CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-061

Generic Name: Pergolide Mesylate Tablets, 0.05 mg (base), 0.25mg (base), and 1 mg (base)

Sponsor: TEVA Pharmaceuticals USA

Approval Date: November 27, 2002
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APPLICATION NUMBER:

76-061

APPROVAL LETTER
TEVA Pharmaceuticals USA  
Attention: Philip Erickson  
1090 Horsham Road  
PO Box 1090  
North Wales, PA 19454-1090

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Pergolide Mesylate Tablets, 0.05 mg (base), 0.25 mg (base), and 1 mg (base).

Reference is also made to your amendments dated May 11, and November 30, 2001; and March 14, May 17, and August 8, 2002. We also refer to your correspondence dated April 6, and September 12, 2001, addressing patent issues noted below.

The listed drug product (RLD) referenced in your application, Permax® Tablets of Eli Lilly & Co., is subject to periods of patent protection. As noted in the agency’s publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, (the “Orange Book”) the patents on October 26, 2007 (U.S. Patent No. 4,797,405 (the '405 patent), and October 19, 2009 (U.S. Patent No. 5,114,948 (the '948 patent). Your application contains patent certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that that patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of this drug product. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against TEVA Pharmaceuticals USA (TEVA) for infringement of one or more of the patents which were the subject of the paragraph IV certifications. This action must be brought against TEVA prior to the expiration of forty-five days from the date the notice you provided to the patent/NDs holder(s) under paragraph (2)(B)(i) was received. You have notified FDA that TEVA complied with the requirements of Section 505(j)(2)(B) of the
Act. You have also notified the agency that Eli Lilly and Company (Lilly), as holder of the NDA for Permax® Tablets and as owner of the previously referenced patents granted Elan Pharmaceuticals, Inc. (Elan), an exclusive license to market Permax® Tablets in the United States and to be the exclusive licensee of both patents. Furthermore, you have stated that Elan and Lilly dismissed their complaint against TEVA, and that TEVA was not served with a patent litigation suit within the 45-day period. You have submitted a copy of a Notice of Voluntary Dismissal from the court dated July 23, 2001. Thus, you have concluded that Elan and Lilly have waived their right to pursue legal action under the scope of the Waxman-Hatch Act regarding TEVA’s patent certification.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Pergolide Mesylate Tablets, 0.05 mg (base), 0.25 mg (base), and 0.1 mg (base), to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Permax® Tablets of Eli Lilly & Co.). 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 abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application 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.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.
We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

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

[Signature]

11/27/02

APPEARS THIS WAY ON ORIGINAL
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-061

Final Printed Labeling
PERGOLIDE MESYLATE Tablets
0.25 mg*

- Each tablet contains pergolide mesylate equivalent to 0.25 mg pergolide.

Rx only

NDC 0093-7159-01

PERGOLIDE MESYLATE Tablets
0.05 mg*

- Each tablet contains pergolide mesylate equivalent to 0.05 mg pergolide.

Rx only

NDC 0093-7160-01

Visual Dosage: See package insert for full prescribing information.

Store at controlled room temperature, between 25° C to 30° C (77° F to 86° F) (See USP). Expose to light may affect the stability of the product. Keep this and all medications out of the reach of children.

Made in USA

Manufactured by:

TEVA PHARMACEUTICAL IND. LTD
Jerusalem, 91110, Israel

Manufactured for:

TEVA PHARMACEUTICALS USA
Selnoville, PA 18080
PERGOLIDE MESYLATE TABLETS

DESCRIPTION
Pergolide mesylate is an ergot derivative dopamine receptor agonist at both D1 and D2 receptor sites. Pergolide mesylate is chemically designated as 6-[(4-Methylphenyl)methyl]-N,N-dimethyl-7-propargylamine methanesulfonate. The structural formula is as follows:

![Structural formula of pergolide mesylate]

The molecular weight of the base is 314.5. 1 mg of base corresponds to 3.18 μmol.

Pergolide mesylate is provided for oral administration in tablets containing 0.5 mg (0.159 mmol) and 1.0 mg (0.318 mmol) of pergolide mesylate base per tablet. The 0.5 mg tablet contains ferric oxide yellow and stearic acid. The 1.0 mg tablet contains ferric oxide red.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Pergolide mesylate is a selective dopamine receptor agonist. Pergolide is 10 to 1000 times more potent than bromocriptine or a dopamine receptor agonist used in medical therapy. Pergolide mesylate stimulates the release of dopamine in the striatum. This increase in dopamine release results in a decrease in striatal dopamine levels. The dopamine released appears to be metabolized by monoamine oxidase-A and catechol-O-methyltransferase. Pergolide mesylate is believed to exert its therapeutic effect by directly stimulating post-synaptic dopamine receptors in the nigrostriatal system.

Pharmacokinetics
Information on oral bioavailability of pergolide mesylate is unavailable because of the lack of a sufficiently sensitive assay to detect the drug after the administration of a single dose. However, following oral administration of 10 mg of pergolide mesylate, approximately 50% of the administered radioactivity can be recovered from the urine and 3% from expired CO2, suggesting that a significant fraction is absorbed. Nothing can be concluded about the extent of presystemic clearance, if any.

The major route of excretion is the kidney.

Pergolide is approximately 90% bound to plasma proteins. This extent of protein binding may be important to consider when pergolide mesylate is coadministered with other drugs known to affect protein binding.

INDICATIONS AND USAGE
Pergolide mesylate is indicated as adjunctive treatment to levodopa/carbidopa in the management of the signs and symptoms of Parkinson's disease.

EVIDENCE TO SUPPORT THE EFFICACY OF PERGOLIDE MESYLATE AS AN ADJUNCTIVE TREATMENT TO LEVODOPA/ CARBIDOPA IN THE MANAGEMENT OF THE SIGNS AND SYMPTOMS OF PARKINSON'S DISEASE
Evidence to support the efficacy of pergolide mesylate as an adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease who are responsive to levodopa/carbidopa treatment but have experience severe dyskinesia and/or on-off phenomenon. On average, the patients evaluated had been on levodopa/carbidopa for 3.9 years (range: 2 days to 16.8 years). The administration of pergolide mesylate permitted a 30% to 50% reduction in the daily dose of levodopa/carbidopa. On average, these patients treated with pergolide mesylate maintained an equivalent or better clinical status than they achieved at baseline.

CONTRAINDICATIONS
Pergolide mesylate is contraindicated in patients who are hypersensitive to this drug or other ergot derivatives.

WARNINGS
Symptomatic Hypotension
In clinical trials, approximately 10% of patients taking pergolide mesylate with levodopa versus 7% taking placebo with levodopa experienced symptomatic orthostatic hypotension and/or sustained hypertension, especially during initial treatment with gradual dosages. The incidence of this hypotension usually develops. It is therefore important to warn patients of this risk, to begin dosage with low doses, and to increase the dosage in carefully adjusted increments over a period of 3 to 4 weeks (see DOSAGE AND ADMINISTRATION).

HALLUCINATIONS
In controlled trials, pergolide mesylate with levodopa caused hallucinations in about 14% of patients as opposed to 2% taking placebo with levodopa. This was of sufficient severity to cause discontinuation of treatment in about 2% of those enrolled; tolerance to this untoward effect was not observed.

Fatigue
In the placebo-controlled trial, 2 of 187 patients treated with placebo died as compared with 1 of 188 patients treated with pergolide mesylate. Of the 2,229 patients treated with pergolide mesylate in premarketing studies evaluated as of October 1986, 143 died while on the drug or shortly after discontinuing it. Because the patients population under evaluation was elderly, 60% and at high risk for death, it seems unlikely that pergolide mesylate played any role in these deaths, but the possibility that pergolide shortens survival of patients cannot be excluded with absolute certainty.

In a case-by-case review of the clinical course of the patients who died after disclosure any unique set of signs, symptoms, or laboratory results that would suggest that treatment with pergolide caused their deaths. Side-effect (68%) of the patients who died were 75 years of age or older. No death (other than a suicide) occurred within the first month of treatment. Mortality among patients treated with pergolide mesylate is similar to that of persons with Parkinson's disease.

In post-marketing surveillance, the most frequently reported serious adverse reactions were hallucinations (26%), dizziness (26%), and syncope (17%). Other serious adverse reactions reported after marketing exposure included pancreatitis and disseminated intravascular coagulation. The most common serious adverse reactions reported with pergolide mesylate were hallucinations (26%) and dizziness (26%).

ADVERSE REACTIONS
The most frequent adverse reactions were dizziness, hallucinations, and syncope (26%). Other adverse reactions reported at an incidence of 2% or more were: nausea, vomiting, anorexia, weight gain, constipation, diarrhea, headache, and hyponatremia.

PRECAUTIONS
General
Cautions should be exercised when administering pergolide mesylate to patients prone to cardiac dysrhythmias.

In a study comparing pergolide mesylate and placebo, patients taking pergolide mesylate were found to have significantly more episodes of atrial premature contractions (APCs) and sinus tachycardia.

Dosage and Administration
The use of pergolide mesylate in patients on levodopa may cause and/or exacerbate preexisting states of confusion and hallucinations (see WARNINGS) and prescribing syndrome. Also, the abrupt discontinuation of pergolide mesylate or the change in dosage of ergot dopamine receptor agonists may cause exacerbation of these symptoms in patients on levodopa.

A dopamine agonist, such as pergolide mesylate, may be used alone or in combination with levodopa/carbidopa. However, the use of pergolide mesylate in patients with severe Parkinson's disease and those who are highly dependent on levodopa/carbidopa may cause an increase in the incidence of hallucinations and delusions. Therefore, close monitoring of these patients is recommended.

Dosage and Administration
The dosage of pergolide mesylate should be increased gradually over a period of 3 to 4 weeks to minimize the risk of adverse reactions. If a patient is taking another dopamine receptor agonist or a COMT inhibitor, pergolide mesylate should not be initiated without a thorough discussion of the potential risks and benefits.

In clinical trials, pergolide mesylate was initiated with a daily dose of 0.5 mg and titrated to an optimal dose, usually 1.0 mg, over a period of 3 to 4 weeks. The dosage may be increased at 3 to 4 week intervals by increasing the dose by 0.5 mg, up to a maximum of 2.5 mg daily.

ADVERSE REACTIONS
The most common adverse reactions reported with pergolide mesylate were dizziness, hallucinations, and syncope (26%). Other adverse reactions reported at an incidence of 2% or more were: nausea, vomiting, anorexia, weight gain, constipation, diarrhea, headache, and hyponatremia.

PRECAUTIONS
General
Cautions should be exercised when administering pergolide mesylate to patients prone to cardiac dysrhythmias.

ANTIDOPAMINE PROPERTIES
Pergolide mesylate is a dopamine receptor agonist and its antiparkinsonian effects are believed to be due to stimulation of dopamine receptors in the nigrostriatal system. Pergolide mesylate is approximately 30% to 50% bound to plasma proteins. Cautions should be exercised if pergolide mesylate is coadministered with other drugs known to affect protein binding.
with ils. This was of sufficient severity to cause discontinuation of treatment in about 3% of those enrolled. Tolerance to the
unwanted effect was not observed.

