl)-carbonyl]-1-[3-(dimethylamino)propyl]- 3-ethylurea. Its empirical formula is $C_{26}H_{37}N_5O_2$, and its molecular weight is 451.62. The structural formula is as follows:



Cabergoline is a white powder soluble in ethyl alcohol, chloroform, and N, N-dimethylformamide (DMF); slightly soluble in 0.1N hydrochloric acid; very slightly soluble in n-hexane; and insoluble in water.

Cabergoline Tablets, for oral administration, contain 0.5 mg of cabergoline. Inactive ingredients consist of leucine, USP, and lactose monohydrate, NF.

CLINICAL PHARMACOLOGY

Mechanism of Action: The secretion of prolactin by the anterior pituitary is mainly under hypothalamic inhibitory control, likely exerted through release of dopamine by tuberoinfundibular neurons. Cabergoline is a long-acting dopamine receptor agonist with a high affinity for D_2 receptors. Results of in vitro studies demonstrate that cabergoline exerts a direct inhibitory effect on the secretion of prolactin by rat pituitary lactotrophs. Cabergoline decreased serum prolactin levels in reserpinized rats. Receptor-binding studies indicate that cabergoline has low affinity for dopamine D_1, α_1- and α_2-adrenergic, and 5-HT_1- and 5-HT_2-serotonin receptors.

Clinical Studies: The prolactin-lowering efficacy of cabergoline was demonstrated in hyperprolactinemic women in two randomized, double-blind, comparative studies, one with placebo and the other with bromocriptine. In the placebo-controlled study (placebo n=20; cabergoline n=168), cabergoline produced a dose-related decrease in serum prolactin levels with prolactin normalized after 4 weeks of treatment in 29%, 76%, 74% and 95% of the patients receiving 0.125, 0.5, 0.75, and 1.0 mg twice weekly respectively.

In the 8-week, double-blind period of the comparative trial with bromocriptine (cabergoline n=223; bromocriptine n=236 in the intent-to-treat analysis), prolactin was normalized in 77% of the patients treated with cabergoline at 0.5 mg twice weekly compared with 59% of those treated with bromocriptine at 2.5 mg twice daily. Restoration of menses occurred in 77% of the women treated with cabergoline, compared with 70% of those treated with bromocriptine. Among patients with galactorrhea, this symptom disappeared in 73% of those treated with cabergoline compared with 56% of those treated with bromocriptine.

Pharmacokinetics

Absorption: Following single oral doses of 0.5 mg to 1.5 mg given to 12 healthy adult volunteers, mean peak plasma levels of 30 to 70 picograms (pg)/mL of cabergoline were observed within 2 to 3 hours. Over the 0.5-to-7 mg dose range, cabergoline plasma levels appeared to be dose-proportional in 12 healthy adult volunteers and nine adult parkinsonian patients. A repeat-dose study in 12 healthy volunteers suggests that steady-state levels following a once-weekly dosing schedule are expected to be twofold to threefold higher than after a single dose. The absolute bioavailability of cabergoline is unknown. A significant fraction of the administered dose undergoes a first-pass effect. The elimination half-life of cabergoline estimated from urinary data of 12 healthy subjects ranged between 63 to 69 hours. The prolonged prolactin-lowering effect of cabergoline may be related to its slow elimination and long half-life.

Distribution: In animals, based on total radioactivity, cabergoline (and/or its metabolites) has shown extensive tissue distribution. Radioactivity in the pituitary exceeded that in plasma by >100-fold and was eliminated with a half-life of approximately 60 hours. This finding is consistent with the long-lasting prolactin-lowering effect of the drug. Whole body autoradiography studies in pregnant rats showed no fetal uptake but high levels in the uterine wall. Significant radioactivity (parent plus metabolites) detected in the milk of lactating rats suggests a potential for exposure to nursing infants. The drug is extensively distributed throughout the body. Cabergoline is moderately bound (40% to 42%) to human plasma proteins in a concentration-independent manner. Concomitant dosing of highly protein-bound drugs is unlikely to affect its disposition.

Metabolism: In both animals and humans, cabergoline is extensively metabolized, predominately via hydrolysis of the acylurea bond or the urea moiety. Cytochrome P-450 mediated metabolism appears to be minimal. Cabergoline does not cause enzyme induction and/or inhibition in the rat. Hydrolysis of the acylurea or urea moiety abolishes the prolactin-lowering effect of cabergoline, and major metabolites identified thus far do not contribute to the therapeutic effect.

Excretion: After oral dosing of radioactive cabergoline to five healthy volunteers, approximately 22% and 60% of the dose was excreted within 20 days in the urine and feces, respectively. Less than 4% of the dose was excreted unchanged in the urine. Nonrenal and renal clearances for cabergoline are about 3.2 L/min and 0.08 L/min, respectively. Urinary excretion in hyperprolactinemic patients was similar.

Special Populations

Renal Insufficiency: The pharmacokinetics of cabergoline were not altered in 12 patients with moderate-to-severe renal insufficiency as assessed by creatinine clearance.

Hepatic Insufficiency: In 12 patients with mild-to-moderate hepatic dysfunction (Child-Pugh score ≤10), no effect on mean cabergoline C_{max} or area under the plasma concentration curve (AUC) was observed. However, patients with severe insufficiency (Child-Pugh score >10) show a substantial increase in the mean cabergoline C_{max} and AUC, and thus necessitate caution.

Elderly: Effect of age on the pharmacokinetics of cabergoline has not been studied.

Food-Drug Interaction

In 12 healthy adult volunteers, food did not alter cabergoline kinetics.

Pharmacodynamics

Dose response with inhibition of plasma prolactin, onset of maximal effect, and duration of effect has been documented following single cabergoline doses to healthy volunteers (0.05 to 1.5 mg) and hyperprolactinemic patients (0.3 to 1 mg). In volunteers, prolactin inhibition was evident at doses >0.2 mg, while doses ≥0.5 mg caused maximal suppression in most subjects. Higher doses produce prolactin suppression in a greater proportion of subjects and with an earlier onset and longer duration of action. In 12 healthy volunteers, 0.5, 1, and 1.5 mg doses resulted in complete prolactin inhibition, with a maximum effect within 3 hours in 92% to 100% of subjects after the 1 and 1.5 mg doses compared with 50% of subjects after the 0.5 mg dose.

In hyperprolactinemic patients (N=51), the maximal prolactin decrease after a 0.6 mg single dose of cabergoline was comparable to 2.5 mg bromocriptine; however, the duration of effect was markedly longer (14 days vs. 24 hours). The time to maximal effect was shorter for bromocriptine than cabergoline (6 hours vs. 48 hours).

In 72 healthy volunteers, single or multiple doses (up to 2 mg) of cabergoline resulted in selective inhibition of prolactin with no apparent effect on other anterior pituitary hormones (GH, FSH, LH, ACTH, and TSH) or cortisol.

INDICATIONS AND USAGE

Cabergoline tablets are indicated for the treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas.

CONTRAINDICATIONS

Cabergoline tablets are contraindicated in patients with

- Uncontrolled hypertension or known hypersensitivity to ergot derivatives.
- History of pulmonary, pericardial, cardiac valvular, or retroperitoneal fibrotic disorders. (See **PRECAUTIONS, Fibrosis**).

WARNINGS

Valvulopathy: Post marketing cases of cardiac valvulopathy have been reported in patients receiving carbergoline. These cases have generally occurred during long-term administration of high doses of cabergoline (>2 mg/day) used for the treatment of Parkinson's disease. Rare cases have been reported associated with short-term treatment (<6 months) or in patients receiving lower doses for the treatment of hyperprolactinemia.

Physicians should use the lowest effective dose of cabergoline for the treatment of hyperprolactinemia and should periodically reassess the need for continuing therapy with cabergoline. In addition, patients receiving long term treatment with cabergoline should undergo periodic reassessment of their cardiac status, and echocardiography should be considered. Any patient who develops signs or symptoms of cardiac disease, including dyspnea, edema, congestive heart failure, or a new cardiac murmur, while being treated with cabergoline should be evaluated for possible valvulopathy.

Cabergoline should be used with caution in patients who have hemodynamically significant valvular disease or have been exposed to other medications associated with valvulopathy.

Pregnancy: Dopamine agonists in general should not be used in patients with pregnancy-induced hypertension, for example, preeclampsia, eclampsia, and post partum hypertension, unless the potential benefit is judged to outweigh the possible risk.

PRECAUTIONS

General: Initial doses higher than 1.0 mg may produce orthostatic hypotension. Care should be exercised when administering cabergoline with other medications known to lower blood pressure.

Postpartum Lactation Inhibition or Suppression: Cabergoline is not indicated for the inhibition or suppression of physiologic lactation. Use of bromocriptine, another dopamine agonist for this purpose, has been associated with cases of hypertension, stroke, and seizures.

Hepatic Impairment: Since cabergoline is extensively metabolized by the liver, caution should be used, and careful monitoring exercised, when administering cabergoline to patients with hepatic impairment.

Fibrosis: As with other ergot derivatives, pleural effusion or pulmonary fibrosis have been reported following long-term administration of cabergoline. Some reports were in patients previously treated with ergotinic dopamine agonists. Cabergoline should not be used in patients with a history of, or current signs and/or clinical symptoms of, respiratory or cardiac disorders linked to fibrotic tissue.

Following diagnosis of pleural effusion or pulmonary fibrosis, the discontinuance of cabergoline has been reported to result in improvement of signs and symptoms.

Erythrocyte sedimentation rate (ESR) has been found to be abnormally increased in association with pleural effusion/fibrosis. Chest x-ray examination is recommended in cases of unexplained ESR increases to abnormal values. Serum creatinine measurements can also be used to help in the diagnosis of fibrotic disorder.

Psychiatric: Pathological gambling, increased libido, and hypersexuality have been reported in patients treated with dopamine agonists including cabergoline. This has been generally reversible upon reduction of the dose or treatment discontinuation (See **Post-marketing Surveillance data**).

Information for Patients: Patients should be instructed to notify their physician if they suspect they are pregnant, become pregnant, or intend to become pregnant during therapy. A pregnancy test should be done if there is any suspicion of pregnancy and continuation of treatment should be discussed with their physician.

Patients should notify their physician if they develop shortness of breath, persistent cough, difficulty with breathing when lying down, or swelling in their extremities.

Drug Interactions: Cabergoline should not be administered concurrently with D_2-antagonists, such as phenothiazines, butyrophenones, thioxanthenes, or metoclopramide.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenicity studies were conducted in mice and rats with cabergoline given by gavage at doses up to 0.98 mg/kg/day and 0.32 mg/kg/day, respectively. These doses are 7 times and 4 times the maximum recommended human dose calculated on a body surface area basis using total mg/m^2/week in rodents and mg/m^2/week for a 50 kg human.

There was a slight increase in the incidence of cervical and uterine leiomyomas and uterine leiomyosarcomas in mice. In rats, there was a slight increase in malignant tumors of the cervix and uterus and interstitial cell adenomas. The occurrence of tumors in female rodents may be related to the prolonged suppression of prolactin secretion because prolactin is needed in rodents for the maintenance of the corpus luteum. In the absence of prolactin, the estrogen/progesterone ratio is increased, thereby increasing the risk for uterine tumors. In male rodents, the decrease in serum prolactin levels was associated with an increase in serum luteinizing hormone, which is thought to be a compensatory effect to maintain testicular steroid synthesis. Since these hormonal mechanisms are thought to be species-specific, the relevance of these tumors to humans is not known.

The mutagenic potential of cabergoline was evaluated and found to be negative in a battery of in vitro tests. These tests included the bacterial mutation (Ames) test with *Salmonella typhimurium,* the gene mutation assay with *Schizosaccharomyces pombe* P_1 and V79 Chinese hamster cells, DNA damage and repair in *Saccharomyces cerevisiae* D_4, and chromosomal aberrations in human lymphocytes. Cabergoline was also negative in the bone marrow micronucleus test in the mouse.

In female rats, a daily dose of 0.003 mg/kg for 2 weeks prior to mating and throughout the mating period inhibited conception. This dose represents approximately 1/28 the maximum recommended human dose calculated on a body surface area basis using total mg/m^2/week in rats and mg/m^2/week for a 50 kg human.

Pregnancy: Teratogenic Effects: Category B. Reproduction studies have been performed with cabergoline in mice, rats, and rabbits administered by gavage.

(Multiples of the maximum recommended human dose in this section are calculated on a body surface area basis using total mg/m^2/week for animals and mg/m^2/week for a 50 kg human.)

There were maternotoxic effects but no teratogenic effects in mice given cabergoline at doses up to 8 mg/kg/day (approximately 55 times the maximum recommended human dose) during the period of organogenesis.

A dose of 0.012 mg/kg/day (approximately 1/7 the maximum recommended human dose) during the period of organogenesis in rats caused an increase in post-implantation embryofetal losses. These losses could be due to the prolactin inhibitory properties of cabergoline in rats. At daily doses of 0.5 mg/kg/day (approximately 19 times the maximum recommended human dose) during the period of organogenesis in the rabbit, cabergoline caused maternotoxicity characterized by a loss of body weight and decreased food consumption. Doses of 4 mg/kg/day (approximately 150 times the maximum recommended human dose) during the period of organogenesis in the rabbit caused an increased occurrence of various malformations. However, in another study in rabbits, no treatment-related malformations or embryofetotoxicity were observed at doses up to 8 mg/kg/day (approximately 300 times the maximum recommended human dose).

In rats, doses higher than 0.003 mg/kg/day (approximately 1/28 the maximum recommended human dose) from 6 days before parturition and throughout the lactation period inhibited growth and caused death of offspring due to decreased milk secretion.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cabergoline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Use of cabergoline for the inhibition or suppression of physiologic lactation is not recommended (see **PRECAUTIONS** section).

The prolactin-lowering action of cabergoline suggests that it will interfere with lactation. Due to this interference with lactation, cabergoline should not be given to women postpartum who are breastfeeding or who are planning to breastfeed.

Pediatric Use: Safety and effectiveness of cabergoline in pediatric patients have not been established.

Geriatric Use: Clinical studies of cabergoline did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The safety of cabergoline tablets has been evaluated in more than 900 patients with hyperprolactinemic disorders. Most adverse events were mild or moderate in severity.

In a 4-week, double-blind, placebo-controlled study, treatment consisted of placebo or cabergoline at fixed doses of 0.125, 0.5, 0.75, or 1.0 mg twice weekly. Doses were halved during the first week. Since a possible dose-related effect was observed for nausea only, the four cabergoline treatment groups have been combined. The incidence of the most common adverse events during the placebo-controlled study is presented in the following table.

Incidence of Reported Adverse Events During the 4-Week, Double-Blind, Placebo-Controlled Trial

Adverse Event*	Cabergoline (n=168) 0.125 to 1 mg two times a week	Placebo (n=20)
	Number (percent)	
Gastrointestinal		
Nausea	45 (27)	4 (20)
Constipation	16 (10)	0
Abdominal pain	9 (5)	1 (5)
Dyspepsia	4 (2)	0
Vomiting	4 (2)	0
Central and Peripheral Nervous System		
Headache	43 (26)	5 (25)
Dizziness	25 (15)	1 (5)
Paresthesia	2 (1)	0
Vertigo	2 (1)	0
Body As a Whole		
Asthenia	15 (9)	2 (10)
Fatigue	12 (7)	0
Hot flashes	2 (1)	1 (5)
Psychiatric		
Somnolence	9 (5)	1 (5)
Depression	5 (3)	1 (5)
Nervousness	4 (2)	0
Autonomic Nervous System		
Postural hypotension	6 (4)	0
Reproductive – Female		
Breast pain	2 (1)	0
Dysmenorrhea	2 (1)	0
Vision		
Abnormal vision	2 (1)	0

*Reported at ≥1% for cabergoline

In the 8-week, double-blind period of the comparative trial with bromocriptine, cabergoline (at a dose of 0.5 mg twice weekly) was discontinued because of an adverse event in 4 of 221 patients (2%) while bromocriptine (at a dose of 2.5 mg two times a day) was discontinued in 14 of 231 patients (6%). The most common reasons for discontinuation from cabergoline were headache, nausea and vomiting (3, 2 and 2 patients respectively); the most common reasons for discontinuation from bromocriptine were nausea, vomiting, headache, and dizziness or vertigo (10, 3, 3, and 3 patients respectively). The incidence of the most common adverse events during the double-blind portion of the comparative trial with bromocriptine is presented in the following table.

Incidence of Reported Adverse Events During the 8-Week, Double-Blind Period of the Comparative Trial With Bromocriptine

Adverse Event*	Cabergoline (n=221)	Bromocriptine (n=231)
	Number (percent)	
Gastrointestinal		
Nausea	63 (29)	100 (43)
Constipation	15 (7)	21 (9)
Abdominal pain	12 (5)	19 (8)
Dyspepsia	11 (5)	16 (7)
Vomiting	9 (4)	16 (7)
Dry mouth	5 (2)	2 (1)
Diarrhea	4 (2)	7 (3)
Flatulence	4 (2)	3 (1)
Throat irritation	2 (1)	0
Toothache	2 (1)	0
Central and Peripheral Nervous System		
Headache	58 (26)	62 (27)
Dizziness	38 (17)	42 (18)
Vertigo	9 (4)	10 (4)
Paresthesia	5 (2)	6 (3)
Body As a Whole		
Asthenia	13 (6)	15 (6)
Fatigue	10 (5)	18 (8)
Syncope	3 (1)	3 (1)
Influenza-like symptoms	2 (1)	0
Malaise	2 (1)	0
Periorbital edema	2 (1)	2 (1)
Peripheral edema	2 (1)	1
Psychiatric		
Depression	7 (3)	5 (2)
Somnolence	5 (2)	5 (2)
Anorexia	3 (1)	3 (1)
Anxiety	3 (1)	3 (1)
Insomnia	3 (1)	2 (1)
Impaired concentration	2 (1)	1
Nervousness	2 (1)	5 (2)
Cardiovascular		
Hot flashes	6 (3)	3 (1)
Hypotension	3 (1)	4 (2)
Dependent edema	2 (1)	1
Palpitation	2 (1)	5 (2)
Reproductive – Female		
Breast pain	5 (2)	8 (3)
Dysmenorrhea	2 (1)	1
Skin and Appendages		
Acne	3 (1)	0
Pruritus	2 (1)	1
Musculoskeletal		
Pain	4 (2)	6 (3)
Arthralgia	2 (1)	0
Respiratory		
Rhinitis	2 (1)	9 (4)
Vision		
Abnormal vision	2 (1)	2 (1)

*Reported at ≥1% for cabergoline

Other adverse events that were reported at an incidence of <1.0% in the overall clinical studies follow.

Body As a Whole: facial edema, influenza-like symptoms, malaise
Cardiovascular System: hypotension, syncope, palpitations
Digestive System: dry mouth, flatulence, diarrhea, anorexia
Metabolic and Nutritional System: weight loss, weight gain
Nervous System: somnolence, nervousness, paresthesia, insomnia, anxiety
Respiratory System: nasal stuffiness, epistaxis
Skin and Appendages: acne, pruritus
Special Senses: abnormal vision
Urogenital System: dysmenorrhea, increased libido

The safety of cabergoline has been evaluated in approximately 1,200 patients with Parkinson's disease in controlled and uncontrolled studies at dosages of up to 11.5 mg/day which greatly exceeds the maximum recommended dosage of cabergoline for hyperprolactinemic disorders. In addition to the adverse events that occurred in the patients with hyperprolactinemic disorders, the most common adverse events in patients with Parkinson's disease were dyskinesia, hallucinations, confusion, and peripheral edema. Heart failure, pleural effusion, pulmonary fibrosis, and gastric or duodenal ulcer occurred rarely. One case of constrictive pericarditis has been reported.

Post-marketing Surveillance data: The following events have been reported in association with cabergoline: valvulopathy and fibrosis, (See **WARNINGS, Valvulopathy** and **PRECAUTIONS, Fibrosis**).

Others events have been reported in association with cabergoline: hypersexuality, increased libido, pathological gambling (See **PRECAUTIONS, Psychiatric**). In addition, during post-marketing surveillance, cases of alopecia, aggression and psychotic disorder have been reported in patients taking cabergoline. Some of these reports have been in patients who have had prior adverse reactions to dopamine agonist products.

OVERDOSAGE

Overdosage might be expected to produce nasal congestion, syncope, or hallucinations. Measures to support blood pressure should be taken if necessary.

DOSAGE AND ADMINISTRATION

The recommended dosage of cabergoline tablets for initiation of therapy is 0.25 mg twice a week. Dosage may be increased by 0.25 mg twice weekly up to a dosage of 1 mg twice a week according to the patient's serum prolactin level. Before initiating treatment, cardiovascular evaluation should be performed and echocardiography should be considered to assess for valvular disease.

Dosage increases should not occur more rapidly than every 4 weeks, so that the physician can assess the patient's response to each dosage level. If the patient does not respond adequately, and no additional benefit is observed with higher doses, the lowest dose that achieved maximal response should be used and other therapeutic approaches considered. Patients receiving long term treatment with cabergoline should undergo periodic assessment of their cardiac status and echocardiography should be considered.

After a normal serum prolactin level has been maintained for 6 months, cabergoline may be discontinued, with periodic monitoring of the serum prolactin level to determine whether or when treatment with cabergoline should be reinstituted. The durability of efficacy beyond 24 months of therapy with cabergoline has not been established.

HOW SUPPLIED

Cabergoline Tablets 0.5 mg are white to off-white, capsule shaped, flat-faced, bevel-edged tablets with 'C' breakline '5' on one side and 'Ↄ' partial bisect 'Ↄ' on the other side.

Cabergoline Tablets 0.5 mg are available as follows:

Bottles of 8 tablets NDC 16252-536-08

STORAGE

Store at controlled room temperature 20°-25°C (68°-77°F); Excursions permitted to 15°-30°C (59°-86°F). [See USP].

Manufactured by:
COBALT PHARMACEUTICALS INC.
Mississauga, Ontario L5N 2B8, Canada

Manufactured for:
COBALT LABORATORIES
Cobalt Laboratories Inc.
Bonita Springs, Florida,
U.S.A., 34134

Item Number: 103-773-01
Date: March 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-035

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-035 Dates of Submission: 15 DEC 2005 (original)

Applicant's Name: Cobalt

Established Name: Cabergoline Tablets 0.5 mg

Labeling Deficiencies:

1. **CONTAINER** [redacted]:

   A. The RLD smallest package size a package size of 8 (unit-of-use). We would consider your package size of [redacted] and not a [redacted]. You may provide a package size of 8 as a unit-of-use package. Revise the HOW SUPPLIED section of the insert to delete the [redacted]. Please ensure that the [redacted] package and smaller that you plan to market have child resistant closure.

   B. Place [redacted] to "See package insert…

   C. Revise storage statement as indicated below.

   D. Will you provide a carton to protect the glass bottle from possible breakage? If so please submit the carton for review.

2. **INSERT:**

   A. DESCRIPTION, cite the specific kind of lactose.

   B. HOW SUPPLIED

      a. Delete the package size of [redacted]

      b. Indicate the strength 0.5 mg of the product in the first sentence.

      c. You indicate "…with C breakline 5 on one side…" with the 5 indicate. Your 5 may be interpreted as the strength of the product since it is so close to 0.5 mg the true strength of the product. Please comment on the code for this product and whether you see it as being miss interpreted as a 5 mg strength. I recommend changing the code to include for digits.

      d. Revise the storage statement so that it reads Store at 20-25C (68-77F). See USP controlled room temperature. Excursions permitted to 15 - 30)C (59-86 F).

Please revise your labels and labeling, as instructed above, and submit electronic final printed labels and labeling. The immediate container labels and carton labeling may be submitted either electronically or in hard copy.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL

Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32. Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

The guidance above specify labeling to be submitted in SPL format. To assist in our review, we request that labeling also be submitted in PDF and MS Word format. We refer you to the electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: Providing Regulatory Submissions in Electronic Format – NDAs (January, 1999) and draft guidance providing Regulatory Submissions in Electronic Format – Content of Labeling ((February 2004).

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html or http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the latest approved labeling for the reference listed drug with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	78-035
Date of Submission	
Applicant	Cobalt Pharm
Drug Name	Cabergoline Tablets
Strength(s)	0.5 mg

Container Labels
0.5 mg- (b) (4)
(b) (4)

Ccarton Labeling Requested

Package Insert Labeling

BASIS OF APPROVAL: 20-664

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4526892	12/29/05	none	Novel ergoline derivatives formed by reaction of an 8-carboxy ergoline with a carbodiimide and having hypotensive and antiprolatinic activity.	PIII	Same As

Exclusivity Data For NDA			
Code/sup	**Expiration**	**Description**	***Labeling impact***
NCE	12/23/01	NCE	Same As

Reference Listed Drug

RLD on the 356(h) form	Dostinex
NDA Number	20-664
RLD established name	Cabergoline
Firm	Pharmacia and Upjohn
Currently apprvoved PI	S-004
AP Date	4/17/00

Note: RLD has (b) (4) supplements.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. **USP 24**		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			x
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	x		

NOTE TO THE CHEMIST: We are recommending that the (b) (4)
this package size. The smaller package must have CRC. Applicant has included bulk labels

FOR THE RECORD:

1. MODEL LABELING- Review based on the labeling of Dostinex (Pharmacia & Upjohn, Cabergoline Tablets, NDA 20664/S-004, approved 4/17/00; revised 8/99.

2. PATENTS/EXCLUSIVITIES - See above

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM Cobalt Pharmaceutical, Canada. Dr. James Parker, at Strategic Bioscience Corp. Is the USA.

4. CONTAINER/CLOSURE in 30cc, [redacted] amber glass bottles of **0.5 mg** [redacted] and [redacted] 10122 vol 1.20

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   NDA - CRT 20 - 25C (68 - 77 F)
   ANDA – CRT 20 - 25C (68 - 77 F)
   USP - none

6. DISPENSING STATEMENTS COMPARISON
   NDA – none
   ANDA – request "Unit-of-Use. Dispense in original container"
   USP
7. Scoring:
   NDA - scored
   ANDA -scored
   USP -none

8. PACKAGING CONFIGURATIONS

   Product Line:
   RLD: The **innovator** markets a 0.5 mg tablet (8s)
   ANDA: The **applicant** proposes to market their product **0.5 mg** [redacted] with CRC page 10059-10078 vol 1.3

9. HOW SUPPLIED SECTION
   The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

10. INACTIVE INGREDIENTS
    The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 9868 vol 1.20

Date of Review: 9/5/06 Date of Submission: Dec 12, 2005

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cc:

ANDA: 78-035
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Review

10-3-06

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-035 Dates of Submission: 25 APR 2007

Applicant's Name: Cobalt

Established Name: Cabergoline Tablets 0.5 mg

Labeling Deficiencies: Draft Labels and Labeling

1. CONTAINER (8s):

A. Your previous submission provided for (b) (4) and (b) (4) are these package sizes no longer being proposed. Regarding your bulk package labels- Our labeling division does not review those particular bulk package sizes. Please comment.

B. Will you provide a carton to protect the glass bottle from possible breakage? If so please submit the carton for review.

2. INSERT:

A. DESCRIPTION, cite the specific kind of lactose (anhydrous or mono..).

B. HOW SUPPLIED- Please cite the strength "0.5 mg" of the product in the first sentence with the established name.

C. Please update your labeling to be in accord with the most recent labeling S-008 approved on 12/12/2006 for the reference listed drug.

Please submit final printed electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug (or your previous submission) with all differences annotated and explained

SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	78-035
Date of Submission	
Applicant	Cobalt Pharm
Drug Name	Cabergoline Tablets
Strength(s)	0.5 mg

Container Labels
0.5 mg- 8s
(b) (4)
Carton Labeling
Requested

Package Insert Labeling

BASIS OF APPROVAL: 20-664

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None				PIII	Same As

Exclusivity Data For NDA			
Code/sup	**Expiration**	**Description**	***Labeling impact***
None		NCE	Same As

Reference Listed Drug

RLD on the 356(h) form	Dostinex
NDA Number	20-664
RLD established name	Cabergoline
Firm	Pharmacia and Upjohn
Currently approved PI	SL-008
AP Date	12/12/2006

Note: RLD has (b) (4) chemistry supplements.

NOTE TO THE CHEMIST: We are recommending that the (b) (4) this package size. The smaller package must have CRC. Applicant has included bulk labels

FOR THE RECORD:

1. MODEL LABELING- Review based on the labeling of Dostinex (Pharmacia & Upjohn, Cabergoline Tablets, NDA 20664/S-004, approved 4/17/00; revised 8/99.

2. PATENTS/EXCLUSIVITIES - See above

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM Cobalt Pharmaceutical, Canada. Dr. James Parker, at Strategic Bioscience Corp. Is the USA.

4. CONTAINER/CLOSURE in 30cc, [redacted], amber glass bottles of 0.**5 mg** ([redacted], and [redacted]) 10122 vol 1.20

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   NDA - CRT 20 - 25C (68 - 77 F)
   ANDA – CRT 20 - 25C (68 - 77 F)
   USP - none

6. DISPENSING STATEMENTS COMPARISON
   NDA – none
   ANDA – request "Unit-of-Use. Dispense in original container"
   USP
7. Scoring:
   NDA - scored
   ANDA -scored
   USP -none

8. PACKAGING CONFIGURATIONS

   Product Line:
   RLD: The **innovator** markets a 0.5 mg tablet (8s)
   ANDA: The **applicant** proposes to market their product 0.**5 mg** ([redacted] unit- of- use) with CRC page 10059-10078 vol 1.3

9. HOW SUPPLIED SECTION
   The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

10. INACTIVE INGREDIENTS
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 9868 vol 1.20

Date of Review: 5/16/2007 Date of Submission: 4/25/2007

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   ANDA: 78-035
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/s/

Angela Payne
5/22/2007 07:23:17 AM
LABELING REVIEWER

John Grace
5/23/2007 06:54:05 PM
LABELING REVIEWER

APPROVAL SUMMARY #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	78-035
Date of Submission	08 AUG 2007
Applicant	Cobalt Pharm
Drug Name	Cabergoline Tablets
Strength(s)	0.5 mg

LABELS AND LABELING

Container Labels	
0.5 mg- 8s	\\Cdsesub1\nonectd\N78035\N_000\2007-08-08\Bottle lable of 8's.pdf
Carton Labeling	
8s	\\Cdsesub1\nonectd\N78035\N_000\2007-08-08\Carton for Bottle of 8's.pdf
Package Insert Labeling	\\Cdsesub1\nonectd\N78035\N_000\2007-08-08\Package Insert.pdf

BASIS OF APPROVAL: 20-664

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None				PIII	Same As

Exclusivity Data For NDA			
Code/sup	**Expiration**	**Description**	***Labeling impact***
None		NCE	Same As

Reference Listed Drug

RLD on the 356(h) form	Dostinex
NDA Number	20-664
RLD established name	Cabergoline
Firm	Pharmacia and Upjohn
Currently approved PI	SL-008
AP Date	12/12/2006

Note: RLD has (b) (4) chemistry supplements.

NOTE TO THE CHEMIST: We are recommending that the (b) (4) this package size. The smaller package must have CRC. Applicant has included bulk labels

FOR THE RECORD:

1. MODEL LABELING- Review based on the labeling of Dostinex (Pharmacia & Upjohn, Cabergoline Tablets, NDA 20664/S-004, approved 4/17/00; revised 8/99.

2. PATENTS/EXCLUSIVITIES - See above

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM Cobalt Pharmaceutical, Canada. Dr. James Parker, at Strategic Bioscience Corp. Is the USA.

4. CONTAINER/CLOSURE in 30cc, [redacted], amber glass bottles of 0.**5 mg** ([redacted], and [redacted]) 10122 vol 1.20

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   NDA - CRT 20 - 25C (68 - 77 F)
   ANDA – CRT 20 - 25C (68 - 77 F)
   USP - none

6. DISPENSING STATEMENTS COMPARISON
   NDA – none
   ANDA – request "Unit-of-Use. Dispense in original container"
   USP
7. Scoring:
   NDA - scored
   ANDA -scored
   USP -none

8. PACKAGING CONFIGURATIONS

   Product Line:
   RLD: The **innovator** markets a 0.5 mg tablet (8s)
   ANDA: The **applicant** proposes to market their product 0.**5 mg** [redacted] unit- of- use) with CRC page 10059-10078 vol 1.3.
   Firm will no longer market the[redacted] and [redacted] as of the 8/9/07 submission.

9. HOW SUPPLIED SECTION
   The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

10. INACTIVE INGREDIENTS
    The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 9868 vol 1.20

Date of Review: 8/196/2007 Date of Submission: 08 AUG 2007

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/s/

Angela Payne
9/19/2007 08:51:09 AM
LABELING REVIEWER

John Grace
9/23/2007 07:48:22 PM
LABELING REVIEWER

APPROVAL SUMMARY #2
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION:

ANDA Number	78-035
Date of Submission	14 APR 2008
Applicant	Cobalt Pharm
Drug Name	Cabergoline Tablets
Strength(s)	0.5 mg

LABELS AND LABELING

Container Labels	
0.5 mg- 8s	\\Fdswa150\nonectd\N78035\N_000\2008-04-14\Labels\Bottle of 8's.pdf
Carton Labeling	
8s	\\Fdswa150\nonectd\N78035\N_000\2008-04-14\Labels\Carton for Bottle of 8's.pdf
Package Insert Labeling	\\Fdswa150\nonectd\N78035\N_000\2008-04-14\Labels\Package Insert.pdf

2. NOTE TO THE CHEMIST: We are recommending that the (b) (4) (b) (4) this package size. The smaller package must have CRC. Applicant has included bulk labels

3. MODEL LABELING- Review based on the labeling of Dostinex (Pharmacia & Upjohn, Cabergoline Tablets, NDA 20664).

Reference Listed Drug	
RLD on the 356(h) form	Dostinex
NDA Number	20-664
RLD established name	Cabergoline
Firm	Pharmacia and Upjohn
Currently approved PI	SL-010
AP Date	12/19/2007
Note:	

4. PATENTS/EXCLUSIVITIES - See above

BASIS OF APPROVAL: 20-664

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None				PIII	Same As

Exclusivity Data For NDA			
Code/sup	Expiration	Description	*Labeling impact*
None		NCE	Same As

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM Manufactured by Cobalt Pharmaceuticals, Canada. For Cobalt Laboratories in Florida, Dr. James Parker, at Strategic Bioscience Corp.iIs the USA rep.

6. CONTAINER/CLOSURE in 30cc, [redacted] amber glass bottles of 0.5 **mg** [redacted] 10122 vol 1.20

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   NDA - CRT 20 - 25C (68 - 77 F)
   ANDA – CRT 20 - 25C (68 - 77 F)
   USP - none

8. DISPENSING STATEMENTS COMPARISON
   NDA – none
   ANDA – request "Unit-of-Use. Dispense in original container"
   USP
9. Scoring:
   NDA - scored
   ANDA -scored
   USP -none

10. PACKAGING CONFIGURATIONS

    Product Line:
    RLD: The **innovator** markets a 0.5 mg tablet (8s)
    ANDA: The **applicant** proposes to market their product 0.5 **mg** [redacted] unit- of- use) with CRC page 10059-10078 vol 1.3.
    Firm will no longer market the [redacted] and [redacted] as of the 8/9/07 submission.

11. HOW SUPPLIED SECTION
    The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

12. INACTIVE INGREDIENTS
    The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 9868 vol 1.20

Date of Review: 4/16/2008 Date of Submission: 14 APR 2008

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ANDA: 78-035
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Review

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/s/

Angela Payne
4/17/2008 04:52:51 PM
LABELING REVIEWER

priority review

John Grace
4/18/2008 10:14:25 AM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-035

CHEMISTRY REVIEWS

Chemistry Review Data Sheet

ANDA 78-035

Cabergoline Tablets, 0.5 mg

Cobalt Pharmaceuticals Inc.

Bita Mirzai-Azarm
Division of Chemistry I

Chemistry Review #1

Table of Contents

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B. Description of How the Drug Product is Intended to be Used 8

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A. Reviewer's Signature

B. Endorsement Block

C. CC Block

Chemistry Assessment **10**

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....

S DRUG SUBSTANCE [Name, Manufacturer]

P DRUG PRODUCT [Name, Dosage form]

A APPENDICES

R REGIONAL INFORMATION

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....

A. Labeling & Package Insert

B. Environmental Assessment Or Claim Of Categorical Exclusion

III. List Of Deficiencies To Be Communicated .....

Chemistry Review Data Sheet

1. ANDA 78-035

2. REVIEW #:1

3. REVIEW DATE: 09-AUG-2006

4. REVIEWER: Bita Mirzai-Azarm

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	08-DEC-2005
Amendment	06-MAR-2006
Amendment	06-APR-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Cobalt Pharmaceuticals Inc.
Address:	6500 Kitimat Road Mississauga, Ontario Canada L5N 2B8
Representative:	Dr. James Parker Strategic Bioscience Corporation 93 Birch Hill Road, Stow, MA
Telephone:	978-897-9494
Fax:	978-461-0333

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN):

Cabergoline Tablets

9. LEGAL BASIS FOR SUBMISSION:

The basis for the proposed ANDA is the reference listed drug (RLD), Dostinex® Tablets (NDA no. 20-664). This RLD is manufactured by Pharmacia.

10. PHARMACOL. CATEGORY:

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

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY:

0.5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

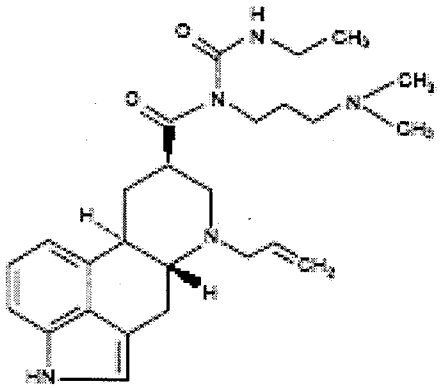
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CABERGOLINE

1-[(6-allylergolin-8β-yl)-carbonyl]-1-[3-(dimethylamino)-propyl]-3-ethylurea

Molecular formula: $C_{26}H_{37}N_5O_2$
Molecular weight: 451.62



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Inadequate	28-AUG-2006	B. Mirzai-Azarm
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	Exclusion under 21 CFR 25.31		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-224

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry – Minor N/A letter recommended.
Labeling – Pending
Bio – Pending
EER - Pending

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance Cabergoline is a white powder soluble in ethyl alcohol, chloroform, and N, N-dimethylformamide; slightly soluble in 0.1N hydrochloric acid; very slightly soluble in n-hexane; and insoluble in water.

The manufacturer of the drug substance used by the applicant is (b) (4) (b) (4) (DMF # (b) (4)).

Cabergoline is a dopamine receptor agonist. Each Cabergoline tablet, for oral administration, contains 0.5 mg of Cabergoline and has the following inactive ingredients: Leucine, USP and Lactose, NF.

DP is labeled for an oral use and is dispensed in glass bottles.

Both the drug substance (DS) and drug product (DP) do not have USP monographs. However, DS has a EP monograph.

B. Description of How the Drug Product is Intended to be Used

The recommended dose for the Cabergoline Tablets is 0.25 mg/twice weekly. Dosage may be increased by 0.25 mg twice weekly up to a dosage of 1 mg twice a week according to the patient's serum prolactin level.

Maximum Dose = 1 mg/twice weekly.

DS IT and QT limits are 0.10% and 0.15% respectively.

DP IT and QT limits are 0.5% and 1.0% respectively.

HOW SUPPLIED

Cabergoline Tablets are white to off-white, capsule shaped tablets embossed with C 'breakline'5 on one side and Σ partial (b) (4) Σ on the other side.

Cabergoline tablets (0.5 mg) are packaged in bottles of (b) (4) and (b) (4) tablets.

Store at controlled room temperature 20° - 25°C (68° - 77°F); Excursions permitted to 15° - 30°C (59° - 86°F). [See USP].

C. Basis for Approvability or Not-Approval Recommendation

Not approvable. The response to chemistry deficiencies will be a MINOR amendment.

Following this page, 16 pages withheld in full - (b)(4)

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-035

APPLICANT: Cobalt Pharmaceuticals Inc.

DRUG PRODUCT: Cabergoline Tablets, 0.5 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.
9.

10. [redacted] (b) (4)

11.

12.

13.

14.

15.

16. DMF [redacted] (b) (4) is deficient and the deficiencies have been communicated to the DMF holder. Please ensure a response.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide the available long term stability data for drug product.

2. Information related to labeling and bioequivalence is pending review. After the reviews are completed, any deficiencies found will be communicated to you under separate cover.

3. An acceptable compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

Sincerely yours,

M Smela for 9/26/06

Rashmikant M. Patel, Ph. D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 78-035
DIV FILE
Field Copy

Endorsements:

HFD-625/B.M.Azarm/8/30/06, 9/5/06 (revised) Bita M. Azarm 9/25/06.