Fatalities
In the placebo-controlled trial, 2 of 387 patients treated with placebo died as compared with 1 of 185 patients treated with per-
pagide myelate. Of the 2,299 patients treated with pergolide myelate in premarketing studies evaluated as of October 1969, 143 patients died on the study drug. Although these deaths occurred after dosage was withdrawn (142), because the placebo population was much larger, it is likely that the small number in the treatment group is still significant. When sought, however, no direct relationship to the study drug was established. Because the follow-up was brief, it is likely that pergolide myelate played any role in these deaths, but the possibility that pergolide myelate’s survival of patients could not be excluded with absolute certainty.

In particular, a case-by-case review of the clinical course of the patients who did not disclose any unique set of signs, symp-
toms, or laboratory tests that would suggest that treatment with pergolide caused their deaths. Fifty-eight percent (58%) of the patients who died were over 65 years of age or older. At death (other than from suicide) occurred within the first month of treat-
ment; most of the patients who died had been on pergolide for years. A major frequency of the causes of death by organ sys-
tem is: Primarily: cardiovascular, 8.8%; infections, 8.5%; respiratory, 7.6%; neoplasms, 4.1%; gastrointestinal, 3.0%; neurologic, 2.5%; extraskeletal myeloid, 3.0%. Stroke, 2.1%, Dementia, 2.1%, Injury, 1.4%, Suicide, 1.4%, Dehydration, 0.5%, Hemorrhage, 0.5., 0.5%

Serious Infections and Arthritis
There were rare reports of pleural, pericardial, pleural effusions, arthritis, pericardial effusion or respiratory disorders in patients being pergolide. Some patients had experienced similar events while being treated with the arginine derivative bromocri-
tine. Pergolide should be used with caution in patients with a history of these conditions, particularly those who expect-
ence the risk of such events while being given somatremographs. Patients with a history of such events should be carefully monitored clinically and with appropriate radiographic and laboratory studies while taking pergolide.

PRECAUTIONS

General
Caution should be exercised when administering pergolide myelate to patients prone to cardiac dysrhythmias.

In a study comparing pergolide myelate and placebo, patients taking pergolide myelate were found to have significantly more episodes of atrial premature contractions (APCs) and sinus tachycardias.

The use of pergolide myelate is patients on dopa may cause and exacerbate pre-existing states of confusion and hallucinations (see WARNINGS) and parkinsonian disturbances. Also, abrupt discontinuation of pergolide myelate in patients receiving it chronically as an adjuvant to dopa may precipitate the onset of hallucinations and confusion; these may occur within a span of 24 to 72 hours. Discontinuation of pergolide must be undertaken gradually wherever possible, even if the patient is to remain on dopa.

A complex syndrome resembling the mesolimnic malignant syndrome (NMS) characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability, with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antipsychotic therapy, including pergolide.

Information for Patients
Patients and their families should be informed of the unusual adverse consequences of the use of pergolide myelate (see ADVERSE REACTIONS) and the risk of hyperpyrexia (see WARNINGS). Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding their infants.

Laboratory Tests
No specific laboratory tests are deemed essential for the management of patients on pergolide myelate. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions
Dopamine agonists, such as the neuroleptics (phenothiazines, butyrophenones, thiothixenes) or metoclopramide, ordinarily should not be administered concomitantly with pergolide myelate (a dopamine agonist); these agents may diminish the effectiveness of pergolide myelate.

Because pergolide myelate is approximately 90% bound to plasma proteins, caution should be exercised if pergolide myelate is concomitantly with other drugs known to affect protein binding.

Contraindications, Warnings, and Precautions of Adverse Effects
A double-blind, placebo-controlled study was conducted in mice using dietary levels of pergolide myelate equivalent to oral doses of 0.6, 0.125, 0.0625, and 0.03 mg/kg/day in males and 0.6, 0.125, and 0.0625 mg/kg/day in females. A tumor study in rats was conducted using 3.7, 30, and 300 mg/kg/day in males and 0.6, 0.125, and 0.0625 mg/kg/day in females. A Syrian study in rats was conducted using 0.5, 1.0, and 2.0 mg/kg/day in females. A Syrian study in rats was conducted using 0.2, 0.4, 8.0, and 20.0 mg/kg/day in females. The highest doses tested in the mice and rats were approximately 340 and 12 times the maximum human oral dose administered in controlled clinical trials (10 mg/kg/day equivalent to 0.7 mg/kg/day). A low incidence of uterine neoplasms occurred in both rats and mice. Endometrial adenomas and carcinomas were observed in rats. Both uterine neoplasms were observed in mice. The incidence of these neoplasms is probably attributable to the high estradiol/progesterone ratio that would occur in rodents as a result of the progestogen-inhibiting action of pergolide myelate. The etiologic mechanisms believed to be involved in the rodents are not present in humans. However, there is no known correlation between uterine malignancies occurring in peripatidal-treated rodents and human risk, there is no human data available to substantiate this conclusion.

Pergolide myelate was evaluated for mutagenicity in a battery of tests that included an Ames bacterial mutation assay, a DNA repair assay in cultured human lymphocytes, an in vitro mammalian cell mutation assay in cultured Chinese hamster, and a determination of chromosome abberations in bone marrow cells of Chinese hamsters. A weak mutagenic response was noted in the mammalian cell mutation assay only after metabolic activation with rat liver microsomes. No mutagenic effects were observed in the other two in vitro assays and in the in vivo assay. The relevance of these findings in humans is unknown.

A fertility study in male and female mice showed that fertility was maintained at 0.6 and 1.7 mg/kg/day but decreased at 5.6 mg/kg/day. Prostate has been reported to be increased in some studies and decreased in some prospective levels required for classification in mice and, therefore, the increased fertility at the high dose may have occurred because of decreased prostatic levels.

Usage in Pregnancy – Pregnancy Category B
Reproductive studies were conducted in male and female mice at doses of 0.1, 1.6, and 4.5 mg/kg/day and in rabbits at doses of 0.1, 1.6, and 4.5 mg/kg/day. The highest doses tested in mice and rabbits were 375 and 135 times the 6 mg/kg/day maximum human dose administered in controlled clinical trials. In these studies, there was no evidence of harm to the fetus due to pergolide myelate.

There are, however, no adequate and well-controlled studies in pregnant women. Among women who received pergolide myelate for estrogen replacement in postmenopausal states, there were 22 pregnancies that resulted in healthy babies and 9 pregnancies that resulted in congenital abnormalities (3 major, 6 minor). A causal relationship has not been established. Because human data are limited and 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. The pharmacologic action of pergolide myelate suggests that it may interfere with lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions to pergolide myelate in nursing infants, 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.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Commonly Observed
In premarketing clinical trials, the most commonly observed adverse events associated with use of pergolide myelate were not seen at an equivalent incidence among all treated patients. Among placebo-controlled clinical trials comprising pergolide myelate with placbo. In a double-
blind, controlled study of 6 months duration, patients with Parkinson's disease were continued on placebo or pergolide for between the placebo and pergolide groups. The proportion of patients who reported an adverse event in the placebo group was similar to the placebo group. The only significant difference was in the number of patients who reported an adverse event in the placebo group. The adverse events most commonly caused discontinuation were related to the nervous system (15.5%), primarily hallucinations (7.8%) and confusion (7.8%).

Facilities – See WARNINGS
Incidence in Controlled Clinical Trials
The table that follows enumerates adverse events that occurred at a frequency of 1% or more among patients taking pergolide myelate who participated in the premarketing controlled clinical trials comprising pergolide myelate with placebo. In a double-
blind, controlled study of 6 months duration, patients with Parkinson's disease were continued on placebo or pergolide for between the placebo and pergolide groups. The proportion of patients who reported an adverse event in the placebo group was similar to the placebo group. The only significant difference was in the number of patients who reported an adverse event in the placebo group. The adverse events most commonly caused discontinuation were related to the nervous system (15.5%), primarily hallucinations (7.8%) and confusion (7.8%).

Percentage of Patients Reporting Events

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Event</th>
<th>Placebo</th>
<th>Pergolide</th>
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<tbody>
<tr>
<td>N = 187</td>
<td>N = 187</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>7.0</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3.9</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Injury, accident</td>
<td>2.1</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.3</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>4.2</td>
<td>4.8</td>
<td></td>
</tr>
</tbody>
</table>
**Body as a Whole**
- Chest pain
- Flu syndrome
- Neck pain
- Back pain
- Surgical procedure
- Chills
- Face edema
- Infection

**Cardiovascular**
- Postural hypotension
- Malignant
- Hypertension
- Syncope
- Hypertension
- Arthritis
- Myocardial infarction

**Diseases**
- Nausea
- Constipation
- Diarrhea
- Dizziness
- Anemia
- Dry Mouth
- Swelling

**Hemic and Lymphatic**
- Metabolic and Nutritional
  - Peripartum edema
  - Edema
  - Weight gain

**Musculoskeletal**
- Ankylosing
- Muscular

**Nervous System**
- Dizziness
- Numbness
- Impaired sensation
- Ataxia
- Hypertension
- Abnormal dreams
- Personality disorder
- Psychosis
- Abnormal gait
- Anemia
- Encephalopathy
- Incoordination
- Paralysis
- Hyperactivity

**Respiratory System**
- Rhinitis
- Gastroesophageal reflux disease
- Epistaxis
- Allergic rhinitis
- Hay fever
- Sinusitis
- Chronic sinusitis
- Breast pain

**Skin and Appendages**
- Rash
- Sweating

**Special Senses**
- Abnormal vision
- Taste perversion
- Eye disorder

**Urinary System**
- Urinary tract infection
- Hematuria

---

*Events reported by at least 1% of patients receiving pergolide mesylate are included.

**Events Observed During the Premarketing Evaluation of PergolideMesylate**

This table reports events observed at any time during treatment with pergolide mesylate. The conditions and duration of exposure to pergolide mesylate varied greatly, making well-controlled studies of each adverse event difficult. There are no reports of death, and no increased risk of these events attributable to pergolide mesylate was observed.

**Excluding**
- Peripheral edema
- Edema
- Weight gain

**Musculoskeletal**
- Ankylosing
- Muscular

**Nervous System**
- Dizziness
- Numbness
- Impaired sensation
- Ataxia
- Hypertension
- Abnormal dreams
- Personality disorder
- Psychosis
- Abnormal gait
- Anemia
- Encephalopathy
- Incoordination
- Paralysis
- Hyperactivity

**Respiratory System**
- Rhinitis
- Gastroesophageal reflux disease
- Epistaxis
- Allergic rhinitis
- Hay fever
- Sinusitis
- Chronic sinusitis
- Breast pain

**Skin and Appendages**
- Rash
- Sweating

**Special Senses**
- Abnormal vision
- Taste perversion
- Eye disorder

**Urinary System**
- Urinary tract infection
- Hematuria

---

**Events in terms of their relative frequency of reporting in the data base.**

**Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS.**

*The following definitions of frequency are used:***

- **Frequent** adverse events are defined as those occurring in at least 1/100 to 1/1000 patients.
- **Infrequent** adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

**Body as a Whole**
- *Frequent* headache, asthenia, accidental injury, pain, abdominal pain, chest pain, back pain, flu syndrome, neck pain, fever, facial edema, edema, weight gain, edema, weight gain, edema.

**Cardiovascular System**
- *Frequent* postural hypotension.

**Cutaneous System**
- *Frequent* nausea, vomiting, dyspepsia, diarrhea, constipation.

**Gastrointestinal System**
- *Frequent* nausea, vomiting, dyspepsia, diarrhea.

**Hematopoietic System**
- *Frequent* rhinitis.

**Hepatic and Biliary System**
- *Frequent* peripheral edema, weight loss, weight gain.

**Musculoskeletal System**
- *Frequent* back pain.

**Neurological System**
- *Frequent* dizziness.

**Respiratory System**
- *Frequent* rhinitis.

**Skin and Appendages System**
- *Frequent* rash.

**Special Senses System**
- *Frequent* abdominal pain.

**Urinary System**
- *Frequent* urinary tract infection.

**Incidence of Hypotension**
- *Frequent* hypotension.

---

**Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS.**

*The following definitions of frequency are used:***

- **Frequent** adverse events are defined as those occurring in at least 1/100 to 1/1000 patients.
- **Infrequent** adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

**Body as a Whole**
- *Frequent* headache, asthenia, accidental injury, pain, abdominal pain, chest pain, back pain, flu syndrome, neck pain, fever, facial edema, edema, weight gain, edema.

**Cardiovascular System**
- *Frequent* postural hypotension.

**Cutaneous System**
- *Frequent* nausea, vomiting, dyspepsia, diarrhea, constipation.

**Gastrointestinal System**
- *Frequent* nausea, vomiting, dyspepsia, diarrhea.

**Hematopoietic System**
- *Frequent* rhinitis.

**Hepatic and Biliary System**
- *Frequent* peripheral edema, weight loss, weight gain.

**Musculoskeletal System**
- *Frequent* back pain.

**Neurological System**
- *Frequent* dizziness.

**Respiratory System**
- *Frequent* rhinitis.

**Skin and Appendages System**
- *Frequent* rash.

**Special Senses System**
- *Frequent* abdominal pain.

**Urinary System**
- *Frequent* urinary tract infection.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-061

CHEMISTRY REVIEW(S)
MINOR AMENDMENT

ANDA 76-061

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)

TO: APPLICANT: TEVA Pharmaceuticals USA
ATTN: Philip Erickson, R.Ph.
FROM: Kassandra Sherrod

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Pergolide Mesylate Tablets, 0.05 mg, 0.25 mg and 1.0 mg.

Reference is also made to your amendment(s) dated: November 30, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 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 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:

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38. Chemistry Comments to be Provided to the Applicant

ANDA: 76-061  APPLICANT: TEVA Pharmaceuticals, USA

DRUG PRODUCT: Pergolide Mesylate Tablets 0.05 mg, 0.25 mg, 1.0 mg

The deficiency presented below represents a MINOR deficiency.

Deficiency:

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
1. CHEMISTRY REVIEW  # 1

2. ANDA # 76-061

3. NAME AND ADDRESS OF APPLICANT
TEVA Pharmaceuticals USA
Attn: Philip Erickson
1090 Horsham Road, P.O. Box 1090
North Wales, PA 19454-1090

4. LEGAL BASIS FOR SUBMISSION
RLD: Permax®
Eli Lilly & Co. (NDA 019385)
Patents (p. 11):
4166182 Exp.: 2/8/2000
4797405 Exp.: 10/26/2007
5114948 Exp.: 10/19/2009

ANDA includes a certification stating that patents for the
RLD will not be infringed by the manufacture or sale of the
proposed product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Pergolide Mesylate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

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10. PHARMACOLOGICAL CATEGORY
Dopamine receptor agonist

11. Rx or OTC
R

12. RELATED DMFs:
DMF — DMF — DMF —
DMF — DMF — DMF —
13. **DOSAGE FORM**
   Tablet; Oral

14. **POTENCIES**
   0.05, 0.25, and 1 mg

15. **CHEMICAL NAME**
   8β-[(Methylthio)methyl]-6-propylergoline monomethanesulfonate
   Molecular weight: 
   Chemical Formula: C_{19}H_{26}N_{2}S•CH_{4}O_{3}S

16. **RECORDS AND REPORTS**
   2/15/01 Labeling review #1

17. **COMMENTS**
   See review

17. **CONCLUSIONS AND RECOMMENDATIONS**
   Not approvable.

19. **REVIEWER:**
   Damaris Maldonado

   **DATE COMPLETED:**
   04/03/2001

**APPEARS THIS WAY ON ORIGINAL**
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pages of trade secret and/or confidential commercial information
1. CHEMISTRY REVIEW # 2

2. ANDA # 76-061

3. NAME AND ADDRESS OF APPLICANT
TEVA Pharmaceuticals USA
Attn: Philip Erickson
1090 Horsham Road, P.O. Box 1090
North Wales, PA 19454-1090

4. LEGAL BASIS FOR SUBMISSION
RLD: Permax®
Eli Lilly & Co. (NDA 019385)
Patents (p. 11):
4166182 Exp.: 2/8/2000
4797405 Exp.: 10/26/2007
5114948 Exp.: 10/19/2009

ANDA includes a certification stating that patents for the RLD will not be infringed by the manufacture or sale of the proposed product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Pergolide Mesylate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

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<td>Amendment</td>
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10. PHARMACOLOGICAL CATEGORY
Dopamine receptor agonist

11. Rx or OTC

12. RELATED DMFS:
DMF DMF DMF
13. **DOSAGE FORM**
   Tablet; Oral

14. **POTENCIES**
   0.05, 0.25, and 1 mg

15. **CHEMICAL NAME**
   8β-[(Methylthio)methyl]-6-propylergoline monomethanesulfonate
   Molecular weight: __________
   Chemical Formula: C₁₉H₂₆N₂S•CH₄O₃S

16. **RECORDS AND REPORTS**
   2/15/01
   Labeling review #1

17. **COMMENTS**
   See review

17. **CONCLUSIONS AND RECOMMENDATIONS**
   Not approvable.

19. **REVIEWER:**
    Damaris Maldonado

   **DATE COMPLETED:**
   9/27/01

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MINOR AMENDMENT

ANDA 76-061

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)

TO: APPLICANT: TEVA Pharmaceuticals USA
ATTN: Philip Erickson, R.Ph.
FROM: Kassandra Sherrod

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Pergolide Mesylate Tablets, 0.05 mg, 0.25 mg, 1 mg.

Reference is also made to your amendment(s) dated: August 22 and September 4, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 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 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:

Chemistry deficiencies

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information
1. CHEMISTRY REVIEW  # 3

2. ANDA # 76-061

3. NAME AND ADDRESS OF APPLICANT
   TEVA Pharmaceuticals USA
   Attn: Philip Erickson
   1090 Horsham Road, P.O. Box 1090
   North Wales, PA 19454-1090

4. LEGAL BASIS FOR SUBMISSION
   RLD: Permax®
       Eli Lilly & Co. (NDA 019385)
   Patents (p. 11):  
   4166182 Exp.: 2/8/2000  
   4797405 Exp.: 10/26/2007  
   5114948 Exp.: 10/19/2009

   ANDA includes a certification stating that patents for the
   RLD will not be infringed by the manufacture or sale of the
   proposed product.

5. SUPPLEMENT(s)
   N/A

6. PROPRIETARY NAME  7. NONPROPRIETARY NAME
   N/A  Pergolide Mesylate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
   N/A

9. AMENDMENTS AND OTHER DATES:

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10. PHARMACOLOGICAL CATEGORY
    Dopamine receptor agonist

11. Rx or OTC
    Rx

12. RELATED DMFs:
13. DOSAGE FORM
   Tablet; Oral

14. POTENCIES
   0.05, 0.25, and 1 mg

15. CHEMICAL NAME
   8β-[(Methylthio)methyl]-6-propylergoline monomethanesulfonate
   Molecular weight: 
   Chemical Formula: C₁₅H₂₄N₂S·CH₄O₃S

16. RECORDS AND REPORTS
   2/15/01 Labeling review #1

17. COMMENTS
   See review

17. CONCLUSIONS AND RECOMMENDATIONS
   Not Approvable

19. REVIEWER: DATE COMPLETED:
    Damaris Maldonado 12/17/01

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1. CHEMISTRY REVIEW  # 4

2. ANDA # 76-061

3. NAME AND ADDRESS OF APPLICANT
   TEVA Pharmaceuticals USA
   Attn: Philip Erickson
   1090 Horsham Road, P.O. Box 1090
   North Wales, PA 19454-1090

4. LEGAL BASIS FOR SUBMISSION
   RLD: Permax®
   Eli Lilly & Co. (NDA 019385)
   Patents (p. 11):
   4166182          Exp.: 2/8/2000
   4797405          Exp.: 10/26/2007
   5114948          Exp.: 10/19/2009

   ANDA includes a certification stating that patents for the
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   proposed product.

5. SUPPLEMENT(s)
   N/A

6. PROPRIETARY NAME
   N/A

7. NONPROPRIETARY NAME
   Pergolide Mesylate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
   N/A

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10. PHARMACOLOGICAL CATEGORY
    Dopamine receptor agonist

11. Rx or OTC
    Rx

12. RELATED DMFs:
13. **DOSAGE FORM**
   Tablet; Oral

14. **POTENCIES**
   0.05, 0.25, and 1 mg

15. **CHEMICAL NAME**
    8β-[(Methylthio)methyl]-6-propylergoline monomethanesulfonate
    Molecular weight: __________
    Chemical Formula: C₁₉H₂₆N₂S•CH₄O₅S

16. **RECORDS AND REPORTS**
    2/15/01 Labeling review #1

17. **COMMENTS**
    See review

17. **CONCLUSIONS AND RECOMMENDATIONS**
    Not Approvable

19. **REVIEWER:**
    Damaris Maldonado

19. **DATE COMPLETED:**
    02/03/02
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MINOR AMENDMENT

ANDA 76-061

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)

TO: APPLICANT: TEVA Pharmaceuticals USA
ATTN: Philip Erickson, R.Ph.
FROM: Kassandra Sherrod

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Pergolide Mesylate Tablets, 0.05 mg, 0.25 mg, 1.0 mg.

Reference is also made to your amendment(s) dated: January 28 and February 1, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 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 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.