HFD-625/M.Semela/9/6/06 M Semela 9/26/06

HFD-617/P.Chen, C.Kiester for/9/15/06 Patel 9/25/06

F/T by: ard/9/25/06

V:~~Chemistry Division//Team 2/TL Folder~~\78035N01RBM.DOC
FIRMSAM\COBALT\LTRS+REV\78035N01RBM.DOC

TYPE OF LETTER: NOT APPROVABLE - MINOR

ANDA 78-035

Cabergoline Tablets, 0.5 mg

Cobalt Pharmaceuticals Inc.

Bita Mirzai-Azarm
Division of Chemistry I

Chemistry Review #2

Table of Contents

Table of Contents **2**

Chemistry Review Data Sheet **3**

The Executive Summary **8**

I. Recommendations .....

A. Recommendation and Conclusion on Approvability

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments .....

A. Description of the Drug Product(s) and Drug Substance(s)

B. Description of How the Drug Product is Intended to be Used

C. Basis for Approvability or Not-Approval Recommendation

Chemistry Assessment **10**

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....

S DRUG SUBSTANCE [Name, Manufacturer]

P DRUG PRODUCT [Name, Dosage form]

A APPENDICES

R REGIONAL INFORMATION

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....

A. Labeling & Package Insert

B. Environmental Assessment Or Claim Of Categorical Exclusion

III. List Of Deficiencies To Be Communicated .....

Chemistry Review Data Sheet

1. ANDA 78-035

2. REVIEW #:2

3. REVIEW DATE: 24-APR-2007

4. REVIEWER: Bita Mirzai-Azarm

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	08-DEC-2005
Refusal to File Response	31-JAN-2006
Amendment	06-MAR-2006
Acceptance for Filing	08-MAR-2006
Amendment	06-APR-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	22-MAR-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Cobalt Pharmaceuticals Inc.
Address:	6500 Kitimat Road Mississauga, Ontario L5N 2B8 Canada
Representative:	Dr. James Parker Strategic Bioscience Corporation 93 Birch Hill Road, Stow, MA 01775
Telephone:	978-897-8404
Fax:	978-461-0333

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN):

Cabergoline Tablets

9. LEGAL BASIS FOR SUBMISSION:

The basis for the proposed ANDA is the reference listed drug (RLD), Dostinex® Tablets (NDA no. 20-664). This RLD is manufactured by Pharmacia & Upjohn Co.

10. PHARMACOL. CATEGORY:

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

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY:

0.5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

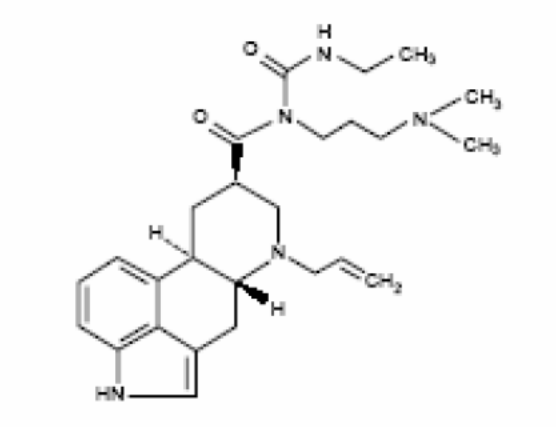
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CABERGOLINE

1-[(6-allylergolin-8β-yl)-carbonyl]-1-[3-(dimethylamino)-propyl]-3-ethylurea

Molecular formula: $C_{26}H_{37}N_5O_2$
Molecular weight: 451.62



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Inadequate	23-APR-2007	B. Mirzai-Azarm
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	09-NOV-2006	S. Adams
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Acceptable	28-DEC-2006	Sarah M. Robertson
EA	Exclusion under 21 CFR 25.31	CR #1	Bita Mirzai-Azarm
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:

Minor Amendment.

The Chemistry Review for ANDA 78-224

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry – Not Satisfactory
Labeling – Pending
Bio – Acceptable (12/28/06)
EER – Acceptable (11/9/06)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Routine stability commitment provided.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance Cabergoline is a white powder soluble in ethyl alcohol, chloroform, and N, N-dimethylformamide; slightly soluble in 0.1N hydrochloric acid; very slightly soluble in n-hexane; and insoluble in water.

The manufacturer of the drug substance used by the applicant is (b) (4) (b) (4) (DMF # (b) (4)).

Cabergoline is a dopamine receptor agonist. Each Cabergoline tablet, for oral administration, contains 0.5 mg of Cabergoline and has the following inactive ingredients: Leucine, USP and Lactose, NF.

DP is labeled for an oral use and is dispensed in glass bottles.

Both the drug substance (DS) and drug product (DP) do not have USP monographs. However, DS has a EP monograph.

B. Description of How the Drug Product is Intended to be Used

The recommended dose for the Cabergoline Tablets is 0.25 mg/twice weekly. Dosage may be increased by 0.25 mg twice weekly up to a dosage of 1 mg twice a week according to the patient's serum prolactin level.

Maximum Dose = 1 mg/twice weekly.

DS IT and QT limits are 0.10% and 0.15% respectively.

DP IT and QT limits are 0.5% and 1.0% respectively.

HOW SUPPLIED

Cabergoline Tablets are white to off-white, capsule shaped tablets embossed with C 'breakline'5 on one side and ⊃ partial (b) (4) ⊃ on the other side.

Cabergoline tablets (0.5 mg) are packaged in bottles of (b) (4) and (b) (4) tablets.

Store at controlled room temperature 20° - 25ºC (68° - 77ºF); Excursions permitted to 15° - 30ºC (59° - 86ºF). [See USP].

C. Basis for Approvability or Not-Approval Recommendation

Chemistry – Not Satisfactory
Labeling – Pending
Bio – Acceptable (12/28/06)
EER – Acceptable (11/9/06)

Following this page, 12 pages withheld in full - (b)(4)

34. BIOEQUIVALENCE

Acceptable on 12/28/06 per Sarah M. Robertson.

USP Apparatus:	II (Paddle) @ 50 rpm
Medium:	0.1 N HCl (at 37°C)
Volume:	500 mL
Specification:	NLT (Q) (b)(4)% at 15 min

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Categorical Exclusion under 21 CFR 25.31 (a).

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-035

APPLICANT: Cobalt Pharmaceuticals Inc.

DRUG PRODUCT: Cabergoline Tablets, 0.5 mg

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies:

1. DMF [redacted] (b) (4) remains deficient and the deficiencies have been communicated to the DMF holder. Please ensure a response.

2. Please clarify which facility will perform [redacted] (b) (4) routinely on the drug substance.

3. We acknowledge that [redacted] (b) (4)

4. We acknowledge that you [redacted] (b) (4) specifications for the drug product. Please provide assurance (e.g. SOP) that the [redacted] (b) (4) testing.

5. Please note that [redacted] (b) (4)

6. Please revise the [redacted] (b) (4) .

7. The [redacted] (b) (4) based on the available data.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

1. Information related to labeling is pending review. After the review is completed, any deficiencies found will be communicated to you under separate cover.

2. Please provide all available long term stability data.

3. The proposed limit for [redacted] (b) (4) is pending safety review.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph. D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 78-035
DIV FILE
Field Copy

Endorsements:

HFD-625/B.M.Azarm/4/24/07, 4/30/07 (revised)

HFD-625/M.Semela/

HFD-617/E.Chuh/

F/T by:

V:\Chem Div I\Team2\TL Folder\Draft\78035N02RBM.DOC

TYPE OF LETTER: NA MINOR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bita Mirzai-Azarm
4/30/2007 11:01:43 AM
CHEMIST

Esther Chuh
4/30/2007 05:39:25 PM
CSO

Michael Smela
5/1/2007 08:23:18 AM
CHEMIST

ANDA 78-035

Cabergoline Tablets, 0.5 mg

Cobalt Pharmaceuticals Inc.

Bita Mirzai-Azarm
Division of Chemistry I

Chemistry Review #3

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Chemistry Review Data Sheet **3**

The Executive Summary **8**

I. Recommendations .....

A. Recommendation and Conclusion on Approvability

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments .....

A. Description of the Drug Product(s) and Drug Substance(s)

B. Description of How the Drug Product is Intended to be Used

C. Basis for Approvability or Not-Approval Recommendation

Chemistry Assessment **10**

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....

S DRUG SUBSTANCE [Name, Manufacturer]

P DRUG PRODUCT [Name, Dosage form]

A APPENDICES

R REGIONAL INFORMATION

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....

A. Labeling & Package Insert

B. Environmental Assessment Or Claim Of Categorical Exclusion

III. List Of Deficiencies To Be Communicated .....

Chemistry Review Data Sheet

1. ANDA 78-035

2. REVIEW #:3

3. REVIEW DATE: 26-MAR-2008

4. REVIEWER: Bita Mirzai-Azarm

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	08-DEC-2005
Refusal to File Response	31-JAN-2006
Amendment	06-MAR-2006
Acceptance for Filing	08-MAR-2006
Amendment	06-APR-2006
Amendment	22-MAR-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
*Amendment	25-APR-2007
Major Amendment	11-JUN-2007
Telephone Amendment	24-MAR-2008
Telephone Amendment	04-APR-2008

**** Cobalt Pharmaceuticals Inc., proposed to change the manufacturing site of Cabergoline Tablets from*** [redacted] (b) (4) ***to its own manufacturing site. Cobalt would be the site responsible for testing of the drug substance, excipients, packaging components and finished product. Cobalt will be the release and stability site for the production batches.***

Because of the proposed change the minor amendment of 11-JUN-2007 is considered MAJOR.

7. NAME & ADDRESS OF APPLICANT:

Name:	**Cobalt Laboratories Inc.**
Address:	**24840 S. Tamiami Trail, Suite 1 Bonita Springs, Florida 34134**
Responsible Official:	**Mr. Richard Sanzen, R.Ph**
Telephone:	**239-333-2037**
Fax:	**239-390-0295**

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN):

Cabergoline Tablets

9. LEGAL BASIS FOR SUBMISSION:

The basis for the proposed ANDA is the reference listed drug (RLD), Dostinex® Tablets (NDA no. 20-664). This RLD is manufactured by Pharmacia & Upjohn Co.

10. PHARMACOL. CATEGORY:

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

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY:

0.5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

Chemistry Review Data Sheet

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

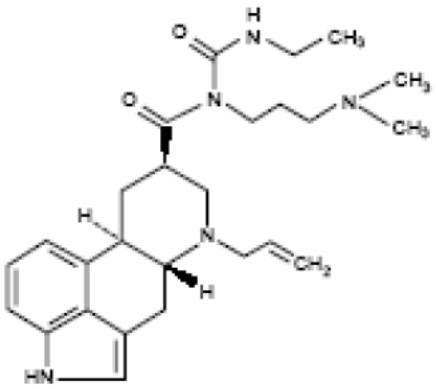
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CABERGOLINE

1-[(6-allylergolin-8β-yl)-carbonyl]-1-[3-(dimethylamino)-propyl]-3-ethylurea

Molecular formula: $C_{26}H_{37}N_5O_2$
Molecular weight: 451.62



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	**Adequate**	26-MAR-2008	B. Mirzai-Azarm
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	**13-MAR-2008**	S. Adams
Methods Validation	N/A		
Labeling	Acceptable	18-APR-2008	A. Payne
Bioequivalence	Acceptable	28-DEC-2006	Sarah M. Robertson
EA	Exclusion under 21 CFR 25.31	CR #1	Bita Mirzai-Azarm
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-035

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry – Acceptable
Labeling – Acceptable (4/18/2008)
Bio – Acceptable (12/28/06)
EER – Acceptable (3/13/08)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Routine stability commitment provided.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance Cabergoline is a white powder soluble in ethyl alcohol, chloroform, and N, N-dimethylformamide; slightly soluble in 0.1N hydrochloric acid; very slightly soluble in n-hexane; and insoluble in water.

The manufacturer of the drug substance used by the applicant is (b) (4) (b) (4) (DMF # (b) (4)

Cabergoline is a dopamine receptor agonist. Each Cabergoline tablet, for oral administration, contains 0.5 mg of Cabergoline and has the following inactive ingredients: Leucine, USP and Lactose, NF.

DP is labeled for an oral use and is dispensed in glass bottles.

Both the drug substance (DS) and drug product (DP) do not have USP monographs. However, DS has a EP monograph.

B. Description of How the Drug Product is Intended to be Used

The recommended dose for the Cabergoline Tablets is 0.25 mg/twice weekly. Dosage may be increased by 0.25 mg twice weekly up to a dosage of 1 mg twice a week according to the patient's serum prolactin level.

Maximum Dose = 1 mg/twice weekly.

DS IT and QT limits are 0.10% and 0.15% respectively.

DP IT and QT limits are 0.5% and 1.0% respectively.

HOW SUPPLIED
Cabergoline Tablets 0.5 mg are white to off-white, capsule shaped, flat-faced, bevel-edged tablets with 'C' breakline '5' on one side and 'Σ' partial bisect 'Σ' on the other side.

Cabergoline Tablets 0.5 mg are available as follows:

Bottles of 8 tablets NDC (b) (4)

Store at controlled room temperature 20° - 25°C (68° - 77°F); Excursions permitted to 15° - 30°C (59° - 86°F). [See USP].

NOTE: Firm will no longer market the (b) (4) and (b) (4) as of the 4/4/08 submission.

C. Basis for Approvability or Not-Approval Recommendation
Chemistry – Acceptable
Labeling – Acceptable (4/18/2008)
Bio – Acceptable (12/28/06)
EER – Acceptable (3/13/08)

Following this page, 21 pages withheld in full - (b)(4)

Comment (review #3):
Please provide dissolution data on accelerated retains for batch AS82 in accordance with the DBE recommendations.

Response (4/4/08):
The applicant indicated that the dissolution spec. reported on the stability report forms was a typographical error. The corrected stability forms for 6 month long term stability data for batch AS82 is provided and is satisfactory.

30. MICROBIOLOGY
N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
Not needed.

32. LABELING
Satisfactory on 4/18/2008 per Angela Payne.

33. ESTABLISHMENT INSPECTION
Acceptable on 13-MAR-2008 by S. Adams.

34. BIOEQUIVALENCE
Acceptable on 12/28/06 per Sarah M. Robertson.

USP Apparatus:	II (Paddle) @ 50 rpm
Medium:	0.1 N HCl (at 37°C)
Volume:	500 mL
Specification:	NLT (Q (b) (4) at 15 min

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Categorical Exclusion under 21 CFR 25.31 (a).

cc: ANDA 78-035
DIV FILE
Field Copy

Endorsements:

HFD-625/B.M.Azarm/4/8/08

HFD-625/M.Smela/

HFD-617/E.Chuh/

F/T by:

V:\Chem Div I\Team2\TL Folder\Draft\78035N03RBM.DOC

TYPE OF LETTER: Approval

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bita Mirzai-Azarm
4/21/2008 09:47:39 AM
CHEMIST

Michael Smela
4/21/2008 10:58:14 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-035

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION CHECKLIST

ANDA No.	78-035
Drug Product Name	Cabergoline Tablets
Strength	0.5 mg
Applicant Name	Cobalt Pharmaceuticals
Submission Date(s)	March 6, 2006
First Generic	No
Reviewer	Hoainhon Nguyen
File Location	**V:\firmsam\Cobalt\Ltrs&rev\78035d1205.doc**
Clinical Site	SFBC Anapharm, St. Foy Canada
Analytical Site	(b) (4)

Table 1. Submission Content Checklist

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	☒	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☒	☐	☐
Is FDA method in the public dissolution database (on the web)			☒	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are all eight electronic summary biotables present			☒	☐	☐
Are electronic summary biotables in pdf format			☒	☐	☐

NOTE: The FDA-recommended method is as follows:

USP Apparatus:	II (paddle) @ 50 rpm
Dissolution Medium:	0.1 N HCl
Volume of Dissolution Medium:	500 mL

Specification: NLT (b)(4)% (Q) in 15 minutes

7/6/06

Hoainhon Nguyen
Team I
Division of Bioequivalence
Office of Generic Drugs

Moheb H. Makary 7/7/06

Moheb H. Makary
Team I
Division of Bioequivalence
Office of Generic Drugs

CC: ANDA #78-035

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Endorsements: (Final with Dates)
HFD-650/HNguyen
HFD-650/MMakary 7/7/06

BIOEQUIVALENCE - INCOMPLETE Submission date: 12-08-05

[NOTE: The in vitro testing is incomplete. The fasting and fed BE studies and waiver request are pending review]

1. DISSOLUTION (Dissolution Data) Strength: 0.5 mg
Outcome: IC

Outcome Decisions: IC – Acceptable or Incomplete
WinBio Comments: IC

DIVISION OF BIOEQUIVALENCE DISSOLUTION CHECKLIST

ANDA No.	78-035
Drug Product Name	Cabergoline Tablets
Strength	0.5 mg
Applicant Name	Cobalt Pharmaceuticals
Submission Date(s)	August 28, 2006
First Generic	No
Reviewer	Hoainhon Nguyen
File Location	**V:\firmsam\cobaltltrs&rev\78035a0806 .doc**
Clinical Site	SFBC Anapharm, St. Foy Canada
Analytical Site	(b) (4)

EXECUTIVE SUMMARY

This is a review of an amendment of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm has conducted dissolution testing using the FDA-recommended method as requested. The dissolution data met the FDA-recommended specification at S1 level. The firm should acknowledge the FDA-recommended method and specification.

The DBE will review the fasted and fed BE studies at a later date.

Table 1. Submission Content Checklist

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☒	☐	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☒	☐	☐
Is FDA method in the public dissolution database (on the web)			☒	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are all eight electronic summary biotables present			☒	☐	☐
Are electronic summary biotables in pdf format			☒	☐	☐

NOTE: The FDA-recommended method is as follows:

USP Apparatus:	II (paddle) @ 50 rpm
Dissolution Medium:	0.1 N HCl
Volume of Dissolution Medium:	500 mL
Specification:	NLT (b)(4)% (Q) in 15 minutes

TABLE 2: IN VITRO DISSOLUTION DATA, FDA-RECOMMENDED METHOD

78035Dissolution.doc

TABLE 3: IN VITRO DISSOLUTION DATA, FIRM'S METHOD

78035DissolutionFirmsMethod.pdf

COMMENTS:

1. In the current amendment, the firm conducted dissolution testing using the FDA-recommended method. The dissolution data met the FDA-recommended specification at S1 level.

The firm should acknowledge the FDA-recommended dissolution method and specification.

2. The firm had previously submitted appropriate electronic CTD summary tables in pdf format.

3. The firm had previously submitted appropriate SAS data files for the BE studies.

DEFICIENCY COMMENTS:

The firm should acknowledge the FDA-recommended dissolution method and specification.

RECOMMENDATIONS:

The dissolution testing conducted by Cobalt Pharmaceuticals for the test product using the FDA-recommended method is **incomplete.** The firm should acknowledge the FDA-recommended method and specification.

9/19/06

Hoainhon Nguyen
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Office of Generic Drugs

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CC: ANDA #78-035

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Endorsements: (Final with Dates)
HFD-650/HNguyen
HFD-650/MMakary 9/19/06

BIOEQUIVALENCE - INCOMPLETE Submission date: 08-28-2006

[NOTE: The in vitro testing is incomplete. The fasting and fed BE studies are pending review]

1. DISSOLUTION (Dissolution Data)	Strength:	0.4 mg
	Outcome:	**IC**

Outcome Decisions: IC – Incomplete
WinBio Comments: IC

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-035
Drug Product Name	Cabergoline Tablets
Strengths	0.5 mg
Applicant Name	Cobalt Pharmaceuticals
Address	6500 Kitimat Rd, Mississauga, Ontario L5N 2B8 Canada
Contact	James Parker (Phone 905-814-1820, Fax 905-542-0478)
Submission Date(s)	March 6, 2006
Amendment Date(s)	April 6, 2006 (Toxicology) August 28, 2006 (Dissolution) October 13, 2006 (Dissolution)
Reviewer	Sarah Robertson, Pharm.D.
Clinical Site	SFBC Anapharm, 2050, Boul. Rene-Levesque Ouest, Sainte-Foy, Quebec, Canada G1V 2K8
Analytical Site	(b) (4)
First Generic	No

I. Executive Summary

This submission contains two bioequivalence (BE) studies comparing Cobalt's Cabergoline 0.5 mg tablet, to the reference-listed drug (RLD), Dostinex® 0.5 mg tablet (Pharmacia & Upjohn) under fasting and fed conditions. Both studies were single-dose, two-period, crossover studies conducted in healthy volunteers (n=48 each) administered 2 x 0.5 mg tablets per dose.