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1. CHEMISTRY REVIEW # 5

2. ANDA # 76-061

3. NAME AND ADDRESS OF APPLICANT
   TEVA Pharmaceuticals USA
   Attn: Philip Erickson
   1090 Horsham Road, P.O. Box 1090
   North Wales, PA 19454-1090

4. LEGAL BASIS FOR SUBMISSION
   RLD: Permax®
   Eli Lilly & Co. (NDA 019385)
   Patents (p. 11):
   4166182 Exp.: 2/8/2000
   4797405 Exp.: 10/26/2007
   5114948 Exp.: 10/19/2009

   ANDA includes a certification stating that patents for the
   RLD will not be infringed by the manufacture or sale of the
   proposed product.

5. SUPPLEMENT(s)
   N/A

6. PROPRIETARY NAME
   N/A

7. NONPROPRIETARY NAME
   Pergolide Mesylate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
   N/A

9. AMENDMENTS AND OTHER DATES:

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5/17/2002 Tel Amendment
10. **PHARMACOLOGICAL CATEGORY**
   Dopamine receptor agonist

11. **Rx or OTC**
   R

12. **RELATED DMFs:**
   DMF —
   DMF —
   DMF —

13. **DOSAGE FORM**
   Tablet; Oral

14. **POTENCIES**
   0.05, 0.25, and 1 mg

15. **CHEMICAL NAME**
   8β-[(Methylthio)methyl]-6-propylergoline monomethanesulfonate
   Molecular weight: —
   Chemical Formula: C₁₅H₂₈N₂S·CH₄O₃S

16. **RECORDS AND REPORTS**
   2/15/01
   Labeling review #1

17. **COMMENTS**
   See review

18. **CONCLUSIONS AND RECOMMENDATIONS**
   Approval

19. **REVIEWER:**
   Damaris Maldonado
   **DATE COMPLETED:**
   03/28/02
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information
APPLICATION NUMBER:

76-061

BIOEQUIVALENCE REVIEW
Pergolide Mesylate Tablets, 0.05 mg, 0.25 mg, and 1 mg base
ANDA 76-061
Reviewer: Carol Y. Kim

TEVA Pharmaceuticals, USA
North Wales, PA
Submission Date: 5/11/01

Review of an Amendment

I. Objective

In this Amendment, the firm submitted their responses to the Bioequivalence Deficiency letter dated April 18, 2001.

II. Firm’s responses to Deficiency Comments

DBE’s comment #1:

Firm’s response #1:

Reviewer’s comment to firm’s response #1:

The firm’s response is acceptable. The analytical method validation report is now complete and acceptable.

DBE’s comment #2:

Please clarify discrepancies with subjects #38 and #49. According to “Additional Information Form” in Vol. 1.3, p. 1663, the treatment was dispensed to subjects #38 and #49. However, according to a statement on pages 1680 and 1681, both subjects, #38 and #49, were not dosed. Please explain the reason for not dosing subjects #38 and #49. Also explain the reason for omission of subjects #38 and #49 from the randomization scheme (vol. 1.2, p.936-937).

Firm’s response #2:

Subject #38 was withdrawn from the study before the dosing in period I because the study physician noted abnormal vital signs. Subject #49 withdrew voluntarily before receiving the study medication. Both subjects, #38 and #49, were deleted from the study and
omitted from the randomization scheme because they did not receive any study medication. Anapharm states that they have all information on these two subjects in their archive files.

**Reviewer’s comment to firm’s response #2:**

The firm’s response is acceptable.

**DBE’s comment #3:**

Please provide the detailed SOP’s (including SOP ANI 156) listing the criteria for acceptance of values due to pharmacokinetic repeats.

**Firm’s response #3:**

The requested SOPs were submitted.

**Reviewer’s comment to firm’s response #3:**

All repeat assays were carried out in accordance with SOPs ANI 156.06 and ANI 7000.04.

**DBE’s comment #4:**

Please repeat dissolution testing on all strengths of your proposed Pergolide Mesylate Tablets and the corresponding reference products using the method below. The batches of 0.05 mg strength should be the same as used in the in vivo bioequivalence study

**Firm’s response #4:**
Results of In Vitro Dissolution Profile Summary for Pergolide Mesylate Tablets

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<tr>
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<td>Lot # K-26417</td>
<td>Lot #: 3MN75M</td>
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<td>Sampling times (min)</td>
<td>Mean (%)</td>
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<td>94</td>
</tr>
</tbody>
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Reviewer's comment to firm's response #4:

The firm conducted the dissolution testing using the FDA-recommended method. The dissolution data are acceptable. The dissolution data met the following specifications: NLT — Q of the labeled amount of pergolide in 30 minutes.

DBE comment #5:

Firm's response #5:

Reviewer's comment to firm's response #5

The firm's response is acceptable.
III. Comments

1. The single-dose bioequivalence study, 00147, under fasting conditions, conducted by Teva Pharmaceuticals, USA, on its Pergolide Mesylate Tablets, 0.05 mg, lot #K-26417, comparing it to PermaxR Tablets, 0.05 mg, lot #3MN75M, manufactured by Eli-Lilly, is found acceptable by the Division of Bioequivalence.

2. The dissolution method conducted by Teva Pharmaceuticals, USA, on its Pergolide Mesylate Tablets, 0.05 mg (lot #K-26417), 0.25 mg (lot #K-26483), and 1mg (lot #K-26484) is acceptable.

3. The waivers of in vivo bioequivalence study requirements for the 0.25 mg and 1 mg strength tablets of the test product are granted based on 21 CFR 320.22 (d) (2).

4. [Signature]

   Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The firm should be informed of the recommendations.

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BY BDAVII
FT INITIALLED BY BDAVII

Concur: [Signature]
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date: 5/3/01
Date: 6/19/2001
BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #76-061 APPLICANT: TEVA Pharmaceuticals, USA

DRUG PRODUCT: Pergolide Mesylate Tablets, 0.05 mg, 0.25 mg, and 1 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing should be incorporated into your stability and quality control programs:

[ ]

Not less than — (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency 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. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
CC: ANDA #76061
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer C. Kim
HFD-658/ Bio team leader B. Davit

V:\FIRMSnz\teva\ltre\rev\76061\sta.501

Endorsements: (Final with Dates)
HFD-658/ Reviewer C. Kim
HFD-658/ Bio team Leader B. Davit
HFD-658/ Reviewer N. Tran
HFD-650/ S. Mazzella
HFD-650/ D. Conner

BIOEQUIVALENCY - Acceptable

1. Study Amendment (STA)
Strengths: 0.05 mg, 0.25 mg, and 1 mg
Outcome: AC

Outcome Decision: AC - acceptable
Fig. 1: Dissolution comparison of pergolide tablets, ANDA# 76061, in 500 ml SGF containing 20 mg of L-cysteine.
---Original Message---

From: Tran, Nhan L
Sent: Friday, May 04, 2001 10:46 AM
To: CDER-OGDBIO
Cc: Patel, Rashmikant M; Gill, Devinder S; Mueller, Albert J; Schwartz, Paul; Smela Jr, Michael; Fang, Florence S; Adams, Richard C; Arwine, Brenda T; Ouderkirk, Larry A

Subject: PERGOLIDE MESYLATE TABLET--AN UPDATE

Dear Colleagues:

According to the latest information (NDA 19-385), please note that the Q value for Pergolide Mesylate Tablet in the FDA Handbook of Dissolution (page 90) has been changed to NLT (Q) = in 30 minutes. This is considered as the FDA "interim" specification for this drug product.

Thanks,
OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-061

SPONSOR: TEVA Pharmaceuticals, USA

DRUG AND DOSAGE FORM: Pergolide Mesylate Tablets

STRENGTH(S): 0.05 mg, 0.25 mg, and 1 mg base

TYPES OF STUDIES: STF X  STP  MULT  OTHER X

CLINICAL STUDY SITE(S): __________

ANALYTICAL SITE(S): __________

STUDY SUMMARY: In a single-dose fasting BE study, Pergolide Mesylate Tablets, 0.05 mg, was shown to be bioequivalent to Permax® Tablets, 0.05 mg. The waivers for 0.25 mg and 1 mg strengths are granted.

Formulation is acceptable.

DISSOLUTION: acceptable

DSI INSPECTION STATUS

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<tr>
<th>Inspection needed: YES / NO</th>
<th>Inspection status:</th>
<th>Inspection results:</th>
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</thead>
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</tr>
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<td>New facility</td>
<td>Inspection completed: (date)</td>
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<td>For cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other</td>
<td></td>
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</tr>
</tbody>
</table>

PRIMARY REVIEWER: Carol Y. Kim    BRANCH: 3

INITIAL:  [Signature]    DATE: 5/31/01

TEAM LEADER: Barbara M. Davit    BRANCH: 3

INITIAL:  [Signature]    DATE: 5/31/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.

INITIAL:  [Signature]    DATE: 6/22/001
BIOEQUIVALENCY AMENDMENT

ANDA 76-061

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)

TO: APPLICANT: TEVA Pharmaceuticals USA
ATTN: Phillip Erickson

FROM: Steven Mazzella
PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on December 21, 2000, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Pergolide Mesylate Tablets, 0.05 mg, 0.25 mg, and 1 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 2 pages. 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 direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.
BIOEQUIVALENCY DEFICIENCIES

ANDA: #76-061  APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Pergolide Mesylate Tablets, 0.05 mg, 0.25 mg, and 1.0 mg

The Division of Bioequivalence has completed its review. The following deficiencies have been identified:

1. Please submit data to support the long-term stability of pergolide in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (116 days).

2. Please clarify discrepancies with subjects #38 and #49. According to "Additional Information Form" in Vol. 1.3, p. 1663, the treatment was dispensed to subjects #38 and #49. However, according to a statement on pages 1680 and 1681, both subjects, #38 and #49, were not dosed. Please explain the reason for not dosing subjects #38 and #49. Also explain the reason for omission of subjects #38 and #49 from the randomization scheme (vol. 1.2, p.936-937).

3. Please provide the detailed SOP's (including SOP ANI 156) listing the criteria for acceptance of values due to pharmacokinetic repeats.

4. Please repeat dissolution testing on all strengths of your proposed Pergolide Mesylate Tablets and the corresponding reference products using the method below. The batches of 0.05 mg strength should be the same as used in the in vivo bioequivalence study.
Sincerely yours,

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

I. Introduction

First Generic: Yes

Indication: For adjunct treatment with levodopa/carbidopa in the management of the signs and symptoms of Parkinson’s disease

Contents of Submission:
- Fasting BE: 0.05 mg
- Waiver requests: 0.25 and 1 mg
- In vitro dissolution data: 0.05, 0.25 and 1 mg

RLD: Permax (pergolide mesylate) Tablets, 0.05, 0.25, and 1 mg, manufactured by Eli Lilly and Company (NDA# 19385, 12/30/98)

Initial dose: 0.05 mg/day for the first 2 days

II. Background

1. 8/14/00: OGD #00-355, Teva requested using 0.05 mg strength pergolide mesylate and prochlorperazine in the BE study based on toxicity results obtained in a pilot study.

2. 9/15/00: OGD Medical Officer accepted the firm’s proposal for a 2-way single dose fasting BE study using 0.1 mg dose (2 X 0.05 mg) plus prochlorperazine (anti-emetic drug).

Based on the Medical Officer’s comments, the DBE recommended the following in OGD #00-355:

a. Conduct a fasting BE study on 0.1 mg dose (2 X 0.05 mg) of pergolide mesylate plus 10 mg prochlorperazine
b. The higher strengths, 0.25 mg and 1 mg, would be eligible for waivers based on the acceptable in vivo BE study, comparative dissolution data, and formulation proportionality.
c. Measure pergolide in plasma
3. December 2000: The RLD was changed from 1 mg to 0.05 mg base of pergolide mesylate in the 20th edition of the Orange Book, Supplement 12.

4. The Permax R label does not mention food. Therefore, a BE study under fed conditions was not submitted.

5. Only pergolide plasma concentrations and pharmacokinetic parameters are reported in this review. This is consistent with the recommendations in the recently-posted (10/27/00) CDER Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally-Administered Drug Products -- General Considerations.

III. Pharmacokinetics

The information on oral systemic bioavailability of pergolide is limited. After oral administration of radiolabeled pergolide, 55% is eliminated in urine, indicating significant absorption. At least 10 metabolites have been detected, including N-despropylpergolide, pergolide sulfoxide and pergolide sulfone. The latter two metabolites are dopamine agonists in animals.

IV. Study No. 00147: Randomized, 2-Way Crossover, Comparative Bioavailability Study comparing Teva's Pergolide Mesylate Tablets, 0.05 mg, and Eli-Lilly's Permax R Tablets, 0.05 mg, administered as a 0.1 mg Dose (2 x 0.05 mg) in Healthy Male Volunteers Under Fasting Conditions

Study Information

Clinical Facility: 

Principal Investigator: 

Clinical Study Dates: Group 1: 
Period 1: 8/12/00 Period 2: 9/9/00 
Group 2: 
Period 1: 10/21/00 Period 2: 11/18/00

Analytical Facility: 

Analytical Director: 

Analytical Study Dates: 11/02/00-12/06/00 
Storage Period: No > 116 days at -20°C

TREATMENT INFORMATION

Treatment ID: A B 
Test or Reference: T R 
Product Name: Pergolide Mesylate Tablet Permax R Tablet 
Manufacturer: TEVA Eli-Lilly
Manufacture Date: 7/10/00  N/A  
Expiration Date:  -  8/1/02 
ANDA Batch Size:  -  
Full Batch Size:  
Batch/Lot Number:  K-26417  3MN75M 
Strength:  0.05 mg  0.05 mg 
Dosage Form:  Tablet  Tablet 
Dose Administered*:  2 tablets (2 X 0.05 mg)  2 tablets (2 X 0.05 mg) 
Study Condition:  fasting  fasting 
Length of Fasting:  Overnight pre-dosing  Overnight pre-dosing 
4 hours post-dosing  4 hours post-dosing 

*Concomitant medication administered with all treatments:
Compazine® (prochlorperazine) Tablet, 10 mg, Q6h for two doses, lot #819C67J, Exp. 9/2001

<table>
<thead>
<tr>
<th>RANDOMIZATION</th>
<th>DESIGN</th>
</tr>
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<tbody>
<tr>
<td>Randomized:</td>
<td>Y</td>
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<tr>
<td>No. of Sequences:</td>
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<td>No. of Periods:</td>
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<tr>
<td>Washout Period:</td>
<td>28 days</td>
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<td>Center</td>
<td>single</td>
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<table>
<thead>
<tr>
<th>DOSSING</th>
<th>SUBJECTS</th>
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</thead>
<tbody>
<tr>
<td>Single or Multiple Dose:</td>
<td>single</td>
</tr>
<tr>
<td>Steady State:</td>
<td>N</td>
</tr>
<tr>
<td>Volume of Liquid Intake:</td>
<td>240 mL</td>
</tr>
<tr>
<td>Route of Administration:</td>
<td>oral</td>
</tr>
<tr>
<td>IRB Approval:</td>
<td>Y</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>Y</td>
</tr>
<tr>
<td>Obtained:</td>
<td></td>
</tr>
<tr>
<td>No. of Subjects Enrolled:</td>
<td>74</td>
</tr>
<tr>
<td>No. of Subjects Completing:</td>
<td>49</td>
</tr>
<tr>
<td>No. of Subjects Plasma Analyzed:</td>
<td>48</td>
</tr>
<tr>
<td>No. of Dropouts:</td>
<td>1</td>
</tr>
<tr>
<td>Sex(es) Included:</td>
<td>Males</td>
</tr>
<tr>
<td>Age:</td>
<td>18-55 years</td>
</tr>
<tr>
<td>Healthy Volunteers Only:</td>
<td>Y</td>
</tr>
<tr>
<td>No. of Adverse Events:</td>
<td>306</td>
</tr>
</tbody>
</table>

Inclusion/Exclusion Criteria: Vol. 1.3 (p. 1374-1376)
Housing: The night before dosing until after the 36 hour blood draw
Blood Sampling: 0, 0.5, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, and 36 hours post dose
Volume: 10 ml

Study Results
1) Clinical

Group: Subjects were randomized into these two groups at study enrollment.
<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject no*</td>
<td>#1-48 (except #38)</td>
<td>#50-76</td>
</tr>
<tr>
<td>Dosing dates</td>
<td>8/12/00 and 9/9/00</td>
<td>10/21/00 and 11/18/00</td>
</tr>
</tbody>
</table>

*Subjects 38 and 49 were not included in the random assignment

<table>
<thead>
<tr>
<th></th>
<th>Subjects (total= 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samples analyzed</td>
<td>2,3,4,8,10,12,13,14,17,19,20,21,22,23,24,25,26,27,28,29,34,35,39,40,41,43,44,45,46,47,50,51,52,54,56,57,58,59,60,62,65,66,69,70,72,74,75,76</td>
</tr>
</tbody>
</table>

**Adverse Events:**
- Total - 306 adverse events in association to the study drug
- 115 events (42 subjects) - treatment A, drug related
- 191 events (54 subjects) - treatment B, drug related
- The common adverse events were vomiting, mild dizziness, nausea, and headache. See attachment #1.
- Eighteen subjects experiencing an episode of vomiting within 4 hours of dosing did not complete the study. Subject #27 vomited 4 hours 34 minutes after dosing and was retained in the study. The withdrawal of subjects who vomited within 4 hours of dosing was stipulated in the protocol.

**Withdrawn/Dropouts:**

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawn by the study coordinator due to vomiting which started within 4 hours post-dose in period 1</td>
<td>1, 5, 6, 7, 9, 15, 16, 18, 33, 36, 37, 48, 53, 55, 63, 64, 67, 73</td>
</tr>
<tr>
<td>Elected to withdraw for personal reasons in period 1</td>
<td>31</td>
</tr>
<tr>
<td>Elected to withdraw prior to period 2 dosing due to personal reasons</td>
<td>11, 30, 32, 61, 71</td>
</tr>
<tr>
<td>Elected to withdraw prior to period 2 dosing due to adverse event</td>
<td>42</td>
</tr>
<tr>
<td>Excluded form statistical analyses as per SOP since Ke could not be estimated</td>
<td>22</td>
</tr>
</tbody>
</table>

**Protocol Deviations:** minor deviations were noted.

2) Analytical (Not to be Released Under FOI)

**Pre-Study Assay Validation:**
Redacted 2

pages of trade

secret and /or

confidential

commercial

information
Table 1

Mean(CV) Plasma Concentrations of pergolide (pg/ml)

Test = Teva's Pergolide Mesylate Tablets, 0.05 mg, Dose Administered = 2 tablets (2 X 0.05 mg), fasting
Reference = PermaxR Tablets, 0.05 mg, Dose Administered = 2 tablets (2 X 0.05 mg), fasting

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Test</th>
<th>%CV</th>
<th>Reference</th>
<th>%CV</th>
<th>Ratio (T/R)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.75</td>
<td>-</td>
<td>0.0</td>
<td>-</td>
<td>0.96</td>
</tr>
<tr>
<td>0.5</td>
<td>13.80</td>
<td>59.73</td>
<td>16.33</td>
<td>82.58</td>
<td>0.85</td>
</tr>
<tr>
<td>1</td>
<td>18.00</td>
<td>56.95</td>
<td>20.52</td>
<td>74.36</td>
<td>0.88</td>
</tr>
<tr>
<td>1.33</td>
<td>21.77</td>
<td>53.44</td>
<td>22.98</td>
<td>64.85</td>
<td>0.95</td>
</tr>
<tr>
<td>1.67</td>
<td>24.30</td>
<td>49.86</td>
<td>25.83</td>
<td>50.66</td>
<td>0.94</td>
</tr>
<tr>
<td>2</td>
<td>24.69</td>
<td>45.43</td>
<td>27.11</td>
<td>45.17</td>
<td>0.91</td>
</tr>
<tr>
<td>2.5</td>
<td>27.53</td>
<td>49.14</td>
<td>28.03</td>
<td>40.58</td>
<td>0.98</td>
</tr>
<tr>
<td>3</td>
<td>28.05</td>
<td>47.60</td>
<td>29.41</td>
<td>42.48</td>
<td>0.95</td>
</tr>
<tr>
<td>4</td>
<td>25.92</td>
<td>44.54</td>
<td>26.50</td>
<td>40.99</td>
<td>0.98</td>
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<tr>
<td>5</td>
<td>24.71</td>
<td>51.23</td>
<td>25.23</td>
<td>42.43</td>
<td>0.98</td>
</tr>
<tr>
<td>6</td>
<td>20.56</td>
<td>52.17</td>
<td>20.75</td>
<td>45.77</td>
<td>0.99</td>
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<tr>
<td>8</td>
<td>12.00</td>
<td>55.60</td>
<td>12.19</td>
<td>49.58</td>
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<tr>
<td>12</td>
<td>4.42</td>
<td>82.85</td>
<td>4.81</td>
<td>67.88</td>
<td>0.92</td>
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<tr>
<td>24</td>
<td>1.07</td>
<td>166.15</td>
<td>1.05</td>
<td>181.07</td>
<td>1.02</td>
</tr>
</tbody>
</table>

*calculated by the reviewer

Analysis of variance was performed on each pharmacokinetic parameter using SAS PROC GLM. Mean reported pharmacokinetic parameters for pergolide mesylate are shown in Table 2. The Geometric means of the ln-transformed pharmacokinetic parameters, means, and the 90% confidence intervals of test product versus reference product are presented in Table 3.