Results of the statistical analyses for the fasting study are (point estimate, 90% CI): LAUCT of 1.03, 96.1 – 109.4%; LAUCI of 1.03, 96.6 – 109.4%; and LCmax of 0.97, 90.2 – 103.9%. Results of the fed study are (point estimate, 90% CI): LAUCT of 1.03, 98.5 – 107.2%; LAUCI of 1.02, 97.2 – 106.1%; and LCmax of 1.07, 101.3 – 113.1%. The results of the fasting and fed BE studies are acceptable.

A review of the dissolution data completed on 09/19/06 found the firm's dissolution testing incomplete, pending the firm's acknowledgment of the FDA-recommended specification. The firm has subsequently acknowledged acceptance of the dissolution method and specification.

The application is complete.

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III. Submission Summary

A. Drug Product Information

Test Product	Cabergoline Tablets, 0.5 mg
Reference Product	Dostinex® Tablets, 0.5 mg
RLD Manufacturer	Pharmacia & Upjohn
NDA No.	20-664
RLD Approval Date	12/23/1996
Indication	Treatment of hyperprolactemia disorders, idiopathic or due to pituitary adenomas

B. PK/PD Information

Bioavailability	Absolute bioavailability unknown. A significant fraction of drug undergoes first-pass metabolism.
Food Effect	No effect
Tmax	Mean peak plasma levels of 30 – 70 pg/mL were observed within 2 – 3 hours in 12 healthy volunteers
Metabolism and Excretion	Extensively metabolized in the liver, predominately via hydrolysis of the acylurea bond or the urea moiety. Cytochrome P-450 mediated metabolism appears to be minimal. Major metabolites do not appear to contribute to the therapeutic effect. Approximately 22% and 60% of the dose was excreted within 20 days of dosing in urine and feces, respectively. Less than 4% of the dose was excreted unchanged in the urine.
Half-life	63 – 69 hours
Relevant OGD or DBE History	There is one approved generic for the RLD: 76-310 (Par, approved 12/29/05)

Protocols

01-024 ((b) (4) 05/01/01); 01-027 ((b) (4) 05/14/01)

Control Documents

02-101 ((b) (4) 03-106 ((b) (4) 03-156 ((b) (4) 03-649 ((b) (4) 03-781 ((b) (4) 04-262 (Teva); 05-0117 ((b) (4) 05-1366 ((b) (4) 06-0987 ((b) (4) 06-1493 ((b) (4)

The DBE makes the following recommendations to establish bioequivalence of Cabergoline Tablets:

1. The following studies are recommended to establish bioequivalence of Cabergoline tablets:
    a. A single-dose fasting *in-vivo* bioequivalence study comparing Cabergoline Tablets, 1 mg (2 tablets of 0.5 mg), to the reference listed drug (RLD), Dostinex® (cabergoline) Tablets, 1 mg (2 tablets of 0.5 mg).
    b. A single-dose fed *in-vivo* bioequivalence study comparing Cabergoline Tablets, 1 mg (2 tablets of 0.5 mg), to the RLD (2 tablets of 0.5 mg).
2. Only the parent drug, cabergoline, should be measured for the bioequivalence studies. The data should be analyzed using the 90% confidence interval approach.
3. A sensitive and specific assay such as LC-MS/MS should be used to reliably measure plasma cabergoline concentrations with a 1 mg dose (2 tablets of 0.5 mg).

The FDA recommends the following dissolution method and specification:

Medium: 0.1 N HCl
Volume: 500 mL
Apparatus: II (Paddle)
Speed: 50 rpm
Sampling: 5, 10, 15 and 30 min.
Specification: NLT (b)(4)% at 15 min.

Agency Guidance CDER BA/BE Guidance
Drug Specific Issues None
Application Specific Issue The original submission (December 12, 2005) was refused for filing due to an inactive ingredient exceeding the IIG limit.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	3

D. Pre-Study Bioanalytical Method Validation

Bioanalytical method validation report location	Appendix 4.2 of bioanalytical report
Analyte	Cabergoline

Internal standard (IS)	(b) (4)
Method description	This method involves the extraction of cabergoline and the internal standard from human EDTA K_2 or K_3 Plasma by automated solid phase extraction (MultiPROBE II systems). Samples are kept frozen at -20°C prior to analysis using LC/MS/MS.
Limit of quantitation (pg/mL)	1.00
Average recovery of drug range (%)	MultiPROBE II EX: 71.67 to 75.77 MultiPROBE II EX HT : 75.59 to 78.66
Average recovery of IS (%)	MultiPROBE II EX: 77.16 MultiPROBE II EX HT : 74.57
Standard curve concentrations range (pg/mL)	1.00 to 50.10
QC concentration (pg/mL)	QC1: 3.01 QC2: 15.06 QC3: 35.14
QC Intraday precision range (%)	MultiPROBE II EX: 1.97 to 6.47 MultiPROBE II EX HT : 1.20 to 9.76
QC Intraday accuracy range (%)	MultiPROBE II EX: 88.17 to 99.53 MultiPROBE II EX HT : 94.10 to 98.17
QC Interday precision range (%)	3.34 to 4.76
QC Interday accuracy range (%)	95.99 to 96.56
Bench-top stability (hrs)	17 hours at room temperature
Stock stability (days)	Analyte: 167 days at -20°C
Processed stability (hrs)	74 hours at room temperature
Freeze-thaw stability (cycles)	4 at -20°C and 4 at -80°C
Long-term storage stability (days)	185 days at -20°C and 7 days at -80°C
Dilution integrity	QC3 diluted 2 fold: CV (%) 2.07 %Nominal (%) 95.04 % DQC diluted 20 fold: CV (%) 1.29 % Nominal (%) 93.20 %
Selectivity	Human plasma samples (EDTA K_2 or K_3 as anti-coagulant) from 10 different individual human blank sources were tested for interfering peaks at the retention time of cabergoline and the internal standard. One of the sources showed significant interference at the retention time of cabergoline and none at the retention time of the internal standard.
SOPs submitted	Yes
20% Validation Chromatograms included	Yes
Random or Serial Selection of Chromatograms	Random Selection
Bioanalytical method is acceptable	Yes

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	50397
Study Design	Randomized two-way crossover study under fasting conditions
No. of subjects enrolled	52
No. of subjects completing	48
No. of subjects analyzed	48
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 27 Female: 21
Test product	Cabergoline 0.5 mg Tablet
Reference product	Dostinex® 0.5 mg Tablet
Strength tested	0.5 mg
Dose	2 x 0.5 mg

Summary of Statistical Analysis – Cabergoline		
Parameter	**Point Estimate**	**90% Confidence Interval**
LAUC$_{0\text{-}t}$	1.03	96.1 – 109.4%
LAUCinf	1.03	96.6 – 109.4%
LC$_{max}$	0.97	90.2 – 103.9%

Reanalysis of Study Samples – Cabergoline

Study No.50397 Randomized Open-label, 2-way Crossover, Bioequivalence Study of Cabergoline 0.5 mg Tablet and Dostinex Following a 1 mg Dose in Healthy Subjects under Fasting Conditions								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of Total Assays		Actual number		% of Total Assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0	0	0.0	0.0	0	0	0.0	0.0
Analytical repeat	13	13	0.52	0.52	13	13	0.53	0.53
Unacceptable internal standard response	6	6	0.24	0.24	6	6	0.24	0.24
Loss of sample	1	0	0.04	0.0	1	0	0.04	0.0
Sample concentration above upper limit of quantification	1	2	0.04	0.08	1	2	0.04	0.08
Sample concentration above or below modified calibration curve range	5	5	0.20	0.20	5	5	0.20	0.20
Total	13	13	0.52	0.52	13	13	0.52	0.52

Did use of recalculated plasma concentration data change study outcome? No

2. Single-dose Fed Bioequivalence Study

Study Summary	
Study No.	50398
Study Design	Randomized two-way crossover study under fed conditions
No. of subjects enrolled	52
No. of subjects completing	48
No. of subjects analyzed	47 (1 subject not included in analysis due to vomiting)
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male 19; Female 28
Test product	Cabergoline 0.5 mg Tablet
Reference product	Dostinex® 0.5 mg Tablet
Strength tested	0.5 mg
Dose	2 x 0.5 mg

Summary of Statistical Analysis - Cabergoline		
Parameter	**Point Estimate**	**90% Confidence Interval**
LAUC$_{0-t}$	1.03	98.5 – 107.2%
LAUCinf	1.02	97.2 – 106.1%
LC$_{max}$	1.07	101.34 – 113.10%

Reanalysis of Study Samples – Cabergoline

Study No. 50398 Randomized Open-label, 2-way Crossover, Bioequivalence Study of Cabergoline 0.5 mg Tablet and Dostinex Following a 1 mg Dose in Healthy Subjects under Fed Conditions								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of Total Assays		Actual number		% of Total Assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0	0	0.0	0.0	0	0	0.0	0.0
Analytical repeat	35	24	1.40	0.96	34	24	1.36	0.96
Unacceptable internal standard response	9	10	0.36	0.40	9	10	0.36	0.40
Sample concentration above upper limit of quantitation	9	0	0.36	0.0	9	0	0.36	0.0
Sample concentration above or below modified calibration curve range	15	14	0.60	0.56	15	14	0.60	0.56
Sample reanalyzed to obtain confirming value	2	0	0.08	0.0	1	0	0.04	0.0
Total	35	24	1.40	0.96	34	24	1.36	0.96

Did use of recalculated plasma concentration data change study outcome? No

F. Formulation

Location in appendix	Section B, Page 28
Are inactive ingredients within IIG limits?	No†
If no, list ingredients outside of limits	Leucine
If a tablet, is the product scored?	Yes
If yes, which strengths are scored?	0.5 mg
Is scoring of RLD the same as test?	Yes
Is the formulation acceptable?	Yes
If not acceptable, why?	

†The inactive ingredient Leucine exceeds the IIG database limit for an oral tablet formulation (b) (4) mg/tablet). A pharmacology/toxicology review conducted by Lynnda Reid, Ph.D. finds the firm's proposed amount of leucine (b) (4) /tablet) acceptable.

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA
Medium	0.1 N HCl
Volume (mL)	500 mL
USP Apparatus type	Type II (Paddle)
Rotation (rpm)	50 rpm
FDA-recommended specifications	NLT (b) (4) % (Q) in 15 minutes
F2 metric calculated?	Yes (f_2 = 54)
If no, reason why F2 not calculated	
Is method acceptable?	Yes
If not then why?	

Comments: The firm submitted the results of dissolution testing using the FDA-recommended method in an amendment to their original submission (August 28, 2006), and acknowledged acceptance of the FDA-recommended specification in a subsequent amendment (October 13, 2006).

H. Waiver Request(s)

None

I. Deficiency Comments

None

J. Recommendations

1. The *in vivo* bioequivalence study conducted under fasting conditions by Cobalt Pharmaceuticals on the drug product, Cabergoline 0.5 mg tablets, Lot F0604 (manufactured by (b) (4)) comparing it to Pharmacia & Upjohn's Dostinex Tablets, 0.5 mg, Lot #A526A, is acceptable.

2. The *in vivo* bioequivalence study conducted under fed conditions by Cobalt Pharmaceuticals on the drug product, Cabergoline 0.5 mg tablets, Lot F0604 (manufactured by (b) (4)) comparing it to Pharmacia & Upjohn Co.'s Dostinex Tablets, 0.5 mg, Lot #A526A, is acceptable.

3. The *in vitro* dissolution testing conducted by the firm on its Cabergoline 0.5 mg tablets is acceptable. The DBE acknowledges firm's acceptance of the following dissolution method and specification:

USP Apparatus:	II (Paddle) @ 50 rpm
Medium:	0.1 N HCl (at 37°C)
Volume:	500 mL
Specification:	NLT (Q) (b) (4)% at 15 min.

The firm should be informed of the above recommendations.

Sarah Robertson, Pharm.D.
Division of Bioequivalence
Review Branch III

Chandra Charasia, Ph.D.
Acting Team Leader, Division of Bioequivalence
Review Branch III

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	50397
Study Title	Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Cabergoline 0.5 mg Tablet and Dostinex Following a 1 mg Dose in Healthy Subjects under Fasting Conditions
Clinical Site	SFBC Anapharm, Montreal, Canada
Principal Investigator	Richard Larouce, M.D.
Study/Dosing Dates	07/28/05 (Period I) and 09/1/05 (Period II)
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	10/18/05 – 10/25/05
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	89 days

Treatment ID	**A**	**B**
Test or Reference	Test	Reference
Product Name	Cabergoline Tablets	Dostinex® Tablets
Manufacturer	(b) (4)	Pharmacia & Upjohn Co.
Batch/Lot No.	F0604	A526A
Manufacture Date	06/2005	N/A
Expiration Date	N/A	02/2007
Strength	0.5 mg	0.5 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	96.0%	94.7%
Content Uniformity (mean, %RSD)	96.3% (2.6)	Not provided
Formulation	See Appendix Section B	Not provided
Dose Administered	2 x 0.5 mg	2 x 0.5 mg
Route of Administration	Orally with 240 mL of water	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	35 days
Randomization Scheme	AB: 1, 5, 7 – 9, 14 – 16, 18 – 20, 26, 27, 29, 31, 33, 35, 38, 40 – 42, 44, 46, 51, 52 BA: 2, 3, 4, 6, 10 – 13, 17, 21 – 25, 28, 30, 32, 34, 36, 37, 39, 43, 45, 47 – 50
Blood Sampling Times	Pre-dose, 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4, 5, 6, 8, 12, 16, 24, 48, 96, 144, 216, 288 and 312 hours
Blood Volume Collected/Sample	6 mL
Blood Sample Processing/Storage	Plasma separated after centrifuging, then flash-frozen at -80°C and stored at -20°C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Overnight (≥ 10 hours pre-dose) and until 4 hours post-dose
Length of Confinement	10 hours pre-dose and until 24 hours post-dose
Safety Monitoring	Vital signs were measured prior to each dose and at specified blood draw times.

Comments on Study Design: The study design is acceptable.

b) Clinical Results

Table 1 Demographics of Study Subjects

		Safety population	PK population		
Category		**Total**	**Randomization**		**Total**
			AB	**BA**	
Age (years)	Mean ± SD	46 ± 11	44 ± 12	47 ± 10	46 ± 11
	Range	20 – 60	20 – 60	25 – 60	20 – 60
	Median	50	48	50	50
	N	52	23	25	48
Age Groups	< 18	0	0	0	0
	18-40	17 (32.7%)	9 (39.1%)	7 (28.0%)	16 (33.3%)
	41-64	35 (67.3%)	14 (60.9%)	18 (72.0%)	32 (66.7%)
	65-75	0	0	0	0
	> 75	0	0	0	0
Gender	Female	24 (46.2%)	7 (30.4%)	14 (56.0%)	21 (43.8%)
	Male	28 (53.8%)	16 (69.6%)	11 (44.0%)	27 (56.3%)
Race	Asian	1 (1.9%)	1 (4.3%)	0	1 (2.1%)
	Oriental	1 (1.9%)	1 (4.3%)	0	1 (2.1%)
	Black	4 (7.7%)	1 (4.3%)	2 (8.0%)	3 (6.3%)
	Caucasian	42 (80.8%)	18 (78.3%)	21 (84.0%)	39 (81.3%)
	American Hispanic	4 (7.7%)	2 (8.7%)	2 (8.0%)	4 (8.3%)
Height (cm)	Mean ± SD	168.5 ± 8.8	171.2 ± 7.4	165.9 ± 9.7	168.4 ± 9.0
	Range	152.5 – 188.5	159.0 – 183.0	152.5 – 188.5	152.5 – 188.5
	Median	168.5	171.0	165.0	168.5
	N	52	23	25	48
Weight (kg)	Mean ± SD	70.2 ± 10.3	72.6 ± 8.5	67.9 ± 11.3	70.2 ± 10.2
	Range	50.2 – 92.1	56.0 – 88.7	50.2 – 92.1	50.2 – 92.1
	Median	67.9	71.2	65.0	68.3
	N	52	23	25	48
BMI (kg/m^2)	Mean ± SD	24.6 ± 2.6	24.8 ± 2.5	24.6 ± 2.5	24.7 ± 2.5
	Range	19.9 – 29.9	19.9 – 29.8	20.4 – 29.4	19.9 – 29.8
	Median	24.4	25.2	24.2	24.7
	N	52	23	25	48

Table 2 Dropout Information

(Additional information on page p 4959, vol. 1.10)

Subject No	Reason	Period	Replaced?
14	Elected to withdraw prior to drug administration for personal reasons	II	No
15	Elected to withdraw prior to drug administration for personal reasons	II	No
28	Elected to withdraw prior to drug administration for personal reasons	II	No
35	Withdrawn from study due to severe vomiting that occurred 1 hour 13 min. after dosing	I	No

Table 3 Study Adverse Events

System Class	Project No. 50397*	
COSTART	A	B
Cardiac disorders		
Palpitat	1 (1.3%)	
Eye disorders		
Conjunctivitis		
Eye dis	1 (1.3%)	
Pain eye	1 (1.3%)	
Pruritus		
Vision abnorm	1 (1.3%)	
Gastrointestinal disorders		
Constip		1 (1.3%)
Diarrhea	1 (1.3%)	1 (1.3%)
Dry mouth		
Dyspepsia		1 (1.3%)
Nausea	5 (6.3%)	4 (5.0%)
Pain abdo	2 (2.5%)	
Vomit	2 (2.5%)	1 (1.3%)
General disorders and administration site conditions		
Asthenia	1 (1.3%)	2 (2.5%)
Chills	2 (2.5%)	
Vasodilat	1 (1.3%)	
Infections and infestations		
Herpes simplex	1 (1.3%)	
Infect fung		
Injury, poisoning and procedural complications		
Ecchymosis inject site		1 (1.3%)
Edema inject site		2 (2.5%)
Inject site react		
Injury accid	1 (1.3%)	
Pain inject site		
Investigations		
Hypertens		1 (1.3%)
Hypotens	3 (3.8%)	3 (3.8%)
Tachycardia	2 (2.5%)	
Musculoskeletal and connective tissues disorders		

System Class	Project No. 50397*	
COSTART	A	B
Myalgia	1 (1.3%)	
Pain		
Pain back		
Nervous system and connective tissue disorders		
Dizziness	2 (2.5%)	2 (2.5%)
Headache	8 (10.0%)	2 (2.5%)
Hypesthesia	1 (1.3%)	
Somnolence	1 (1.3%)	3 (3.8%)
Vertigo		1 (1.3%)
Psychiatric disorders		
Confus		1 (1.3%)
Depersonal		
Insomnia		
Nervousness		1 (1.3%)
Thinking abnorm		
Respiratory, thoracic and mediatinal disorders		
Cough inc		
Pharyngitis		
Rhinitis	1 (1.3%)	
Skin and subcutaneous tissue disorders		
Ecchymosis		
Pruritus		
Rash		
Vascular disorders		
Vasodilat	1 (1.3%)	1 (1.3%)
TOTAL	**40**	**28**

* 12 adverse events in Project No. 50397 could not be assigned to a treatment group.

Comments: There were a total of 80 post-dose adverse events – 40 events (50%) following treatment A, 28 events (31%) following treatment B, and 12 events (15%) that could not be assigned to a treatment group. Of the 80 adverse events, 39 were mild, 16 were moderate, 4 were severe, and 21 were clinically significant post-study laboratory results.

Table 4 Protocol Deviation

In addition to blood draw deviations (See sect. 14.3, vol. 1.10), the following protocol deviations occurred:

Subject	Deviation	Period (Treatment)	Excluded from analysis?
1 – 52	Humidity of medication storage facility rose above the range specified in facility SOP on 8 occasions for durations ≤ 1 min.	II (A, B)	No
1 – 52	Whether or not flash-freeze was performed on 144-hour post-dose samples could not be confirmed	II (A, B)	No
14, 37	A serum pregnancy test was performed at screening instead of a urine test	N/A	No

09	Subject consumed 1 glass of red wine 3 hrs 44 min after drug administration	I (A)	No
14	Subject consumed 1 cola beverage 6 days after drug administration	I (A)	No
22	Subject consumed 1 cup of coffee 12 days after drug administration	I (B)	No
26	Subject consumed 1 cola beverage 1 day, 22 hours after drug administration	I (A)	No
43	Subjects 24-hour post-dose vital signs were not performed, and subject was confined for only 22 hours post-dose instead of 24 hours	II (A)	No

Comments on Dropouts/Adverse Events/Protocol Deviations: The reported adverse events and protocol deviations are not likely to compromise the integrity of study.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

Analysis	Cabergoline
QC Conc. (pg/mL)	3.01, 7.53, 15.06, 35.14
Inter day Precision (%CV)	3.00 – 7.95%
Inter day Accuracy (%)	95.93 – 100.33%
Cal. Standards Conc. (pg/mL)	1.00 – 50.10
Inter day Precision (%CV)	4.33 – 7.00%
Inter day Accuracy (%)	97.41 – 101.75%
Linearity Range	$R^2 \geq 0.9911$

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially selected

Comments on Chromatograms: Acceptable

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	**Date of SOP**	**SOP Title**
(b) (4) 156.09	09/23/05	Sample Reassays and Reporting of Final Concentrations
(b) (4) 157.04	04/28/03	Application of Chromatographic Methods to Routine Drug Analysis

(b) (4) 157.05	06/30/05	Chromatographic Acceptance Criteria and Verification of Chromatogram

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	-

Summary/Conclusions, Study Assays: All of the analytical runs passed the acceptance criteria. Twenty-six individual samples were re-assayed – 12 for unacceptable I.S. response, 1 for loss of sample during processing and 13 for sample concentrations above or below limit of quantitation or modified calibration range. The study assay results are acceptable.

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters (N=48)

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
PARAMETER					
AUCT	1213.51	48.99	1188.57	51.61	1.02
AUCI	1502.62	44.39	1469.35	47.45	1.02
CMAX	20.22	44.41	21.08	54.19	0.96
TMAX	2.26	125.24	1.53	115.43	1.48
KE	0.01	33.96	0.01	32.14	0.97
THALF	129.91	35.23	123.71	30.84	1.05

Units: AUC=pg*hr/mL, Cmax=pg/mL, Tmax=hr

Table 9 Least Squares Geometric Means and 90% Confidence Intervals (N=48)

	Test LS Mean	Ref LS Mean	Ratio LS Means	Lower 90% CI	Upper 90% CI
LAUCT	1078.95	1052.44	1.03	96.12	109.35
LAUCI	1365.10	1328.45	1.03	96.56	109.35
LCMAX	18.42	19.03	0.97	90.16	103.91

Table 10 Additional Study Information

Root mean square error, LAUCT	0.188084
Root mean square error, LAUCI	0.181270
Root mean square error, LCmax	0.206895
Ke and AUCi determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	1
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic Analysis: Acceptable.

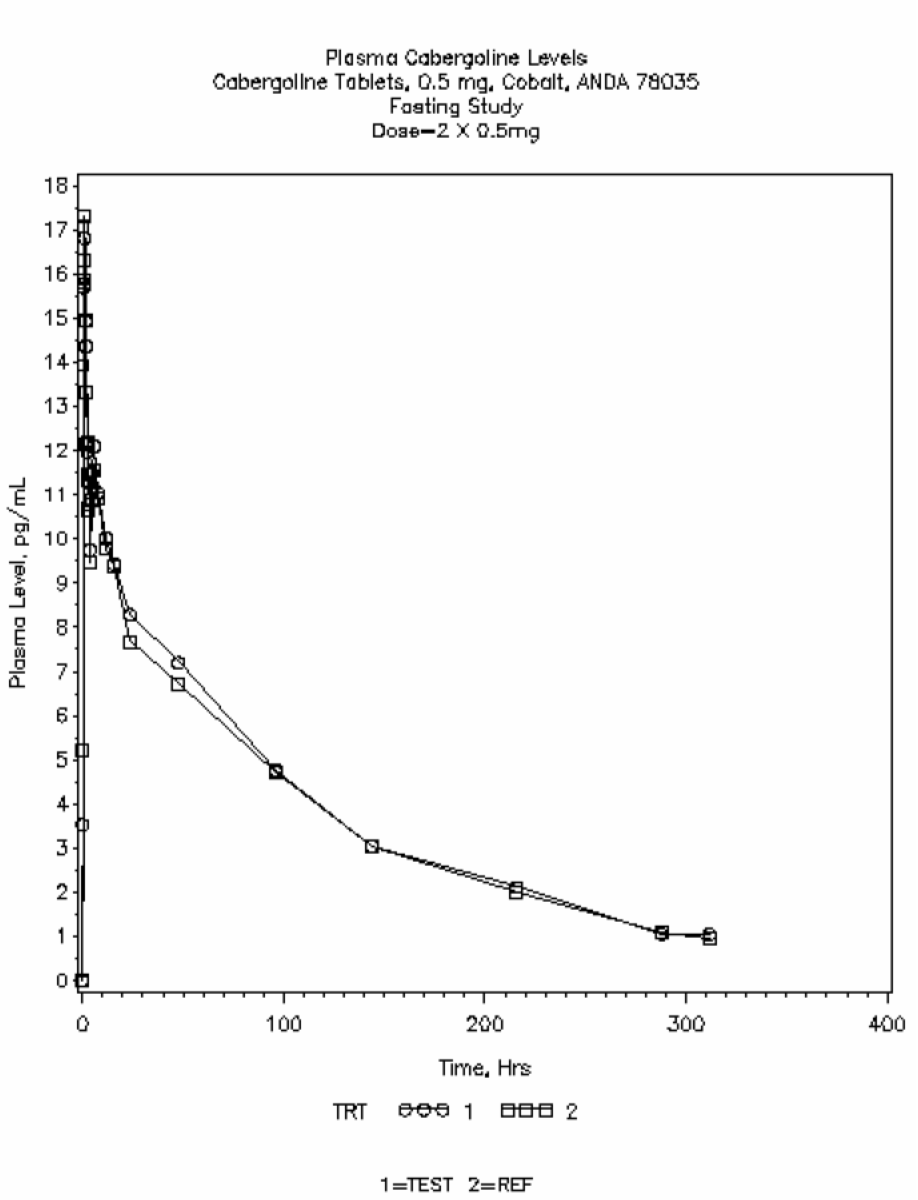
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The 90% confidence intervals for LAUCt, LAUCi, and LCmax are within the acceptable range limits of 80-125%.

Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (N=48)

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
Time (hr)					
0	0.00	.	0.00	.	.
0.25	3.53	122.52	5.23	101.21	0.68
0.5	13.94	64.78	17.09	73.60	0.82
0.75	15.70	55.17	17.30	57.61	0.91
1	15.79	46.75	16.33	52.11	0.97
1.33	16.81	42.15	15.89	45.02	1.06
1.67	14.93	42.27	14.94	42.44	1.00
2	14.37	48.91	13.33	39.35	1.08
2.33	12.20	38.73	12.16	35.79	1.00
2.67	11.98	39.76	12.18	39.60	0.98
3	11.29	40.34	11.45	38.06	0.99
3.33	10.79	42.91	10.68	38.53	1.01
3.67	11.28	42.21	11.08	36.93	1.02
4	9.76	46.36	9.46	40.75	1.03
5	11.50	46.19	10.87	41.52	1.06
6	12.11	45.73	11.55	41.24	1.05
8	11.04	53.07	10.95	58.33	1.01
12	10.02	52.88	9.78	54.18	1.02
16	9.43	52.65	9.39	57.34	1.00
24	8.28	56.68	7.69	58.06	1.08

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
48	7.20	54.81	6.70	54.15	1.07
96	4.78	41.98	4.73	49.29	1.01
144	3.04	48.21	3.05	47.55	1.00
216	2.12	49.60	2.02	55.69	1.05
288	1.06	87.09	1.11	87.69	0.96
312	1.06	79.38	0.96	98.01	1.10

Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	# 50398
Study Title	Randomized, Open-Label, 2-Way Crossover, Bioequivalence Study of Cabergoline 0.5 mg Tablet and Dostinex Following a 1 mg Dose in Healthy Subjects under Fed Conditions
Clinical Site	SFBC Anapharm, Montreal, Canada
Principal Investigator	Richard Larouce, M.D.
Study/Dosing Dates	09/08/05 (Period I) and 10/13/05 (Period II)
Analytical Site	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	10/29/05 – 11/19/05
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	72 days

Treatment ID	**A**	**B**
Test or Reference	Test	Reference
Product Name	Cabergoline Tablets	Dostinex® Tablets
Manufacturer	(b) (4)	Pharmacia & Upjohn Co.
Batch/Lot No.	F0604	A526A
Manufacture Date	06/2005	N/A
Expiration Date	N/A	02/2007
Strength	0.5 mg	0.5 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	96.0%	94.7%
Content Uniformity (mean, %RSD)	96.3% (2.6)	Not provided
Formulation	See Appendix Section B	Not provided
Dose Administered	2 x 0.5 mg	2 x 0.5 mg
Route of Administration	Orally with 240 mL of water	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	35 days
Randomization Scheme	AB: 1 – 3, 6, 10, 12, 13, 15, 17, 19, 20, 23, 27 – 29, 31, 33 – 35, 37, 42 – 45, 49, 51 BA: 4, 5, 7 – 9, 11, 14, 16, 18, 21, 22, 24 – 26, 30, 32, 36, 38 – 41, 46 – 48, 50, 52
Blood Sampling Times	Pre-dose, 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4, 5, 6, 8, 12, 16, 24, 48, 96, 144, 216, 288 and 312 hours
Blood Volume Collected/Sample	6 mL
Blood Sample Processing/Storage	Plasma separated after centrifuging, then flash-frozen at -80°C and stored at -20°C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Overnight (≥ 10 hours and 30 min. pre-dose) and 4 hours post-dose
Contents of Meal	High-fat, high-calorie breakfast (approx. 150 calories from protein, 250 from carbohydrates and 500 – 600 from fat)
Length of Confinement	10 hours pre-dose and until 24 hours post-dose
Safety Monitoring	Vital signs were measured prior to each dose and at specified blood draw times.

Comments on Study Design: The study design is acceptable.

b) Clinical Results

Table 12 Demographics of Study Subjects

		Safety population	**PK population**		
Category		**Total**	**Randomization**		**Total**
			AB	**BA**	
Age (years)	Mean ± SD	47 ± 14	46 ± 13	47 ± 15	46 ± 14
	Range	22 - 72	22 - 67	23 - 72	22 - 72
	Median	49	47	51	48
	N	52	22	25	47
Age Groups	< 18	0	0	0	0
	18-40	20 (38.5%)	7 (31.8%)	11(44.0%)	18 (38.3%)
	41-64	27 (51.9%)	13 (59.1%)	12 (48.0%)	25 (53.2%)
	65-75	5 (9.6%)	2 (9.1%)	2 (8.0%)	4 (8.5%)
	> 75	0	0	0	0

Category		Safety population	PK population		
		Total	Randomization		Total
			AB	BA	
Gender	Female	30 (57.7%)	12 (54.5%)	16 (64.0%)	28 (59.6%)
	Male	22 (42.3%)	10 (45.4%)	9 (36.0%)	19 (40.4%)
Race	Asian	0	0	0	0
	Black	0	0	0	0
	Caucasian	50 (96.2%)	22 (100.0%)	23 (92.0%)	45 (95.7%)
	American Hispanic	2 (3.9%)	0	2 (8.0%)	2 (4.3%)
Height (cm)	Mean ± SD	169.4 ± 8.9	170.6 ± 9.8	168.4 ± 8.6	169.5 ± 9.1
	Range	156.0 - 189.0	156.0 - 187.0	157.0 - 189.0	156.0 - 189.0
	Median	168.5	169.5	166.5	168.0
	N	52	22	25	47
Weight (kg)	Mean ± SD	72.0 ± 11.8	74.2 ± 14.9	71.3 ± 8.8	72.7 ± 12.0
	Range	51.2 - 103.6	51.2 - 103.6	51.6 - 91.5	51.2 - 103.6
	Median	71.5	74.8	71.8	72.7
	N	52	22	25	47
BMI (kg/m^2)	Mean ± SD	25.0 ± 3.1	25.3 ± 3.5	25.2 ± 2.7	25.2 ± 3.1
	Range	19.1 - 29.9	19.1 - 29.6	19.8 - 29.9	19.1 - 29.9
	Median	25.2	25.6	25.0	25.4
	N	52	22	25	47

Table 13 Dropout and Exclusion Information

(Additional information on page p 113, vol. 1.1)

Subject No	Reason	Period	Replaced?
06	Elected to withdraw prior to drug administration for personal reasons	II	No
13	Withdrawn from study prior to drug administration for not completing critical meal	II	No
49	Elected to withdraw prior to drug administration for personal reasons	II	No
52	Withdrawn from study prior to drug administration for not completing critical meal	II	No
34	Excluded from statistical analysis because of vomiting that occurred 4 hours, 8 minutes after drug administration in Period II	N/A	No

Table 14 Study Adverse Events

System Class	Project No. 50398*	
COSTART	A	B
Cardiac disorders		
Palpitat		
Eye disorders		
Conjunctivitis	1 (1.1%)	1 (1.1%)
Eye dis		
Pain eye		
Pruritus	1 (1.1%)	
Vision abnorm		
Gastrointestinal disorders		
Constip	1 (1.1%)	1 (1.1%)
Diarrhea		1 (1.1%)
Dry mouth	1 (1.1%)	
Dyspepsia		
Nausea	5 (5.7%)	2 (2.3%)
Pain abdo		1 (1.1%)
Vomit	2 (2.3%)	1 (1.1%)
General disorders and administration site conditions		
Asthenia		1 (1.1%)
Chills		
Vasodilat		
Infections and infestations		
Herpes simplex		
Infect fung	1 (1.1%)	
Injury, poisoning and procedural complications		
Ecchymosis inject site		
Edema inject site		
Inject site react		1 (1.1%)
Injury accid	1 (1.1%)	
Pain inject site	1 (1.1%)	1 (1.1%)
Investigations		
Hypertens	3 (3.4%)	1 (1.1%)
Hypotens	5 (5.7%)	5 (5.7%)
Tachycardia		
Musculoskeletal and connective tissues disorders		
Myalgia		
Pain		2 (2.3%)
Pain back	1 (1.1%)	
Nervous system and connective tissue disorders		
Dizziness	6 (6.9%)	3 (3.4%)
Headache	2 (2.3%)	5 (5.7%)
Hypesthesia	1 (1.1%)	
Somnolence	1 (1.1%)	1 (1.1%)
Vertigo		
Psychiatric disorders		
Confus		
Depersonal		1 (1.1%)
Insomnia	1 (1.1%)	
Nervousness		
Thinking abnorm	1 (1.1%)	

System Class	Project No. 50398*	
COSTART	A	B
Respiratory, thoracic and mediatinal disorders		
Cough inc	1 (1.1%)	1 (1.1%)
Pharyngitis	1 (1.1%)	2 (2.3%)
Rhinitis	1 (1.1%)	
Skin and subcutaneous tissue disorders		
Ecchymosis	1 (1.1%)	
Pruritus	1 (1.1%)	
Rash	1 (1.1%)	1 (1.1%)
Vascular disorders		
Vasodilat	1 (1.1%)	2 (2.3%)
TOTAL	**43**	**34**

* 10 adverse events in Project No. 50398 could not be assigned to a treatment group.

Table 15 Protocol Deviations

In addition to blood draw deviations (See sect. 14.3, vol. 1.2), the following protocol deviations occurred:

Subject	Deviation	Period (Treatment)	Excluded from analysis?
1 – 52	Humidity of medication storage facility rose above the range specified in facility SOP on 8 occasions for durations ≤ 1 min.	II (A, B)	No
1 – 52	Whether or not flash-freeze was performed on the 3-hr and 6-hr post-dose samples could not be confirmed.	II (A, B)	No
06	Post-study procedures were performed 26 days after the last study participation	N/A	No
10	Subject consumed ice cream with chocolate chips 5 days after drug administration	I (A)	No
26	Subject consumed chocolate cake 8 days after drug administration	II (A)	No
45	Subject consumed a chocolate muffin 12 days after drug administration	II (B)	No

Comments on Dropouts/Adverse Events/Protocol Deviations:

There were three separate incidents of vomiting that were reported for three subjects. Subject No. 34 was excluded from statistical analysis for emesis that occurred 4 hours, 8 minutes after drug administration. The remaining two incidents of vomiting occurred 8 hours, 6 minutes and 34 days after drug administration.

c) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

Analysis	Cabergoline
QC Conc. (pg/mL)	3.01, 7.53, 15.06, 35.14
Inter day Precision (%CV)	2.30 – 6.67%
Inter day Accuracy (%)	95.68 – 105.15%
Cal. Standards Conc. (pg/mL)	1.00 – 50.10
Inter day Precision (%CV)	3.4 – 6.93%
Inter day Accuracy (%)	97.92 – 101.00%
Linearity Range	$R^2 \geq 0.9906$

Comments on Study Assay Quality Control: Four of 38 runs failed acceptance criteria and were repeated. The assay results are acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially selected

Comments on Chromatograms: Acceptable

Table 17 SOP's dealing with analytical repeats of study samples

SOP No.	**Date of SOP**	**SOP Title**
(b) (4) **156.09**	**09/23/05**	**Sample Reassays and Reporting of Final Concentrations**
(b) (4) **157.04**	**04/28/03**	**Application of Chromatographic Methods to Routine Drug Analysis**
(b) (4) **157.05**	**06/30/05**	**Chromatographic Acceptance Criteria and Verification of Chromatogram**

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	-

Summary/Conclusions, Study Assays: A total of 59 samples (2.37%) were re-assayed – 19 for unacceptable I.S. response, 28 for sample concentrations above or below the limit of quantitation or modified calibration range and 2 samples were reanalyzed to confirm a value (detectable level at time zero). The study assay results are acceptable.

d) Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters (N=47)

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
PARAMETER					
AUCT	1571.40	50.03	1520.76	48.38	1.03
AUCI	1860.26	48.02	1813.17	45.83	1.03
CMAX	29.35	36.02	27.43	31.42	1.07
TMAX	1.83	40.19	1.85	51.12	0.99
KE	0.01	31.60	0.01	27.95	1.03
THALF	112.64	30.04	114.11	30.54	0.99

Units: AUC=pg*hr/mL, Cmax=pg/mL, Tmax=hr

Table 20 Least Squares Geometric Means and 90% Confidence Intervals (N=47)

	Test LS Mean	Ref LS Mean	Ratio LS Means	Lower 90% CI	Upper 90% CI
LAUCT	1390.73	1353.58	1.03	98.47	107.21
LAUCI	1664.61	1639.36	1.02	97.20	106.07
LCMAX	27.70	25.88	1.07	101.34	113.10

Table 21 Additional Study Information

Root mean square error, LAUCT	0.122527
Root mean square error, LAUCI	0.124531
Root mean square error, LCmax	0.158109
Ke and AUCi determined for how many subjects?	46 (of 47 total subjects analyzed)
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	None
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic Analysis: Subject 34 was excluded from the statistical analysis due to vomiting that occurred approximately 4 hours after drug administration. The BA/BE Guidance recommends that subjects be included in the analysis if vomiting occurs later than 2 times the median Tmax. The median Tmax for the fed study is 1.7 hours (test and reference). Review of the subject's concentration data shows drug exposure was consistent with the mean data reported for all subjects for the test and reference products. As such, inclusion of this individual subject is not expected to alter the results of the study. The firm's exclusion of this subject is acceptable.

The pharmacokinetic analysis is acceptable.

Summary and Conclusions, Single-Dose Non-Fasting Bioequivalence Study: The 90% confidence intervals for LAUCt, LAUCi, and LCmax are within the acceptable range limits of 80-125%.