Table 2

Mean pergolide mesylate Plasma Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Test Mean</th>
<th>Test %CV</th>
<th>Ref Mean</th>
<th>Ref %CV</th>
<th>T/R Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCT</td>
<td>356.11</td>
<td>57.04</td>
<td>368.90</td>
<td>47.77</td>
<td>0.97</td>
</tr>
<tr>
<td>AUCI</td>
<td>405.67</td>
<td>51.00</td>
<td>425.06</td>
<td>43.30</td>
<td>0.95</td>
</tr>
<tr>
<td>CMAX</td>
<td>30.87</td>
<td>45.11</td>
<td>33.41</td>
<td>47.77</td>
<td>0.92</td>
</tr>
<tr>
<td>TMAX</td>
<td>3.78</td>
<td>36.25</td>
<td>3.87</td>
<td>37.70</td>
<td>0.98</td>
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<tr>
<td>KEL</td>
<td>0.10</td>
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<td>0.10</td>
<td>34.82</td>
<td>1.00</td>
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<tr>
<td>THALF</td>
<td>7.60</td>
<td>29.97</td>
<td>7.97</td>
<td>29.58</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*AUCT=pg*hr/ml, AUCI=pg*hr/ml, TMAX=hr, CMAX=pg/ml
Table 3
Geometric Mean ratios and 90% confidence intervals for pergolide

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Test</th>
<th>Reference</th>
<th>Geometric Mean Ratio (T/R)</th>
<th>90% CI Lower 90% CI</th>
<th>90% CI Upper 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAUC0-inf</td>
<td>352.95</td>
<td>382.51</td>
<td>0.92</td>
<td>87.95</td>
<td>98.46</td>
</tr>
<tr>
<td>LAUC0-t</td>
<td>285.80</td>
<td>315.15</td>
<td>0.91</td>
<td>84.54</td>
<td>99.15</td>
</tr>
<tr>
<td>LCMAX</td>
<td>27.37</td>
<td>29.74</td>
<td>0.92</td>
<td>84.29</td>
<td>101.19</td>
</tr>
</tbody>
</table>

*LAUC0-inf = pg/hr/ml, LAUC0-t = pg/hr/ml, LCMAX = pg/ml

Comments:

1. The model used for statistical analysis of group effect was: Y = GROUP
   SEQUENCE GROUP*SEQUENCE SUBJECT (SEQUENCE*GROUP)
   PERIOD (GROUP) TREATMENT GROUP*TREATMENT.

2. No significant period (group) effect for pergolide was noted on LAUCT, and
   LCMAX (p>0.1). However, a significant period effect was seen on LAUCI (p<0.1).
   This observation does not effect the integrity of the study.

3. The pharmacokinetic parameters and 90% confidence intervals re-calculated by the
   reviewer were in good agreement with the values determined by the firm.

4. The mean (%CV) AUC₇/AUC₅ ratios of pergolide were 0.88 (10.3), range 0.45 to
   0.96, and 0.88 (6.7), range 0.70 to 0.97, for test and reference, respectively.

5. The 90% confidence intervals of In-transformed AUCl, AUCI, and CMAX for
   pergolide are all within 80-125% range.

Conclusion: The study is incomplete pending receipt of analytical method validation data.

Table 4: Root Mean Square Error (MSE) for In-transformed AUCl and Cmax

<table>
<thead>
<tr>
<th>Perigolide</th>
<th>In AUCl</th>
<th>In Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSE, Test &amp; Reference</td>
<td>0.2274781</td>
<td>0.2682702</td>
</tr>
</tbody>
</table>

V. Dissolution (Not to be released under FOI)
<table>
<thead>
<tr>
<th>Specification</th>
<th>NLT % — Q of labeled amount of pergolide in 30 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference Products</td>
<td>Permax&lt;sup&gt;®&lt;/sup&gt; Tablets, 0.05, 0.25, and 1 mg</td>
</tr>
</tbody>
</table>

**Results of In Vitro Dissolution Profile Summary for Pergolide Mesylate Tablets**

<table>
<thead>
<tr>
<th>Pergolide Mesylate Tablets, 0.05 mg</th>
<th>Permax&lt;sup&gt;®&lt;/sup&gt; Tablets, 0.05 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Reference</td>
</tr>
<tr>
<td>Lot # K-26417</td>
<td>Lot #: 3MN75M</td>
</tr>
<tr>
<td>Exp: 7/19/00</td>
<td>Exp: 7/19/00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sampling times (min)</th>
<th>Mean (%)</th>
<th>Range (%)</th>
<th>%CV</th>
<th>Mean (%)</th>
<th>Range (%)</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>95</td>
<td></td>
<td>2.4</td>
<td>96</td>
<td></td>
<td>3.7</td>
</tr>
<tr>
<td>20</td>
<td>97</td>
<td></td>
<td>1.3</td>
<td>101</td>
<td></td>
<td>2.3</td>
</tr>
<tr>
<td>30</td>
<td>97</td>
<td></td>
<td>0.8</td>
<td>101</td>
<td></td>
<td>1.8</td>
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<table>
<thead>
<tr>
<th>Pergolide Mesylate Tablets, 0.25 mg</th>
<th>Permax&lt;sup&gt;®&lt;/sup&gt; Tablets, 0.25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Reference</td>
</tr>
<tr>
<td>Lot # K-26483</td>
<td>Lot #: 2MX08M</td>
</tr>
<tr>
<td>Exp: 11/01</td>
<td>Exp: 11/01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sampling times (min)</th>
<th>Mean (%)</th>
<th>Range (%)</th>
<th>%CV</th>
<th>Mean (%)</th>
<th>Range (%)</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>93</td>
<td></td>
<td>2.7</td>
<td>91</td>
<td></td>
<td>5.2</td>
</tr>
<tr>
<td>20</td>
<td>96</td>
<td></td>
<td>1.7</td>
<td>98</td>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td>30</td>
<td>97</td>
<td></td>
<td>1.3</td>
<td>98</td>
<td></td>
<td>1.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pergolide Mesylate Tablets, 1 mg</th>
<th>Permax&lt;sup&gt;®&lt;/sup&gt; Tablets, 1 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Reference</td>
</tr>
<tr>
<td>Lot # K-26484</td>
<td>Lot #: 2MT07M</td>
</tr>
<tr>
<td>Exp: 11/01</td>
<td>Exp: 11/01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sampling times (min)</th>
<th>Mean (%)</th>
<th>Range (%)</th>
<th>%CV</th>
<th>Mean (%)</th>
<th>Range (%)</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>91</td>
<td></td>
<td>3.4</td>
<td>94</td>
<td></td>
<td>5.1</td>
</tr>
<tr>
<td>20</td>
<td>94</td>
<td></td>
<td>1.8</td>
<td>99</td>
<td></td>
<td>2.2</td>
</tr>
<tr>
<td>30</td>
<td>95</td>
<td></td>
<td>1.6</td>
<td>98</td>
<td></td>
<td>2.4</td>
</tr>
</tbody>
</table>

**Dissolution testing site:** not reported

**Comments**
VI. Composition of Formulation (not to be released under FOI)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Each tablet (mg)</th>
<th>Each tablet (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.05 mg</td>
<td>0.25 mg</td>
</tr>
<tr>
<td></td>
<td>strength</td>
<td>strength</td>
</tr>
<tr>
<td>Pergolide Mesylate</td>
<td>0.065*</td>
<td>0.325**</td>
</tr>
<tr>
<td>Lactose Monohydrate NF c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactose Monohydrate NF c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregelatinized Starch NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Starch Glycolate NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcrystalline Cellulose NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium Stearate NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Color FD&amp;C Blue No. 2 Aluminium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Color Ferric Oxide NF Yellow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Ferric Oxide NF Red</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*equivalent to 0.05 mg pergolide base
**equivalent to 0.25 mg pergolide base
***equivalent to 1 mg pergolide base

As per Rona Sun, N075269 contains — of Color Ferric Oxide, Yellow. Based on her database, all inactive ingredients are within the limits specified by the FDA Inactive Ingredient Guide (1996). See attached e-mail.

**Assay and Content Uniformity**

<table>
<thead>
<tr>
<th>Product</th>
<th>Assay %</th>
<th>Content Uniformity % (RSD%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test, Pergolide Mesylate Tablets 0.05 mg Lot # K-26417</td>
<td>96.6 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Reference, Permax® Tablets, 0.05 mg Lot # 3MN75M</td>
<td>100.0 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Test, Pergolide Mesylate Tablets 0.25 mg Lot # K-26483</td>
<td>95.7 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Reference, Permax® Tablets, 0.25 mg Lot # 2MX08M</td>
<td>99.3 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Test, Pergolide Mesylate Tablets 1 mg Lot # K-26484</td>
<td>98.0 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Reference, Permax® Tablets, 1 mg Lot # 2MT07M</td>
<td>100.8 (2.7)</td>
<td></td>
</tr>
</tbody>
</table>
VII. Waiver Request

1. The firm requested a waiver of in vivo bioequivalency testing for the 0.25 mg and 1.0 mg tablets.

2. The lists of active and inactive ingredients in the proposed test formulation, Pergolide Mesylate Tablets, are proportionally similar in 0.05 mg, 0.25 mg, and 1.0 mg tablets. The total weight in 0.25 mg and 1.0 mg strength tablets are the same as the amount present in 0.05 mg tablet.

VIII. Deficiency comments

1. The firm should submit data to support the long-term stability of pergolide in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (116 days).

2. The firm should clarify discrepancies with subjects #38 and #49. According to “Additional Information Form” in Vol. 1.3, p. 1663, the treatment was dispensed to subjects #38 and #49. However, according to a statement on page 1680 and 1681, both subjects, #38 and #49, were not dosed. The firm should explain the reason for not dosing subjects #38 and #49. Also explain the reason for omission of subjects #38 and #49 from the randomization scheme (vol. 1.2, p.936-937).

3. The firm should provide the detailed SOP’s (including SOP ANI 156) listing the criteria for acceptance of values due to pharmacokinetic repeats.

4. The firm should repeat dissolution testing on all strengths of the proposed Pergolide Mesylate Tablets and the corresponding reference products using the method below. The batches of 0.05 mg strength should be the same as used in the in vivo bioequivalence study.

IX. Recommendation

1. The single-dose bioequivalence study, 00147, under fasting conditions, conducted by Teva Pharmaceuticals, USA, on its Pergolide Mesylate Tablets, 0.05 mg, lot #K-26417, comparing it to PermaxR Tablets, 0.05 mg, lot #3MN75M, manufactured by Eli-Lilly, has been found incomplete by the Division of Bioequivalence for the reasons given in the deficiency comments.
2. The dissolution testing is found incomplete by the Division of Bioequivalence for the reasons given in the deficiency comments.

3. The request for waivers of *in vivo* bioequivalence testing of Teva's Pergolide Mesylate Tablets, 0.25 mg, and 1.0 mg, is denied at this time for the reasons given in the deficiency comments.

4. Of the 74 enrolled subjects, 18 were dropped from the study due to vomiting within 4 hours of administration of study drug. The Division of Bioequivalence will send this review to the OGD Associate Director for Medical Affairs for consult to determine if it is more appropriate to conduct *in vivo* studies of pergolide mesylate tablets in patients.

The firm should be informed of the deficiency comments.