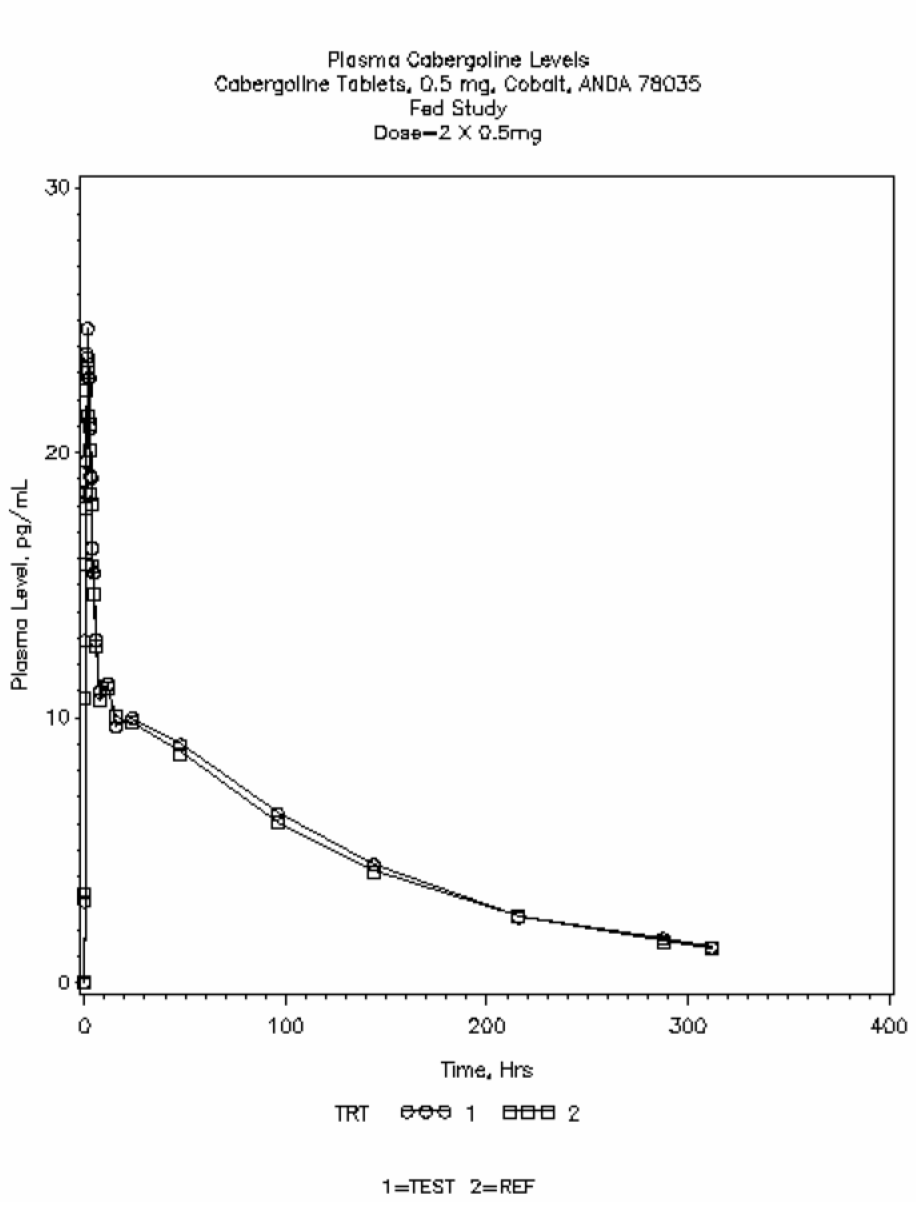
Table 22 Mean Plasma Concentrations, Single-Dose Non-Fasting Bioequivalence Study (N=47)

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
Time (hr)					
0	0.00	.	0.00	.	.
0.25	3.07	138.09	3.39	144.60	0.91
0.5	12.91	77.83	10.76	90.44	1.20
0.75	18.51	69.09	15.83	69.45	1.17
1	19.68	58.03	17.89	55.45	1.10
1.33	23.75	46.52	22.34	42.00	1.06
1.67	24.68	41.90	23.22	38.43	1.06
2	23.61	41.56	23.03	34.42	1.03
2.33	22.82	38.55	21.35	34.31	1.07
2.67	22.82	37.96	21.05	34.65	1.08
3	20.93	40.65	20.08	35.00	1.04
3.33	19.13	44.61	18.47	33.64	1.04
3.67	19.05	40.98	18.05	38.38	1.06
4	16.41	44.26	15.74	37.57	1.04
5	15.47	57.21	14.64	47.24	1.06
6	12.93	45.15	12.72	44.52	1.02
8	10.98	53.45	10.68	51.03	1.03
12	11.27	60.19	11.14	53.95	1.01
16	9.65	59.22	10.07	54.96	0.96
24	10.00	58.88	9.82	56.74	1.02
48	8.98	52.96	8.65	53.73	1.04
96	6.39	49.09	6.07	47.84	1.05

	Test	Test CV%	Ref	Ref CV%	Mean Ratio T/R
144	4.45	55.98	4.21	48.27	1.06
216	2.47	56.92	2.51	56.36	0.98
288	1.65	76.13	1.56	79.14	1.06
312	1.34	83.86	1.30	80.79	1.03

Unit: pg/mL

Figure 2 Mean Plasma Concentrations, Single-Dose Non-Fasting Bioequivalence Study



B. Formulation Data

Quantitative Composition :

Strength (Label Claim)	0.5 mg Tablet	
Component and Standard	**mg/tablet**	**%**
Cabergoline	0.5	0.625
Leucine	(b) (4)	(b) (4)
Lactose (b) (4)		
Total Weight	**80 mg**	**100.00**

Comments: The inactive ingredient Leucine exceeds the IIG database limit for an oral tablet formulation (b) (4)). A pharmacology/toxicology review conducted by Lynda Reid, Ph.D. finds the firm's proposed amount of leucine ((b) (4)/tablet) acceptable.

C. Dissolution Data

Source of Method (USP, FDA or Firm)	FDA
Medium	0.1 N HCl (at 37°C)
Volume (mL)	500 mL
USP Apparatus type	Type II (Paddle)
Rotation (rpm)	50 rpm
Firm's proposed specifications	NLT (Q) (b) (4)% at 15 min.

Study Ref. No.	Product Batch No.	Dosage Form	No. of Dosage Units	Collection Times Mean % Dissolved (Range)				
				5 min	10 min	15 min	20 min	30 min
Comparison of Dissolution Profiles in 0.1 N HCl @ 50 rpm	Cabergoline Tablets Lot # F0604 Mfg Date: 06/2005	0.5 mg Tablets	12	45	83	93	92	91
				(b) (4)				
	DOSTINEX® (cabergoline) Tablets Pharmacia & Upjohn Lot # A526A Expiry: 02/2007	0.5 mg Tablets	12	62	90	90	90	90
				(b) (4)				

Comment: In the October 13, 2006 amendment the firm acknowledged acceptance of the FDA's specification of NLT (Q) (b)(4)% in 15 min.

D. Consult Reviews

N/A

E. SAS Output

1. Fasting

(b) (4)

Following this page, 36 pages withheld in full - (b)(4)

F. Additional Attachments

N/A

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-035 APPLICANT: Cobalt Pharmaceuticals

DRUG PRODUCT: Cabergoline Tablets, 0.5 mg

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

The DBE acknowledges your acceptance of the following dissolution method and specification:

USP Apparatus:	II (Paddle) @ 50 rpm
Medium:	0.1 N HCl (at 37°C)
Volume:	500 mL
Specification:	NLT (Q) (b) (4)% at 15 min.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely Yours,

Dale P. Connor, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 78-035

BIOEQUIVALENCE – Acceptable Submission date: 03/06/06

1. FASTING STUDY (STF) Strength: 0.5 mg
Outcome: **AC**
Clinical Study Site: SFBC Anapharm, Sainte-Foy, Quebec, Canada
Analytical Site: (b) (4)

2. FED STUDY (STP) Strength: 0.5 mg
Outcome: **AC**
Clinical Study Site: SFBC Anapharm, Sainte-Foy, Quebec, Canada
Analytical Site: (b) (4)

Outcome Decisions: **AC = acceptable**

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/s/

Sarah M. Robertson
12/28/2006 06:51:05 AM
BIOPHARMACEUTICS

Chandra S. Chaurasia
12/28/2006 07:34:06 AM
BIOPHARMACEUTICS

Barbara Davit
12/28/2006 01:50:13 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-035

OTHER REVIEWS

2-1 Open Vol.

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
CONSULTATION: 206-0027
FOR INTERNAL USE WITHIN FDA ONLY

Date:	August 10, 2006
From:	Lynnda Reid, PhD Pharmacology Supervisor, DRUP LReid 8/10/06
Through:	Mark Hirsch, MD Acting Deputy Director, DRUP I concur MHirsch MD 8/14/06
To:	Benjamin Danso, Pharm D. Regulatory Project Manager Office of Generic Drug Products
Date of Consultation:	May 3, 2006 (Received August 9, 2006)
RE:	ANDA 78-035: Safety evaluation of the excipient L-leucine at (b) (4) mg per tablet (concentration in reference drug is (b) (4) mg per tablet)

Background information: ANDA 78-035 was filed by Cobalt Pharmaceuticals Inc. on December 12, 2005. The subject of this ANDA was to seek approval to market the generic product Cabergoline Tablets 0.5 mg. The reference listed drug is DOSTINEX® Tablets marketed by Pharmacia and Upjohn (NDA 20-664). The recommended dosage for DOSTINEX® Tablets for initiation of therapy is 0.25 mg twice a week. Dosage may be increased by 0.25 mg twice weekly up to a dosage of 1 mg twice a week according to the patient's serum prolactin level.

Cabergoline is a long-acting dopamine receptor agonist with a high affinity for D2 receptors. Cabergoline is used to suppress prolactin secretion by increasing the presence of dopamine at the level of the tuberoinfundibular neurons. Cabergoline is indicated for the treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas.

The consult from the Office of Generic Drugs (OGD) states that the Sponsor has proposed a generic formulation of cabergoline that contains the excipient L-leucine at a concentration of (b) (4) mg/0.5 mg tablet. On January 31, 2006, OGD issued a 'Refuse to File' letter for the following reason: "*The concentration of the inactive ingredient, in your proposed product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in an oral drug product.*" The concentration of L-leucine in DOSTINEX® is (b) (4) mg per 0.5 mg tablet. The Sponsor was asked to "*provide additional justification to demonstrate safety such as examples of approved drug products administered by the same route of administration, which contain this inactive ingredient in the same concentration range*".

The consult package included the following documents:

1. The abbreviated new drug application cover letter (dated 08-Dec-05) from the Sponsor with a request to market generic cabergoline 0.5 mg tablets.
2. The Refusal to File Letter (dated 31-Jan-06) from OGD for ANDA 78-035.
3. A Refuse to File Response (dated 06-Mar-06) from the Sponsor that included an overview of the published literature on the safety of L-leucine.
4. A note of a telephone conversation between Sandra Middleton (OGD Project Manager) and the Sponsor requesting hard copies of the referenced literature quoted by the Sponsor in the Refuse-to-File Response.
5. Full text copies of the requested references submitted by the Sponsor on 05-Apr-06:
   - A thirteen week oral toxicity study of L-leucine in rats to determine the NOAEL dose for both genders.
   - A review of the human literature on administration of branched chain amino acids (including L-leucine) that did not appear to cause significant adverse events.
   - A review by Life Sciences Research Office for the Food and Drug Administration on the Safety of Amino Acids used as Dietary Supplements (Dated 1992)

DRUP has been asked to provide a consult on the safety of leucine at the proposed concentration of (b) (4) mg per tablet.

Pharmacology/Toxicology Review

L-leucine (hereafter referred to as leucine) is an essential branched-chain amino acid. This reviewer believes that the concentration of (b) (4) mg/tablet found in the proposed generic Cabergoline Tablets is safe based on the following:

- Published Review of the Safety of Amino Acids Used as Dietary Supplement (CFSAN): The recommended dietary intake of leucine, present in both vegetable and animal proteins, is 40 mg/kg body weight/day (~2.5 g/day for a 60.0 kg individual). The recommended maximum dosage of DOSTINEX Tablets is 1 mg twice a week. Therefore, the maximum leucine intake would be (b) (4) mg/day for DOSTINEX Tablets and (b) (4) mg/day for the generic Cabergoline 0.5 mg Tablets. These doses of leucine represent only a small fraction (b) (4) of the recommended daily dietary intake of leucine. Furthermore, the Sponsor estimates the normal dietary intake for humans is somewhere between 7.7 and 10.5 g/day. This small additional intake of leucine is considered negible and of no toxicologic significance by this reviewer.

- Nonclinical study: The listed NOAEL dose for leucine in male and female rats (Tsubuku, 2004) was between 3.2 and 3.8 g/kg per day. The multiple of exposure between the NOAEL dose in rats is approximately (b) (4) fold greater than the proposed maximum exposure to leucine (b) (4) mg/day) following ingestion of Cabergoline 0.5 mg Tablets at the maximum recommended dose of 1 mg/day. This is an acceptable multiple of exposure.

- Published clinical review of branched chain amino acid intake in humans: Matthews (2005) reviewing the current studies of leucine alone and also branched chain amino acids concludes that leucine can be safely consumed in large amounts with no effect on hormone or protein metabolism.

The Review of the Safety of Amino Acids Used as Dietary Supplement did point out the following safety concerns associated with leucine:

1. High chronic leucine doses have been linked to bladder cancer in nonclinical studies. Rat carcinogenicity studies using leucine in combination with a co-carcinogen have shown increases in papilloma, a pre-cursor of bladder cancer. This reviewer does not view carcinogenicity as a significant safety concern given the amount of leucine in the proposed generic Cabergoline Tablets.

2. Individuals with maple syrup urine disease (MSUD - an inborn error of metabolism that causes high plasma levels of branched chain amino acids that result in hypoglycemia and in severe cases mental retardation and death) have excess blood leucine levels and need to monitor their intake of these amino acids daily. However, individuals with MSUD can identify leucine as an inactive ingredient on the proposed generic (and approved brand) label and can consider other alternative approved products for hyperprolactinemia treatment including bromocriptine.

Conclusion:

a. The proposed amount of leucine is acceptable as the amount is far below the Recommended Daily Allowance in a human diet and will not add substantially to the normal dietary intake of this essential amino acid.
b. The supporting literature provided by the Sponsor in humans demonstrates that much larger doses of leucine are unlikely to cause adverse events.
c. The stated NOAEL dose from the submitted nonclinical study represent an appropriate multiple of exposure for leucine compared to the amount proposed for use in the generic cabergoline formulation.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-035

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

COBALT
PHARMACEUTICALS INC.

Original ANDA

78-035
N-000

Office of Generic Drugs
CDER, FTA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Abbreviated New Drug Application
Cabergoline Tablets
0.5 mg

Dear Director, Office of Generic Drugs:

In accordance with statutory, regulatory and guidance provisions, Cobalt Pharmaceuticals Inc. is submitting an original abbreviated new drug application (ANDA) seeking approval to market the product Cabergoline Tablets 0.5 mg. The drug product described above has been shown to be equivalent to the reference listed drug DOSTINEX® Tablets marketed by Pharmacia and Upjohn.

We have submitted comparative information on the cabergoline product and the reference listed drug product DOSTINEX® Tablets. This information is presented in tabular format, comparing active ingredient, inactive ingredients, conditions of use, route of administration, dosage form, strength, bioequivalence, and labeling.

We have enclosed one (1) archival, one (1) review, and one (1) field copy of the application in accordance with 21 CFR § 314.55. As required, two (2) additional separately bound copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient and finished dosage form) are included. The number of volumes in the archival, review and field copies of the ANDA are as follows:

Blue Archival Copy	21 volumes
Analytical Methods Package	1 volume x 2 copies
Orange Review Copy	19 volumes
Red Review Copy	3 volumes
Burgundy Field Copy	2 volumes

6500 KITIMAT ROAD
MISSISSAUGA, ONTARIO
CANADA, L5N 2B8

T 905 814 1820 T 1 866 254 6111 F 905 814 8696

Cobalt Pharmaceuticals Inc. commits to resolve any issues identified in the methods validation process after approval.

We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

For more information on the organization of the ANDA please refer to the "Executive Summary" section.

A letter of authorization, allowing Dr. James Parker of Strategic Bioscience Corporation to act as our U.S. agent, is included in Section XX of this application.

Sincerely,

Tirtho Uppal

Ms. Tirtho Uppal
VP, R&D and Regulatory Affairs
Cobalt Pharmaceuticals Inc.

Dec 8/05
Date

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 78-035 **FIRM NAME:** COBALT PHARMACEUTICALS INC.

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: CABERGOLINE
DOSAGE FORM: TABLETS, 0.5 MG

Bio Assignments:		**Micro Review**
☒ **BPH**	☐ **BCE**	☐
☐ **BST**	☒ **BDI**	

Random Queue: 2
Chem Team Leader: Smela, Michael PM: Peter Chen Labeling Reviewer: Angela Payne

Letter Date: DECEMBER 8, 2005	**Received Date:** DECEMBER 12, 2005
Comments: EC - 1 YES **On Cards:** YES **Therapeutic Code:** 3030900 DOPAMINE AGONISTS	
Archival Format: PAPER **Sections I** **(356H Sections per EDR Email)** **Review copy**: YES E-Media Disposition: YES SENT TO EDR Not applicable to electronic sections Field Copy Certification (Original Signature) YES — Cover page & pg 10432	
Methods Validation Package (3 copies PAPER archive) **YES** (Required for Non-USP drugs)	
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

Reviewing CSO/CST Pamela J. Middleton **Date** 1/30/06	**Recommendation:** ☐ **FILE** ☒ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: [signature]	**Date:** 31 JAN 2006
ADDITIONAL COMMENTS REGARDING THE ANDA: Leucine exceeds max approved. ANDA uses (b) (4) mg/tablets. Max approved is (b) (4) (used by (b) (4)).	
Top 200 Drug Product:	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES ✓ (Statement regarding Rx/OTC Status) RX YES	✓
Sec. II	**Basis for Submission** **NDA# : 20-664** ✓ Ref Listed Drug: DOSTINEX Firm: PHARMACIA ✓ ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	✓
Sec. III	**Patent Certification** 1. Paragraph: III — pg. 12 2. Expiration of Patent: 12/29/05 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** YES pg. 14	✓
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use ✓ 2. Active ingredients ✓ 3. Route of administration ✓ 4. Dosage Form ✓ 5. Strength ✓	✓
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) [redacted] (b) (4) & Bulk (ct) 1. 4 copies of draft (each strength and container) or 12 copies of FPL ✓ 2. 1 RLD label and 1 RLD container label ✓ 3. 1 side by side labeling comparison with all differences annotated and explained ✓ 4. Was a proprietary name request submitted? NO (If yes, send email to Labeling Rvwr indicating such.)	✓
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES — pg. 76 **2. Request for Waiver of In-Vivo Study(ies): NA** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) **4. Lot Numbers of Products used in BE Study(ies):** Project # 50398 & 50397 **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	✓
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 0.5 MG a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) pg. 4932 | pg. 85 b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: YES — pg - 9811	✓

Lot #	Master	Exhibit	Made	Packaged
0.5 mg FOLLOW	[redacted] (b) (4)	[redacted] (b) (4)	[redacted] (b) (4)	[redacted] (b) (4) for this SNDA

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. <u>Solutions</u> (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. <u>Suspensions</u> (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation ✓ 2. Inactive ingredients as appropriate X Leucine (see notes)	☑

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers ✓ b. Type II DMF authorization letters or synthesis pg 9876 # (b) (4) c. COA(s) specifications and test results from drug substance mfgr(s) ✓ d. Applicant certificate of analysis ✓ e. Testing specifications and data from drug product manufacturer(s) ✓ f. Spectra and chromatograms for reference standards and test samples ✓ g. CFN numbers — 2. **Inactive Ingredients** a. Source of inactive ingredients identified pg. 9914 (source only) b. Testing specifications (including identification and characterization) ✓ c. Suppliers' COA (specifications and test results) ✓ d. Applicant certificate of analysis ✓	☑ ✓
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) ✓ 2. CGMP Certification: YES — pg 9934 3. CFN numbers (b) (4) Reg. #	☑
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address ✓ 2. Functions ✓ 3. CGMP Certification/GLP ✓ 4. CFN numbers —	☑ ✓
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) ✓ 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified ✓ (b) (4) 3.If sterile product: Aseptic fill / Terminal sterilization 4.Filter validation (if aseptic fill) 5. Reprocessing Statement — pg. 9978	☑
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation ✓ 2. In-process Controls - Specifications and data ✓	☑ ✓
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) ✓ 2. Components Specification and Test Data (Type III DMF References) ✓ 3. Packaging Configuration and Sizes ✓ 4. Container/Closure Testing ✓ 5. Source of supply and suppliers address ✓	☑ ✓

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data 2. Certificate of Analysis for Finished Dosage Form ✓ pg. 10154	☑
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted ✓ 2. Post Approval Commitments ✓ 3. Expiration Dating Period ✓ 24 months 4. Stability Data Submitted ✓ a. 3 month accelerated stability data ✓ b. Batch numbers on stability records the same as the test batch ✓	☑
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance ✓ 2. Finished Dosage Form ✓ 3. Same lot numbers ✓	☑
Sec. XVII	**Environmental Impact Analysis Statement** ✓	☑
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) - pg. 10425 2. Debarment Certification (original signature): YES - pg. 10420 3. List of Convictions statement (original signature)	☑

OGD Template Revised 04/01/2004 /T.Hinchliffe

ANDA 78-035

JAN 3 1 2006

Strategic Bioscience Corporation
U.S. Agent for: Cobalt Pharmaceuticals
Attention: James Parker, JD, Ph.D.
93 Birch Hill Road
Stow, MA 01775-1308

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated December 8, 2005, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Cabergoline Tablets, 0.5 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> The concentration of the inactive ingredient (Leucine), in your proposed product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in an oral drug product. Therefore, the proposed product cannot be approved as an ANDA [21 CFR 314.127(a)(8)(ii)]. Please provide additional justification to demonstrate safety such as examples of approved drug products administered by the same route of administration, which contain this inactive ingredient in the same concentration range.
>
> Please note that DMF authorization and composition alone is not sufficient data to prove safety. If you choose to provide the composition instead of pharmacology/ toxicology data, you must provide supporting data showing that each component and composition was used in an approved drug product. Although considered supportive, please note that GRAS certification, FEMA certification, DMF authorization, or composition may not be enough to demonstrate safety.