/SS/
Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

/SS/

RD INITIALLED BY BDAVIT
FT INITIALLED BY BDAVIT

Concur: /SS/
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date: 3/22/01

Date: 4/3/2001
BIOEQUIVALENCY - Incomplete

1. Fasting Study (STF)
   Clinical: ________
   Analytical: ________
   Strength: 0.05 mg
   Outcome: IC

2. Dissolution Waiver (DIW)
   Strength: 0.25 mg
   Outcome: IC

3. Dissolution Waiver (DIW)
   Strength: 1.0 mg
   Outcome: IC

Outcome Decisions: IC - incomplete
Fig. 1: Dissolution Comparison for ANDA#76061 Pergolide Mesylate Tablet
Fig 2: Mean plasma concentrations of Pergolide Mesylate, ANDA # 76061, under fasting conditions.
Attachment 1: Adverse events in Study 00147 related to study drug

Subjects who experienced at least one episode of vomiting are highlighted in bold text. All subjects who vomited by 4 hours post-dosing were dropped. Subject #27 was retained in the study.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Trt</th>
<th>Pd</th>
<th>Description</th>
<th>Onset time</th>
<th>Severity</th>
<th>Relationship to study drug</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 A</td>
<td>1</td>
<td>1</td>
<td>nausea</td>
<td>1 h 13 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
</tr>
<tr>
<td>1 A</td>
<td>1</td>
<td>1</td>
<td>vomiting</td>
<td>1 h 16 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
</tr>
<tr>
<td>1 A</td>
<td>1</td>
<td>1</td>
<td>dizziness</td>
<td>5 h 49 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>1 A</td>
<td>1</td>
<td>1</td>
<td>hot flushes</td>
<td>7 h 50 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>2 A</td>
<td>1</td>
<td>1</td>
<td>drowsiness</td>
<td>21 min</td>
<td>mild</td>
<td>probably</td>
<td>spontaneous</td>
</tr>
<tr>
<td>2 B</td>
<td>2</td>
<td>1</td>
<td>drowsiness</td>
<td>38 min</td>
<td>mild</td>
<td>probably</td>
<td>spontaneous</td>
</tr>
<tr>
<td>2 B</td>
<td>2</td>
<td>2</td>
<td>nausea</td>
<td>43 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
</tr>
<tr>
<td>2 B</td>
<td>2</td>
<td>1</td>
<td>headache</td>
<td>1 h 28 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>2 B</td>
<td>2</td>
<td>2</td>
<td>dizziness</td>
<td>1 h 31 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>3 B</td>
<td>1</td>
<td>1</td>
<td>drowsiness</td>
<td>51 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>3 B</td>
<td>1</td>
<td>1</td>
<td>headache</td>
<td>1 h 41 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>3 B</td>
<td>1</td>
<td>1</td>
<td>difficult bowel movement</td>
<td>2 h 20 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>3 B</td>
<td>1</td>
<td>1</td>
<td>heartburn</td>
<td>3 h 52 min</td>
<td>mild</td>
<td>probably</td>
<td>spontaneous</td>
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<tr>
<td>3 A</td>
<td>2</td>
<td>1</td>
<td>abdominal pain</td>
<td>1 h 56 min</td>
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<td>spontaneous</td>
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<td>4 B</td>
<td>2</td>
<td>1</td>
<td>drowsiness</td>
<td>54 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>4 B</td>
<td>2</td>
<td>2</td>
<td>hot flushes</td>
<td>1 h 9 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>5 B</td>
<td>1</td>
<td>1</td>
<td>nausea</td>
<td>22 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>5 B</td>
<td>1</td>
<td>1</td>
<td>dizziness</td>
<td>27 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>5 B</td>
<td>1</td>
<td>1</td>
<td>stuffy nose</td>
<td>40 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>5 B</td>
<td>1</td>
<td>1</td>
<td>heartburn</td>
<td>50 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>5 B</td>
<td>1</td>
<td>1</td>
<td>vomiting</td>
<td>51 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
</tr>
<tr>
<td>5 B</td>
<td>1</td>
<td>1</td>
<td>cold sweat</td>
<td>51 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>5 B</td>
<td>1</td>
<td>1</td>
<td>feels cold</td>
<td>1 h 10 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>5 B</td>
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<td>1</td>
<td>tremors</td>
<td>1 h 12 min</td>
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<td>possibly</td>
<td>spontaneous</td>
</tr>
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<td>5 B</td>
<td>1</td>
<td>1</td>
<td>weakness</td>
<td>1 h 12 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>6 B</td>
<td>1</td>
<td>1</td>
<td>pain in left thigh</td>
<td>30 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>6 B</td>
<td>1</td>
<td>1</td>
<td>vomiting</td>
<td>48 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
</tr>
<tr>
<td>7 A</td>
<td>1</td>
<td>1</td>
<td>hot flushes</td>
<td>32 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>7 A</td>
<td>1</td>
<td>1</td>
<td>vomiting</td>
<td>1 h 13 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
</tr>
<tr>
<td>8 B</td>
<td>1</td>
<td>1</td>
<td>blurred vision</td>
<td>45 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>8 B</td>
<td>1</td>
<td>1</td>
<td>weakness</td>
<td>48 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>8 A</td>
<td>2</td>
<td>1</td>
<td>nausea</td>
<td>50 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
</tr>
<tr>
<td>8 A</td>
<td>2</td>
<td>1</td>
<td>dizziness</td>
<td>50 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>8 A</td>
<td>2</td>
<td>1</td>
<td>blurred vision</td>
<td>1 h 15 min</td>
<td>mild</td>
<td>probably</td>
<td>spontaneous</td>
</tr>
<tr>
<td>8 A</td>
<td>2</td>
<td>1</td>
<td>nausea</td>
<td>1 h 15 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
</tr>
<tr>
<td>8 A</td>
<td>2</td>
<td>1</td>
<td>feels sleepy</td>
<td>1 h 28 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>8 A</td>
<td>2</td>
<td>1</td>
<td>blurred vision</td>
<td>1 h 44 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>8 A</td>
<td>2</td>
<td>1</td>
<td>blurred vision</td>
<td>5 h 46 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>9 B</td>
<td>1</td>
<td>1</td>
<td>vomiting</td>
<td>1 h 6 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
</tr>
<tr>
<td>10 B</td>
<td>2</td>
<td>2</td>
<td>dizziness</td>
<td>57 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>10 B</td>
<td>2</td>
<td>1</td>
<td>headache</td>
<td>1 h 2 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>12 B</td>
<td>1</td>
<td>1</td>
<td>drowsiness</td>
<td>33 min</td>
<td>mild</td>
<td>probably</td>
<td>spontaneous</td>
</tr>
<tr>
<td>12 B</td>
<td>1</td>
<td>1</td>
<td>cold sweat</td>
<td>36 min</td>
<td>mild</td>
<td>probably</td>
<td>spontaneous</td>
</tr>
<tr>
<td>12 B</td>
<td>2</td>
<td>1</td>
<td>cold sweat</td>
<td>1 h 4 min</td>
<td>mild</td>
<td>probably</td>
<td>spontaneous</td>
</tr>
<tr>
<td>12 B</td>
<td>2</td>
<td>2</td>
<td>drowsiness</td>
<td>1 h 8 min</td>
<td>mild</td>
<td>probably</td>
<td>spontaneous</td>
</tr>
<tr>
<td>12 B</td>
<td>2</td>
<td>2</td>
<td>stuffy nose</td>
<td>1 h 18 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>13 A</td>
<td>1</td>
<td>1</td>
<td>nausea</td>
<td>36 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
<tr>
<td>13 A</td>
<td>1</td>
<td>1</td>
<td>shivers</td>
<td>37 min</td>
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<td>1 stuffy nose</td>
<td>3 h 48 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<tr>
<td>39 A</td>
<td>1 muscular pain (ab area)</td>
<td>6 h 14 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
<td>39 B</td>
<td>2 nausea</td>
<td>1 h 22 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
<td>40 A</td>
<td>1 nausea</td>
<td>33 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
<td>40 A</td>
<td>1 hot flushes</td>
<td>33 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
<td>40 B</td>
<td>2 dizziness</td>
<td>32 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<td>2 hot flushes</td>
<td>41 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>41 A</td>
<td>1 hot flushes</td>
<td>1 h 5 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
<td>41 B</td>
<td>2 nausea</td>
<td>1 h 21 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
<td>41 B</td>
<td>2 hot flushes</td>
<td>1 h 21 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<tr>
<td>42 A</td>
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<td>36 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<td>42 A</td>
<td>1 hot flushes</td>
<td>36 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<tr>
<td>43 A</td>
<td>1 nausea</td>
<td>37 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
<td>43 A</td>
<td>1 dizziness</td>
<td>36 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
<td>43 A</td>
<td>2 dizziness</td>
<td>44 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
<td>44 B</td>
<td>1 nausea</td>
<td>34 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
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<td>44 B</td>
<td>1 hot flushes</td>
<td>34 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<tr>
<td>45 B</td>
<td>2 stuffy nose</td>
<td>47 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<tr>
<td>47 A</td>
<td>1 nausea</td>
<td>26 min</td>
<td>mild</td>
<td>probably</td>
<td>with treatment</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<td>47 A</td>
<td>1 shaking in right leg</td>
<td>33 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
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<td>1 shaking in left leg</td>
<td>33 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<tr>
<td>47 A</td>
<td>1 numbness, left hand</td>
<td>33 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<tr>
<td>47 A</td>
<td>1 numbness, right hand</td>
<td>33 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<tr>
<td>47 A</td>
<td>1 dizziness</td>
<td>1 h 43 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<td>47 A</td>
<td>1 nose bleed</td>
<td>22 h 13 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<td>31 min</td>
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<td>probably</td>
<td>spontaneous</td>
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<td>spontaneous</td>
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<tr>
<td>47 B</td>
<td>2 headache</td>
<td>56 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<tr>
<td>47 B</td>
<td>2 nausea</td>
<td>1 h</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<td>47 B</td>
<td>2 weakness</td>
<td>2 h 1 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<tr>
<td>47 B</td>
<td>2 nausea</td>
<td>2 h 3 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
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<tr>
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<td>2 dizziness</td>
<td>4 h 19 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<td>48 B</td>
<td>1 blurred vision</td>
<td>49 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>spontaneous</td>
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<td>48 B</td>
<td>1 nausea</td>
<td>50 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
<td>48 B</td>
<td>1 vomiting</td>
<td>55 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<tr>
<td>48 B</td>
<td>1 stomachache</td>
<td>57 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
<td>50 B</td>
<td>1 nausea</td>
<td>28 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
<td>50 B</td>
<td>1 dizziness</td>
<td>28 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
<td>50 B</td>
<td>1 fainting</td>
<td>29 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
<td>spontaneous</td>
</tr>
<tr>
<td>50 B</td>
<td>1 low blood pressure (82/48)</td>
<td>1 h 50 min</td>
<td>N/A</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<tr>
<td>50 B</td>
<td>1 feels tired</td>
<td>1 h 38 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>50 B</td>
<td>1 dizziness</td>
<td>3 h 54 min</td>
<td>not recorded</td>
<td>possibly</td>
<td>spontaneous</td>
<td>spontaneous</td>
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<td>Subject No.</td>
<td>Trt</td>
<td>Pd</td>
<td>Description</td>
<td>Onset time</td>
<td>Severity</td>
<td>Relationship to study drug</td>
<td>Resolution</td>
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<td>-------------------------------</td>
<td>------------</td>
<td>----------</td>
<td>-----------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>50 A</td>
<td>2</td>
<td>hot flushes</td>
<td>30 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<tr>
<td>51 A</td>
<td>1</td>
<td>nausea</td>
<td>39 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
<td></td>
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<tr>
<td>52 B</td>
<td>2</td>
<td>hot flushes</td>
<td>1 h 21 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>52 B</td>
<td>2</td>
<td>high level of ALT (64 U/L)</td>
<td>1 d 12 h</td>
<td>N/a</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>53 A</td>
<td>1</td>
<td>nausea</td>
<td>24 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
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<tr>
<td>53 A</td>
<td>1</td>
<td>loose stools</td>
<td>27 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
<td></td>
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<tr>
<td>53 A</td>
<td>1</td>
<td>nausea</td>
<td>37 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
<td></td>
</tr>
<tr>
<td>53 A</td>
<td>1</td>
<td>vomiting</td>
<td>39 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
<td></td>
</tr>
<tr>
<td>53 A</td>
<td>1</td>
<td>nausea</td>
<td>52 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
<td></td>
</tr>
<tr>
<td>53 A</td>
<td>1</td>
<td>vomiting</td>
<td>1 h 13 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
<td></td>
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<td>53 A</td>
<td>1</td>
<td>vomiting</td>
<td>2 h 24 min</td>
<td>severe</td>
<td>possibly</td>
<td>with treatment</td>
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<td>54 A</td>
<td>1</td>
<td>hot flushes</td>
<td>17 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td></td>
</tr>
<tr>
<td>54 A</td>
<td>1</td>
<td>nausea</td>
<td>17 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
<td></td>
</tr>
<tr>
<td>54 B</td>
<td>2</td>
<td>hot flushes</td>
<td>52 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>54 B</td>
<td>2</td>
<td>feels nauseous</td>
<td>54 min</td>
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<td>possibly</td>
<td>with treatment</td>
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<td>23 min</td>
<td>mild</td>
<td>possibly</td>
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<td>55 B</td>
<td>1</td>
<td>fainting</td>
<td>36 min</td>
<td>severe</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>40 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
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<tr>
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<td>1</td>
<td>vomiting</td>
<td>58 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
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<td>vomiting</td>
<td>1 h 4 min</td>
<td>severe</td>
<td>possibly</td>
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<td>1 h 39 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
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<td>55 B</td>
<td>1</td>
<td>vomiting</td>
<td>3 h 15 min</td>
<td>moderate</td>
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<td>7 h 40 min</td>
<td>mild</td>
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<td>with treatment</td>
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<td>10 h 55 min</td>
<td>moderate</td>
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<td>56 B</td>
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<td>dizziness</td>
<td>30 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<tr>
<td>56 B</td>
<td>1</td>
<td>tachycardia (112 bpm)</td>
<td>5 h 51 min</td>
<td>N/a</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>2</td>
<td>dizziness</td>
<td>1 h 5 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<tr>
<td>57 A</td>
<td>1</td>
<td>nausea</td>
<td>26 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
<td></td>
</tr>
<tr>
<td>57 A</td>
<td>1</td>
<td>dizziness</td>
<td>26 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td></td>
</tr>
<tr>
<td>57 A</td>
<td>1</td>
<td>numbness, right and left forearm</td>
<td>37 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<tr>
<td>57 B</td>
<td>2</td>
<td>headache</td>
<td>49 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<tr>
<td>57 B</td>
<td>2</td>
<td>nausea</td>
<td>49 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
<td></td>
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<td>2</td>
<td>numbness, right forearm</td>
<td>52 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<tr>
<td>57 B</td>
<td>2</td>
<td>numbness, left forearm</td>
<td>52 min</td>
<td>mild</td>
<td>possibly</td>
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<tr>
<td>57 B</td>
<td>2</td>
<td>numbness, abdomen</td>
<td>1 h 3 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>2</td>
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<td>1 h 6 min</td>
<td>mild</td>
<td>possibly</td>
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<td>numbness, left leg</td>
<td>1 h 6 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
<td></td>
</tr>
<tr>
<td>57 B</td>
<td>2</td>
<td>dry mouth</td>
<td>1 h 6 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>dizziness</td>
<td>45 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
<td></td>
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<tr>
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<td>dry mouth</td>
<td>46 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<tr>
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<td>44 min</td>
<td>mild</td>
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<td>28 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
<td></td>
</tr>
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<td>feels cold</td>
<td>28 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<tr>
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<td>nausea</td>
<td>55 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
<td></td>
</tr>
<tr>
<td>59 B</td>
<td>1</td>
<td>dizziness</td>
<td>55 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>shaking</td>
<td>58 min</td>
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<td>spontaneous</td>
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<td>58 min</td>
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<td>possibly</td>
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<td>1 h 20 min</td>
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<td>1</td>
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<td>31 min</td>
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<td>possibly</td>
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<td>61 A</td>
<td>1</td>
<td>blurred vision</td>
<td>31 min</td>
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<td>49 min</td>
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<td>hot flushes</td>
<td>49 min</td>
<td>moderate</td>
<td>possibly</td>
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<td>1</td>
<td>numbness, left arm</td>
<td>49 min</td>
<td>mild</td>
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<td>49 min</td>
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<td>1 h 1 min</td>
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<td>26 min</td>
<td>moderate</td>
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<td>52 min</td>
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<td>29 min</td>
<td>mild</td>
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<td>29 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
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<td>24 min</td>
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<td>1 h 18 min</td>
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<td>possibly</td>
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<td>moderate</td>
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<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>spontaneous</td>
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<td>mild</td>
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<td>33 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>1 h 42 min</td>
<td>moderate</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>feels like his heart rate increased</td>
<td>16 min</td>
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<td>possibly</td>
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<td>1 h 5 min</td>
<td>mild</td>
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<td>spontaneous</td>
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<td>72 B</td>
<td>1</td>
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<td>1 h 5 min</td>
<td>mild</td>
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<td>1 h 3 min</td>
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<td>severe</td>
<td>possibly</td>
<td>spontaneous</td>
<td></td>
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<td>1 h 2 min</td>
<td>moderate</td>
<td>possibly</td>
<td>with treatment</td>
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<td>1 h 4 min</td>
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<td>possibly</td>
<td>spontaneous</td>
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<td>2 h 29 min</td>
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<td>possibly</td>
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<td>5 h 54 min</td>
<td>moderate</td>
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<td>5 h 54 min</td>
<td>moderate</td>
<td>possibly</td>
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<td>27 d 5 h 42 min</td>
<td>mild</td>
<td>possibly</td>
<td>with treatment</td>
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<td>sensation of cold</td>
<td>12 min</td>
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<td>spontaneous</td>
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<td>possibly</td>
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<td>41 min</td>
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<td>possibly</td>
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<td>55 min</td>
<td>mild</td>
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<td>Pd</td>
<td>Description</td>
<td>Onset time</td>
<td>Severity</td>
<td>Relationship to study drug</td>
<td>Resolution</td>
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<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
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<td>B</td>
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<td>52 min</td>
<td>mild</td>
<td>possibly</td>
<td>spontaneous</td>
</tr>
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<td>76 B</td>
<td>2</td>
<td>B</td>
<td>hot flushes</td>
<td>52 min</td>
<td>mild</td>
<td>possibly</td>
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**Appears this way on original**
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-061