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Saundra T. Middleton
Project Manager
(301) 827-0498

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 78-035
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-92

Endorsement:
HFD-615/M. Shimer, Chief, RSB _____ date 31 JAN 2006
HFD-615/S. Middleton, CSO S. Middleton date 1/30/06
Word File
V:/FIRMSAM\COBALT\LTRS&REV\78035.RTF
F/T by StM 1/30/06
ANDA Refuse to Receive!

COBALT
PHARMACEUTICALS INC.

REFUSAL TO FILE RESPONSE
ANDA 78-035

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Saundra Middleton, Project Manager

RE: Refusal to File Response
ANDA for Cabergoline Tablets 0.5 mg

Please find presented Cobalt's Refusal to File response for Cabergoline Tablets, ANDA 78-035 in response to the Food and Drug Administration letter dated January 31, 2006 (a copy is presented in the response). This response is presented in a comment/response format.

Presented also is a copy of the 356h form for the amendment.

We trust the documentation provided is satisfactory and allows for the continuation of the review for the Cabergoline Tablets ANDA.

If you have any further questions or concerns, please do not hesitate to contact the undersigned or our U.S. agent Dr. James Parker of Strategic Bioscience Corporation.

Sincerely,

for D. Hillman

Ms. Tirtho Uppal
VP, R&D and Regulatory Affairs

March 6, 2006
Date

6500 KITIMAT ROAD
MISSISSAUGA, ONTARIO
CANADA, L5N 2B8

T 905 814 1820 T 1 866 254 6111 F 905 814 8696

COBALT
PHARMACEUTICALS INC.

Will be sent for consult S. Middleton 4/5/06

ORIG AMENDMENT

FDA's REQUEST FOR STUDY REPORTS
ANDA 78-035

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/AC

Attn: Saundra Middleton, Project Manager

RE: FDA's Request for Study Reports for Refusal to File Response
ANDA for Cabergoline Tablets 0.5 mg

As per your telephone contact on April 5, 2006 with Dr. James Parker, of Strategic BioScience Corporation, please find presented two of the referenced studies in their full reports, along with the relevant section of the referenced Safety of Amino Acids Used As Dietary Supplements report.

This response is presented in a comment/response format.

Presented also is a copy of the 356h form for the amendment.

We trust the documentation provided is satisfactory and allows for the continuation of the review for the Cabergoline Tablets ANDA.

If you have any further questions or concerns, please do not hesitate to contact the undersigned or our U.S. agent Dr. James Parker of Strategic Bioscience Corporation.

Sincerely,

D. Uppal

Ms. Tirtho Uppal
VP, R&D and Regulatory Affairs

April 6, 2006
Date

RECEIVED
APR 10 2006
OGD / CDER

6500 KITIMAT ROAD
MISSISSAUGA, ONTARIO
CANADA, L5N 2B8

T 905 814 1820 T 1 866 254 6111 F 905 814 8696

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION** **Consult No: 2006-0027**
TO *(Division/Office)* DCRP - HFD 110 Thru: Colleen LoCicero, ODE I - HFD 101	FROM: Saundra Middleton

DATE: 4/27/2006	IND NO.	ANDA NO. 078035	TYPE OF DOCUMENT Original	DATE OF DOCUMENT 12/8/05,3/6/06 and 4/6/06
NAME OF DRUG CABERGOLINE		PRIORITY CONSIDERATION 30 days	CLASSIFICATION OF DRUG DOPAMINE AGONISTS	DESIRED COMPLETION DATE 5/27/2006

NAME OF FIRM COBALT

REASON FOR REQUEST

I. GENERAL

Γ NEW PROTOCOL	Γ PRE NDA MEETING	Γ RESPONSE TO DEFICPENCY LETTER
Γ PROGRESS REPORT	Γ END OF PHASE II MEETING	Γ FINAL PRINTED LABELING
Γ NEW CORRESPONDENCE	Γ RESUBMISSION	Γ LABELING REVISION
Γ DRUG ADVERTISING	Γ SAFETY/EFFICACY	Γ ORIGINAL NEW CORRESPONDENCE
Γ ADVERSE REACTION REPORT	Γ PAPER NDA	Γ FORMULATIVE REVIEW
Γ MANUFACTURING CHANGE/ADDITION	Γ CONTROL SUPPLEMENT	X *OTHER ('specify below)*
Γ MEETING PLANNED BY _____		

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

□ DISSOLUTION	□ DEFICIENCY LETTER RESPONSE
□ PROTOCOL-- BIOPHARMACEUTICS	□ BIOAVAILABILITY STUDIES
□ IN--VIVO WAIVER REQUEST	□ PHASE IV STUDIES

IV.DRUG EXPERIENCE

□ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	□ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
□ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	□ SUMMARY OF ADVERSE EXPERIENCE
□ CASE REPORTS OF SPECIFIC *REACTIONS(List below)*	POISON RISK ANALYSIS
□ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

□ CLINICAL □ PRECLINICAL

COMMENTS
Colbalt used (b) (4) of Leucine in their formulation which exceeds the maximum approved level of (b) (4) approved amount listed in the IIG. Please review the supporting data.Please provide an electronic copy of the review to Benjamin Danso, HFD-617(benjamin.danso@fda.hhs.gov) followed by a hard copy.Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* □ MAIL □ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

ANDA 78-035 Final Check List for Branch Chief

- ✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.
- ✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.
- ✓ 3) Check for gross errors in letter.
- ✓ 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)
- ✓ 5) Check address and contact person on letter vs. 356h.
- ✓ 6) Check for any t-cons and verify date and correspondence date.
- ✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.
- ✓ 8) Check for any comments or problems raised by reviewer on Check List.
- N/A 9) If first generic, copy BE review and file.
- ✓ 10) Sign Check List.
- ✓ 11) Check electronic Orange Book to verify current patent information and correct RLD.
- N/A 12) Check for MOU patents
- ✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.
- ✓ 14) Review Basis for Submission. Dosing 20-602
- ✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.
- ✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.
- ✓ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.
- ✓ 18) Pull USP information. (USP ____yes ✓ no)
- ✓ 19) Final Grammar review on letter.
- ✓ 20) Verify information in OGD Patent Tracking System.
- ✓ 21) EES slip.
- ✓ 22) Document in record book.

Signature Martin H. Gruni date 3 May 2006

ANDA 78-035

MAY 04 2006

Strategic Bioscience Corporation
U.S. Agent for: Cobalt Pharmaceuticals
Attention: James Parker, JD, Ph.D.
93 Birch Hill Road
Stow, MA 01775-1308

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to our "Refuse to Receive" letter dated January 31, 2006 and your amendment dated March 6, 2006.

Reference is also made to the telephone conversation dated April 5, 2006 and your correspondence dated April 6, 2006

NAME OF DRUG: Cabergoline Tablets, 0.5 mg

DATE OF APPLICATION: December 8, 2005

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 8, 2006

We will correspond with you further after we have had the opportunity to review your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Peter Chen
Project Manager
(301) 827-5773

Sincerely yours,

Wm Peter Rickman
Director,
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 78-035
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-92

Endorsement:
HFD-615/M. Shimer, Chief, RSB _____ date 3 MAY 06
HFD-615/S. Middleton, CSO _____ date 4/27/06
Word Document
V:/FIRMSAM\COBALT\LTRS&REV\78035.ACK
F/T by 4/27/06
ANDA Acknowledgment Letter!

2.1

BIOEQUIVALENCY AMENDMENT

ANDA 78-035

JUL 25 2006

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Cobalt Pharmaceuticals Inc. TEL: 978.897.8404

ATTN: James Parker, Ph.D. FAX: 978.461.0333

FROM: Aaron Sigler PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 06, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cabergoline Tablets, 0.5 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-035 APPLICANT: Cobalt

DRUG PRODUCT: Cabergoline Tablets, 0.5 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiency has been identified:

Please conduct and submit dissolution testing on the test and reference products (12 units each) using the following FDA-recommended method:

USP Apparatus:	II(paddle)@ 50 rpm
Dissolution Medium:	***0.1 N HCl (not 0.01 N HCl)*** (@ 37°C)
Volume of Dissolution Medium:	500 mL
Sampling Times:	5, 10, 15, 20, 30 minutes or until at least 80% of the labeled amount is dissolved.

The results should be submitted in electronic CTD format, with individual data as well as mean, range and CV% data included.

Sincerely yours,

Barbara M. Davit for

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

COBALT
PHARMACEUTICALS INC.

BIOEQUIVALENCY AMENDMENT
ANDA 78-035

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N-AB

RE: Bioequivalency Amendment dated July 25, 2006 for ANDA for Cabergoline Tablets 0.5 mg

Further to the bioequivalency amendment request dated July 25, 2006 for the above referenced ANDA, please find presented our response in a comment/response format with supporting documentation where applicable.

Presented is a copy of the 356h form for the ANDA. A copy of the bioequivalency amendment request to Dr. James Parker of Strategic Bioscience Corporation, U.S. agent for Cobalt Pharmaceuticals Inc., has also been presented.

We trust the documentation provided is satisfactory and allows the submission review to continue.

If you have any further questions or concerns, please do not hesitate to contact the undersigned or our U.S. agent Dr. James Parker of Strategic Bioscience Corporation.

Sincerely,

Ms. Tirtho Uppal
VP, R&D and Regulatory Affairs

August 28, 2006
Date

RECEIVED
AUG 31 2006
OGD / CDER

6500 KITIMAT ROAD
MISSISSAUGA, ONTARIO
CANADA, L5N 2B8

T 905 814 1820 T 1 866 254 6111 F 905 814 8696

MINOR AMENDMENT

ANDA 78-035

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

SEP 28 2006

TO: Strategic Bioscience Corporation
U.S. Agent for Cobalt Pharmaceuticals Inc.
ATTN: James Parker, Ph.D.

TEL: 978.897.8404

FAX: 978.461.0333

FROM: Peter Chen

PROJECT MANAGER: (301) 827-5773

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 06, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cabergoline Tablets, 0.5 mg.

Reference is also made to your amendment dated March 6 and April 6, 2006.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

PC 9/28/06

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-035

APPLICANT: Cobalt Pharmaceuticals Inc.

DRUG PRODUCT: Cabergoline Tablets, 0.5 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.
9.
10.

11. [redacted] (b) (4)

12.

13.

14.

15.

16. DMF [redacted] (b) (4) is deficient and the deficiencies have been communicated to the DMF holder. Please ensure a response.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide the available long term stability data for drug product.

2. Information related to labeling and bioequivalence is pending review. After the reviews are completed, any deficiencies found will be communicated to you under separate cover.

3. An acceptable compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

Sincerely yours,

M Samela for

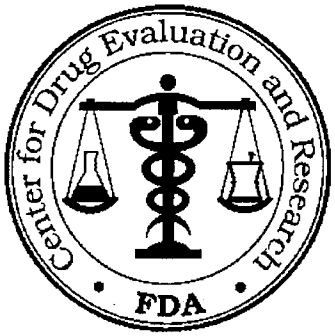
Rashmikant M. Patel, Ph. D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.1

BIOEQUIVALENCY AMENDMENT

ANDA 78-035

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Cobalt Pharmaceuticals Inc. TEL: 978.897.8404

OCT 0 4 2006

ATTN: James Parker, Ph.D. FAX: 978.461.0333

FROM: Aaron Sigler AS PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 06, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cabergoline Tablets, 0.5 mg.

Reference is also made to your amendment dated August 28, 2006.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-035 APPLICANT: Cobalt Pharmaceuticals

DRUG PRODUCT: Cabergoline Tablets, 0.5 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiency has been identified:

We acknowledge that you have conducted dissolution testing using the following FDA-recommended method:

USP Apparatus:	II(paddle)@ 50 rpm
Dissolution Medium:	0.1 N HCl @ 37°C)
Volume of Dissolution Medium:	500 mL

The dissolution data met the following FDA-recommended specification at S1 level:

Not less than (b) (4)% (Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

Please acknowledge the FDA-recommended dissolution method and specification.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

COBALT
PHARMACEUTICALS INC.

Bioequivalency Amendment
ANDA 78-035

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N1AB

RECEIVED
OCT 17 2006
OGD / CDER

RE: Bioequivalency Amendment dated October 04, 2006 for ANDA for Cabergoline Tablets 0.5 mg

Further to the bioequivalency amendment request dated October 04, 2006 for the above referenced ANDA, please find presented our response in a comment/response format with supporting documentation where applicable.

Presented is a copy of the 356h form for the ANDA. A copy of the bioequivalency amendment request to Dr. James Parker of Strategic Bioscience Corporation, U.S. agent for Cobalt Pharmaceuticals Inc., has also been presented.

We trust the documentation provided is satisfactory and allows the submission review to continue.

If you have any further questions or concerns, please do not hesitate to contact the undersigned or our U.S. agent Dr. James Parker of Strategic Bioscience Corporation.

Sincerely,

D. Hillier

Ms. Donna Hillier
Director, Regulatory Affairs

Oct 13, 2006

Date

6500 KITIMAT ROAD
MISSISSAUGA, ONTARIO
CANADA, L5N 2B8

T 905 814 1820 T 1 866 254 6111 F 905 814 8696

COBALT
PHARMACEUTICALS INC.

ORIGINAL

MINOR AMENDMENT
ANDA 78-035

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N-000-AM

RE: Minor Amendment dated September 28, 2006 for ANDA for Cabergoline Tablets 0.5 mg

Further to the minor amendment request dated September 28, 2006 for the above referenced ANDA, please find presented our response in a comment/response format with supporting documentation where applicable.

Presented is a copy of the 356h form for the ANDA. A copy of the minor amendment request to Dr. James Parker of Strategic Bioscience Corporation, U.S. agent for Cobalt Pharmaceuticals Inc., has also been presented.

We trust the documentation provided is satisfactory and allows the submission review to continue.

If you have any further questions or concerns, please do not hesitate to contact the undersigned or our U.S. agent Dr. James Parker of Strategic Bioscience Corporation.

Sincerely,

D. Hillier

Ms. Donna Hillier
Director, Regulatory Affairs

March 22, 2007

Date

RECEIVED
MAR 26 2007
CDER

6500 KITIMAT ROAD
MISSISSAUGA, ONTARIO
CANADA, L5N 2B8

905 814 1820 1 866 254 6111 905 814 8696

COBALT
PHARMACEUTICALS INC.

ORIGINAL

Amendment – Change of Manufacturing Site
ANDA 78-035

NA (Minor) issued 5/1/07 based on review of 3/22/07. When responded, it will be considered major due to this unsolicited amendment.
MS
5/15/07

ORIG AMENDMENT
N-000 - ~~AM~~ AA

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Amendment – Change of Manufacturing Site
Cabergoline Tablets 0.5 mg

Site added per CC 5/14/07 Cobalt Pharmaceuticals

Dear Director, Office of Generic Drugs:

In accordance with statutory, regulatory and guidance provisions, Cobalt Pharmaceuticals Inc., is submitting an amendment to pending ANDA 78-035 seeking approval to change of manufacturing site of the product Cabergoline Tablets 0.5 mg.

Since there is no existing patent for cabergoline, Cobalt requests the co-operation of the FDA to review the amendment-change of manufacturing site application in an expedited manner to allow Cobalt to achieve approval as soon as possible. Please note that there are no major changes in any Chemistry, Manufacturing and Control documents and the chemistry and manufacturing documents are consistent with those provided in the minor amendment response dated March 22, 2007. Cobalt requested that this minor amendment be reviewed in the same review cycle with the March 22, 2007 response. Cobalt has revised its insert text to be in accordance with current approved reference listed drug package insert. Bottle labels and package insert has been revised only for change in pack sizes and to reflect the proposed site of manufacture. Please refer to Introduction to Amendment that is presented in the following pages.

Labeling Assignment Added 5/16/07

Cobalt has submitted comparative information on the Cobalt Pharmaceuticals Inc. product Cabergoline Tablets 0.5 mg (proposed manufacturing site), the (b) (4) (b) (4) Product (original manufacturing site), and the reference listed drug product Dostinex® Tablets. This information is presented in tabular format, comparing active ingredient, inactive ingredients, conditions of use, route of administration, dosage form, strength, bioequivalence, and labeling.

The original ANDA was supported by a bioequivalence study for the test product (manufactured at (b) (4)) against the Reference Listed Drug Dostinex®. In support of this supplement, dissolution testing of the product from the proposed site and product from the original site has been performed. Comparative dissolution profiles are presented that show the products are equivalent with and f_2 value above 50%.

RECEIVED
APR 27 2007
OGD / CDER

6500 KITIMAT ROAD
MISSISSAUGA, ONTARIO
CANADA, L5N 2B8

905 814 1820 1 866 254 6111 905 814 8696

01

The submission is presented in CTD format based on the FDA Guidance, "Submitting Marketing Applications According to the ICH-CTD Format – General Consideration" dated August 2001 and the ANDA checklist for CTD format. We have enclosed one (1) archival, one (1) review, and one (1) field copy of the application in accordance with 21 CFR'314.55. As required, three separately bound method validation packages are provided. The numbers of volumes in the archival, review and field copies of the ANDA are as follows:

Blue Archival Copy	5 volumes
Orange Review Copy	3 volumes
Red Review Copy	4 volumes
Green Field Copy	2 volumes

Cobalt Pharmaceuticals commits to resolve any issues identified in the methods validation process after approval.

We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

A letter of authorization, allowing Dr. James Parker of Strategic Bioscience Corporation to act as our U.S. agent, is included in *Section 1.4.1 Letter of Authorization.*

Sincerely,

Joy D. Hulbert

Ms. Tirtho Uppal
Vice President,
R&D and Regulatory Affairs

Apr 25/07

Date

MINOR AMENDMENT

ANDA 78-035

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Strategic Bioscience Corporation TEL: 978.897.8404

ATTN: James Parker, Ph.D. FAX: 978.461.0333

FROM: Esther Chuh PROJECT MANAGER: (301) 827-5773

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 8, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cabergoline Tablets, 0.5 mg.

Reference is also made to your amendment dated March 22, 2007.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-035

APPLICANT: Cobalt Pharmaceuticals Inc.

DRUG PRODUCT: Cabergoline Tablets, 0.5 mg

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies:

1. DMF (b) (4) remains deficient and the deficiencies have been communicated to the DMF holder. Please ensure a response.

2. Please clarify which facility will perform (b) (4) routinely on the drug substance.

3. We acknowledge that (b) (4) .

4. We acknowledge that you (b) (4) testing.

5. Please note that (b) (4)

6. Please revise the (b) (4)

7. The (b) (4) based on the available data.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

1. Information related to labeling is pending review. After the review is completed, any deficiencies found will be communicated to you under separate cover.

2. Please provide all available long term stability data.

3. The proposed limit for (b) (4) is pending safety review.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph. D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Michael Smela
5/1/2007 08:28:24 AM
For Rashmikant M. Patel, Ph.D.

Record of Telephone Conversation

Cobalt submitted an unsolicited amendment which provides for "change of manufacturing site" on April 25, 2007. Meanwhile, the agency has issued a NA Minor to amendment dated 3/22/07 on 5/1/2007.

Mike Smela requested that Cobalt respond to the NA Minor issued on 5/1/2007 as a Major Amendment and to reference this unsolicited amendment submitted on 4/25/2007.

Also, we requested Mr. Parker to address whether the new proposed site is an alternate site or a new site.

Date:
5/15/2007

ANDA Number:
78-035

Product Name:
Cabergoline 0.5 mg Tablets

Firm Name:
Cobalt Pharmaceuticals Inc.

Firm Representative:
Mr. James Parker

Phone Number:
978-897-8404

FDA Representative:
ESTHER CHUH, Project Manager
MIKE SMELA: Team Leader, Division of Chemistry I, Team II

Signatures:

CC: ANDA

V:\FIRMSAM\ \TELECONS\ .doc

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Esther Chuh
5/16/2007 03:36:37 PM
CSO

Michael Smela
5/16/2007 03:48:22 PM
CHEMIST

Telephone Fax

ANDA 78-035

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301-827-5846

TO: Cobalt Pharmaceuticals TEL: 978-897-8404

ATTN: James Parker- USA Strategic Bioscience FAX: 978-461-0333

FROM: Mrs. Angela Payne

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cabergoline Tablets .

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

See attached labeling comments.

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-035 Dates of Submission: 25 APR 2007

Applicant's Name: Cobalt

Established Name: Cabergoline Tablets 0.5 mg

Labeling Deficiencies: Draft Labels and Labeling

1. **CONTAINER** (8s):

   A. Your previous submission provided for (b) (4) and (b) (4) are these package sizes no longer being proposed. Regarding your bulk package labels- Our labeling division does not review those particular bulk package sizes. Please comment.

   B. Will you provide a carton to protect the glass bottle from possible breakage? If so please submit the carton for review.

2. **INSERT:**

   A. DESCRIPTION, cite the specific kind of lactose (anhydrous or mono..).

   B. HOW SUPPLIED - Please cite the strength "0.5 mg" of the product in the first sentence with the established name.

   C. Please update your labeling to be in accord with the most recent labeling S-008 approved on 12/12/2006 for the reference listed drug.

Please submit final printed electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -
http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug (or your previous submission) with all differences annotated and explained

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Grace
5/23/2007 06:53:17 PM
for Wm Peter Rickman

COBALT
PHARMACEUTICALS INC.

Unsolicited site change amendment (not reviewed in previous cycle) dictates this response to be coded MAJOR. M Smela 6/21/07
called firm 6/21/07 gv

ORIGINAL

MINOR AMENDMENT
ANDA 78-035
SUPPLEMENT AMENDMENT

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/AM AC

RECEIVED
JUN 14 2007
OGD

RE: Minor Amendment dated May 01, 2007 & Telephone Contact Reports dated May 15, 2007 and May 16, 2007 for ANDA for Cabergoline Tablets 0.5 mg

new cancel site Site withdrawn per firm's request 6/21 EC

Further to the minor amendment request dated May 01, 2007, the received chemistry deficiency references the Minor Amendment Response dated March 22, 2007. Just prior to receipt of this amendment Cobalt filed an Amendment – Change in Manufacturing Site from (b) (4) to Cobalt Pharmaceuticals Inc. (dated April 25, 2007). As per Mike Smela of the FDA telephone contact with Cobalt Pharmaceuticals' US agent, Dr. James Parker of Strategic Bioscience Corporation on May 15, 2007 and further with Tirtho Uppal, VP, R&D and Regulatory Affairs on May 16, 2007 Mr. Smela advised that since Cobalt have filed a change of site that the minor amendment received on May 1st will now become a major amendment.

A copy of the telephone contact reports are presented in this response for your reference. Please note that there are no major changes in any Chemistry, Manufacturing and Control documents provided in change of manufacturing site application and the chemistry and manufacturing documents are consistent with those provided in the minor amendment response dated March 22, 2007. Cobalt is requesting that the amendment received on May 1, 2007 continue to treated as a minor amendment and be reviewed in the same review cycle.

New Site

As a result of the change in site amendment commercial product will be supplied only from the Cobalt Pharmaceuticals Inc. site. Hence, Cobalt has revised appropriate documents as per FDA requirements only for its own manufacturing site (Change of Manufacturing Site) and presented in this response. Please find presented our response in a comment/response format with supporting documentation where applicable.

Since there is no existing patent for cabergoline, Cobalt requests the co-operation of the FDA to review this minor amendment response and the associated change in manufacturing site amendment in an expedited manner to allow Cobalt to achieve approval as soon as possible.

Presented is a copy of the 356h form for the ANDA. A copy of the minor amendment request to Dr. James Parker of Strategic Bioscience Corporation, U.S. agent for Cobalt Pharmaceuticals Inc., has also been presented.

6500 KITIMAT ROAD
MISSISSAUGA, ONTARIO
CANADA, L5N 2B8

T 905 814 1820 T 1 866 254 6111 F 905 814 8696

We trust the documentation provided is satisfactory and allows the submission review to continue.

If you have any further questions or concerns, please do not hesitate to contact the undersigned or our U.S. agent Dr. James Parker of Strategic Bioscience Corporation.

Sincerely,

D. Hillier

Ms. Donna Hillier
Director, Regulatory Affairs

June 11, 2007

Date

COBALT
PHARMACEUTICALS INC.

ORIGINAL

LABELING AMENDMENT
ANDA 78-035

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

RE: Labeling Amendment dated May 24, 2007 for ANDA for Cabergoline Tablets 0.5 mg

Please find presented Cobalt's Label Amendment for Cabergoline Tablets 0.5 mg in response to the Food and Drug Administration letter dated May 24, 2007 (copy presented in this response). The amendment is presented in a comment/response format with supporting documentation where required. The side-by-side comparison of the previously submitted insert and the proposed insert has been presented at the end of the section.

Presented is a copy of the 356h form for the ANDA. A copy of the Labeling amendment requests to Dr. James Parker of Strategic Bioscience Corporation, U.S. agent for Cobalt Pharmaceuticals Inc., have also been presented.

Cobalt Pharmaceuticals Inc. is currently in the process of transferring ownership of this ANDA to another company. A letter to this affect is being sent to the FDA for notification of the change. Cobalt apologies if the timing of this response overlaps however this response package had already been compiled. Cobalt Pharmaceuticals Inc. has chosen to continue with the response. All future response will be under the name of the new owner of the ANDA. Again, we apologize for any confusion.

We trust the documentation provided is satisfactory and allows the submission review to continue.

If you have any further questions or concerns, please do not hesitate to contact the undersigned or our U.S. agent Dr. James Parker of Strategic Bioscience Corporation.

Sincerely,

Donna Hillier

Ms. Donna Hillier
Director, Regulatory Affairs

Aug 8, 2007
Date

RECEIVED
AUG 10 2007
OGD

6500 KITIMAT ROAD
MISSISSAUGA, ONTARIO
CANADA, L5N 2B8

T 905 814 1820 T 1 866 254 6111 F 905 814 8696

COBALT
PHARMACEUTICALS INC.

Change in Ownership for ANDA 78-035

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MC

Re: Abbreviated New Drug Application 78-035
Cabergoline Tablets
0.5 mg

In accordance with 21 CFR §314.72, Cobalt Pharmaceuticals Inc., the original applicant of the above referenced ANDA, wishes to advise that a change in ownership of the application has taken place. All rights to the above referenced application have been transferred to:

Cobalt Laboratories
24840 S. Tamiami Trail
Building B, Suite 1
Bonita Springs, Florida
USA, 34134

The change in ownership is effective as of July 23, 2007.

In accordance with 21 CFR §314.72 a complete copy of the ANDA including any amendments and records required to be kept under 21 CFR §314.81 has been given to Cobalt Laboratories, for their files.

Cobalt Laboratories, as the new owner of the application will comply with the requirements for any patent certifications, if applicable, as outlined in the Acceptable for Filing Letter dated May 4, 2006.

Please contact the undersigned if you have any questions or concerns with regard to this letter.

Sincerely,

Joy D. Uppal

Ms. Tirtho Uppal
VP, R&D and Regulatory Affairs

RECEIVED August 7, 2007
Date

AUG 14 2007

OGD

6500 KITIMAT ROAD
MISSISSAUGA, ONTARIO
CANADA, L5N 2B8

T 905 814 1820 T 1 866 254 6111 F 905 814 8696

COBALT
LABORATORIES

Gary Buehler
Director, Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N 175

Re: Abbreviated New Drug Application No. 78-035
Cabergoline Tablets (0.5 mg)
Change in Ownership of Application
Transfer of Regulatory Obligations

Dear Mr. Buehler:

Reference is made to a letter to the Food and Drug Administration (FDA) from Cobalt Pharmaceuticals Inc., dated August 07, 2007, in which Cobalt Pharmaceuticals Inc. transferred ownership and all rights to Abbreviated New Drug Application (ANDA) No. 78-035 for Cabergoline Tablets (0.5 mg). In accordance with 21 CFR §314.72, submitted herewith is Cobalt Laboratories' acceptance of the change in ownership to the above referenced ANDA.

In accordance with 21 CFR §314.72, Cobalt Laboratories acknowledges the following:

(i) Cobalt Laboratories is committed to comply with any agreements, promises, and conditions made by Cobalt Pharmaceuticals Inc. and contained in the application

(ii) The change in ownership is effective as of July 23, 2007

(iii) Cobalt Laboratories has a complete copy of the application, including approval letter, if applicable, supplements and records that are required to be kept under 21 CFR §314.81.

Cobalt Laboratories commits to advising FDA in the next Annual Report about any changes in the drug product's label or labeling to change the product's brand or the name of its manufacturer, packer, or distributor.

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AUG 10 2007

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24840 S. TAMIAMI TRAIL, SUITE 1
BONITA SPRINGS, FLORIDA
U.S.A, 34134

T 239 390 0245 T 866 391 0245 F 239 390 0295

Please note, that all regulatory obligations for ANDA No. 78-035 will be handled by the regulatory designate at Cobalt Laboratories.

The contact information is:

Mr. Richard Sanzen
Director, Regulatory Affairs
Cobalt Laboratories
24840 S. Tamiami Trail
Building B, Suite 1
Bonita Springs, Florida
USA, 34134
Number for FDA Communication: 239-333-2037
Fax (239)-390-0295
richards@cobaltlabs.us

In compliance with the regulations, this submission, which consists of one volume, is submitted in duplicate.

Should you have any questions regarding this submission please do not hesitate to contact me.

Sincerely,

Mr. Richard Sanzen
Director, Regulatory Affairs

AUGUST 9, 2007
Date

RECORD OF TELEPHONE CONVERSATION

FDA:

1. Please revise your stability commitment to cover both bottles of (b)(4) and 8s.

2. Since the original bio batch is still being used to support approval of ANDA. Please submit dissolution data with current spec on 3 month accelerated retains or full-term long-time data.

End of the T-CON

DATE: 14-MAR-2008

ANDA NUMBER: 78-035

PRODUCT NAME:
Cabergoline Tablets, 0.5 mg

INITIATED BY:

FIRM __ FDA _X_

FIRM NAME:
Cobalt Pharmaceuticals Inc.

FIRM REPRESENTATIVE:
Dona Hillier

TELEPHONE NUMBER:
239-333-2037

FDA REPRESENTATIVE:
Bita Mirzai-Azarm (Chem Reviewer)

SIGNATURE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bita Mirzai-Azarm
3/14/2008 11:43:13 AM
CHEMIST

COBALT
LABORATORIES

TELEPHONE AMENDMENT
ANDA 78-035

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N.A.C.

RECEIVED
MAR 25 2008
OGD

RE: Telephone Amendment dated March 14, 2008 for
Cabergoline Tablets 0.5 mg
ANDA 78-035

Please find presented a Telephone Amendment for Cabergoline Tablets 0.5 mg, ANDA 78-035 in response to a telephone contact between the Donna Hillier, Director, Regulatory Affairs of Cobalt Pharmaceuticals Inc. on behalf of Cobalt Laboratories Inc. and Ms. Mirzai-Azarm's, Review Chemist of FDA, dated March 14, 2008. The amendment is presented in a comment/response format with supporting documentation where applicable.

A copy of the telephone contact report is presented in this response for your reference.

Presented is a copy of the 356h form for the ANDA. We trust the documentation provided is satisfactory and allows the submission review to be completed.

As requested, the response is submitted by fax to the attention of the Project Manager and in electronic format to the CEDR.

In addition, a separate CD containing the following electronic files is provided:

- Cover letter
- Table of contents
- FDA 356h & appendix
- Response in Word & PDF

If you have any further questions or concerns, please do not hesitate to contact the undersigned.

Sincerely,

Jay D. Hillier

Mr. Richard Sanzen, R.Ph.
Director, Regulatory Affairs

Mar 20, 2008
Date

24840 S. TAMIAMI TRAIL, SUITE 1
BONITA SPRINGS, FLORIDA
U.S.A, 34134

T 239 390 0245 T 866 391 0245 F 239 390 0295 AN ARROW GROUP COMPANY

RECORD OF TELEPHONE CONVERSATION

FDA:

1. Please revise your stability commitment to cover both bottles of (b)(4) and 8s.

2. Please provide dissolution data on accelerated retains for batch AS82 in accordance with the DBE recommendations.

End of the T-CON

DATE: 02-APR-2008

ANDA NUMBER: 78-035

PRODUCT NAME:
Cabergoline Tablets, 0.5 mg

INITIATED BY:

FIRM __ FDA _X_

FIRM NAME:
Cobalt Pharmaceuticals Inc.

FIRM REPRESENTATIVE:
Richard Sanzen

TELEPHONE NUMBER:
239-333-2037

FDA REPRESENTATIVE:
Bita Mirzai-Azarm (Chem Reviewer)

SIGNATURE

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/s/

Bita Mirzai-Azarm

4/2/2008 12:43:06 PM

CHEMIST

COBALT
LABORATORIES

TELEPHONE AMENDMENT
ANDA 78-035

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N-000-AC

RE: Telephone Amendment dated April 2, 2008 for
Cabergoline Tablets 0.5 mg
ANDA 78-035

Please find presented a Telephone Amendment for Cabergoline Tablets 0.5 mg, ANDA 78-035 in response to a telephone contact between the Ms. Mirzai-Azarm, Review Chemist of FDA and Richard Sanzen, Director, Regulatory Affairs of Cobalt Laboratories Inc. dated April 2, 2008. The amendment is presented in a comment/response format with supporting documentation where applicable.

Presented is a copy of the 356h form for the ANDA. We trust the documentation provided is satisfactory and allows the submission review to be completed.

As requested, the response is submitted by fax to the attention of the Project Manager and in electronic format to the CEDR.

In addition, a separate CD containing the following electronic files is provided:

- Cover letter
- Table of contents
- FDA 356h & appendix
- Response in Word & PDF

If you have any further questions or concerns, please do not hesitate to contact the undersigned.

Sincerely,

Mr. Richard Sanzen, R.Ph.
Director, Regulatory Affairs

Apr 4, 2008
Date

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24840 S. TAMIAMI TRAIL, SUITE 1
BONITA SPRINGS, FLORIDA
U.S.A, 34134

T 239 390 0245 T 866 391 0245 F 239 390 0295

COBALT
LABORATORIES

LABELING AMENDMENT
ANDA 78-035

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Labeling Amendment for
Cabergoline Tablets 0.5 mg
ANDA 78-035

Please find presented a Labeling Amendment for Cabergoline Tablets 0.5 mg, ANDA 78-035 in response to a telephone contact between Ms. Esther Chuh, Project Manager of FDA and Richard Sanzen, Director, Regulatory Affairs of Cobalt Laboratories Inc., ("Cobalt"). The amendment is presented to address an update to the reference listed drug labeling and provide updated container and carton labels reflecting Cobalt due to a change in ownership of this product from Cobalt Pharmaceuticals Inc., to Cobalt who is the sponsor/distributor of this product. A copy of the change in ownership letter dated August 7, 2007 is presented immediately following this cover letter as confirmation of the change.

The side-by-side comparison of the previously submitted insert and the proposed insert has been presented at the end of the section.

Presented is a copy of the 356h form for the ANDA. We trust the documentation provided is satisfactory and allows the submission review to be completed.

Further to the OGD notice for "Submitting Electronic Documents to the Office of Generic Drugs" dated January 9, 2008, the labeling amendment is provided on CD in scanned PDF format.

In addition, a separate CD containing the following electronic files is provided:

- Cover letter
- Table of contents
- FDA 356h & appendix
- Response in MSWord & PDF
- Final Printed Container Labels in PDF
- Final Printed Package Insert in MS Word, PDF and SPL format

24840 S. TAMIAMI TRAIL, SUITE 1
BONITA SPRINGS, FLORIDA
U.S.A, 34134

T 239 390 0245 T 866 391 0245 F 239 390 0295 AN ARROW GROUP COMPANY

COBALT
LABORATORIES

If you have any further questions or concerns, please do not hesitate to contact the undersigned.

Sincerely,

Richard Sanzen, R.Ph.
Director, Regulatory Affairs

Apr 14/08
Date

24840 S. TAMIAMI TRAIL, SUITE 1
BONITA SPRINGS, FLORIDA
U.S.A, 34134

T 239 390 0245 T 866 391 0245 F 239 390 0295

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-035

Cobalt Laboratories, Inc.
Attention: Richard Sanzen
Director, Regulatory Affairs
24840 S. Tamiami Trail
Building B, Suite 1
Bonita Springs, FL 34134

Dear Sir:

We acknowledge receipt of your communication dated August 9, 2007, submitted as required by the provisions of Regulation 21 CFR 314.72(a) and Section 505(k) of the Federal Food, Drug and Cosmetic Act for the abbreviated new drug application (ANDA) for Cabergoline Tablets, 0.5 mg.

Your letter details the transfer of ownership of the ANDA from Cobalt Pharmaceuticals, Inc. to Cobalt Laboratories, Inc.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA about any change in the conditions of the pending application.

The material submitted is being retained as part of your application.

Sincerely yours,

{See appended electronic signature page}

William P. Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Timothy W. Ames
4/18/2008 12:38:24 PM
Signing for Wm. Peter Rickman

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-035 Applicant Cobalt Pharmaceuticlas Inc.
Drug Cabergoline Tablets Strength(s) 0.5 mg

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: | **DRAFT Package** | **FINAL Package**

1. **Martin Shimer** — Date 18 April 2008 | Date 4/21/08
Chief, Reg. Support Branch — Initials MHS | Initials rlw/for

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = _____ NDA# 20-664
Date Checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA submitted on 12/12/2005, BOS=20-664, PIII to the '892. ANDA RTR'd on 1/31/2006. ANDA was ack for filing on 3/8/2006(LO dated 5/4/2006). There are no remaining patents or exclusivities which protect the RLD-Dostinex. This ANDA is eligible for Full Approval.

2. Project Manager, Esther Chuh Team 2 — Date 3/25/2008 | Date _____
Review Support Branch — Initials ec | Initials _____

Original Rec'd date 12/8/2005
Date Acceptable for Filing 3/8/2006
Patent Certification (type) PIII Expired
Date Patent/Exclus.expires Expired 12/29/2005
Citizens' Petition/Legal Case Yes ☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 3/13/2008
Date of Office Bio Review 12/28/2006
Date of Labeling Approv. Sum 4/18/2008
Date of Sterility Assur. App. n/a
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement

Reviewer:
Date 4/18/2008
Name/Initials Angela Payne

Labeling Team Leader:
Date 4/18/2008
Name/Initials John Grace

Comments:
Labeling Approved in DFS 4/18/2008 - EC 4/18/08.

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 4/21/08
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments: N/A. There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

5. Div. Dir./Deputy Dir. Date 4/21/08
Chemistry Div. I Initials RMP

Comments:The CMC is satisfactory for AP.

6. Frank Holcombe **First Generics Only** Date 4/21/08
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
N/A. Multiple ANDAs have been approved for this drug product.

7. Vacant Date _____
Deputy Dir., DLPS Initials _____
RLD = Dostinex Tablets 0.5 mg
Pharmacia & Upjohn Co. NDA 20-664

8. Peter Rickman Date 4/21/08
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments:Bioequivalence studies ((b) (4) manufacturing facility) (fasting and non-fasting) found acceptable. In-vitro dissolution testing also found acceptable. Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 12/28/06.

Final-printed labeling (FPL) found acceptable for apprvosl 9/23/07.

CMC found acceptable for approval (Chemistry Review #3) 4/21/08. This review addresses the change in the site of the manufacture of the drug product from (b) (4) to Cobalt in Canada. Manufacturing site change found acceptable.

OR

8. Robert L. West Date 4/21/08
Deputy Director, OGD Initials rlw/for
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments:Acceptable EES dated 3/13/08 (Verified 4/21/08). No "OAI" Alerts noted.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDA is recommended for approval.

9. Gary Buehler Date 4/21/08
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Esther Chuh Team 2 Date: 4/21/2008

Review Support Branch Initials ec
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
3:25 PM Time notified of approval by phone
3:30 PM Time approval letter faxed

FDA Notification:
4/21/2008 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
4/21/2008 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 020664 Product 001 in the OB_Rx list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through March, 2008
Patent and Generic Drug Product Data Last Updated: April 21, 2008

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/s/

Esther Chuh

4/21/2008 03:34:32 PM