ADMINISTRATIVE DOCUMENTS
APPLICATION SUMMARY / REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT / LABELING REVIEW BRANCH

ANDA Number: 76-061 Date of Submission: Sept 4 & Aug 22, 2001

Applicant's Name: Teva Pharmaceuticals USA
Established Name: Pergolide Mesylate Tablets, 0.05 mg (base), 0.25 mg (base), and 1 mg (base)

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? YES
- Container Labels: (100's) FPL submitted on September 4, 2001 are satisfactory for approval.
- Professional Package Insert Labeling: FPL submitted on 9/4/01 is satisfactory for approval.
- Revisions needed post-approval: Yes

1. CONTAINER (100's)

   We encourage you to differentiate the different strengths from each other by using contrasting colors
   and/or boxing, or any other means.

2. INSERT (TITLE)

   Add "Rx only".

BASIS OF APPROVAL:

- Was this approval based upon a petition? NO
- What is the RLD on the 356(h) form: Permax
- NDA Number: 19-385
- NDA Drug Name: Permax
- NDA Firm: Eli Lilly
- Date of Approval of NDA Insert and supplement #: October 6, 1999;S-026
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? Yes
- Basis of Approval for the Container Labels: Side by Side
- Basis of Approval for the Carton Labeling: None

FOR THE RECORD:

2. INACTIVE INGREDIENTS: Consistent with application. See page 96, vol. 1.1.
3. PATENTS/EXCLUSIVITIES: 4797405 expires 10/26/07 & 5114948 expires 10/19/09.
   Firm submits PIV certification to both patents. No unexpired exclusivity.
4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - NDA: Store at controlled room temperature, 59° to 86°F (15° to 30°C).
   - ANDA: Store at controlled room temperature, between 15° to 30°C (59° to 86°F).
5. DISPENSING STATEMENT COMPARISON
   - NDA: none
   - ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure
     (as required).
6. PACKAGE CONFIGURATION
   - NDA: Bottles of 30's for the 0.05 mg and bottles of 100's for the 0.25 and 1 mg.
   - ANDA: Bottles of 100's for all three strengths.
8. FINISHED DOSAGE FORM
   - NDA: Scored Tablets
   - ANDA: Scored Tablets (see page 674, vol. B1.2)

Date of Review: September 13, 2001
Primary Reviewer: Koug Lee
Team Leader: Charlie Hoppes
cc: ANDA: 76-061
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
V:\FIRMSNZ\TEVAILTRS\REV76061.AP.labeling
Review

Date of Submission: Sept. 4 & Aug 22, 2001
Date: 9/14/01
Date: 9/19/01
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-061             Date of Submission: December 21, 2000
Applicant's Name: Teva Pharmaceuticals USA
Established Name: Pergolide Mesylate Tablets, 0.05 mg (base), 0.25 mg (base), and 1 mg (base)

Labeling Deficiencies:

1. CONTAINER (100's)
   a. We encourage you to differentiate the different strengths by from each other by using contrasting colors and/or boxing, or any other means.
   b. Add an asterisk to the statement "Each tablet contains" for the 0.25 mg and 1 mg strength container labels.
   c. Add "(See USP)" after the storage temperature statement.

2. INSERT
   a. TITLE
      Delete ' ' ' 
   b. DESCRIPTION
      Add the molecular weight and formula.
   c. HOW SUPPLIED
      See comment (1)(b).

Please revise your labeling as instructed above and submit 4 draft labels and package insert labeling for a tentative approval or 12 final printed copies of labels and labeling for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.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 your last submission with all differences annotated and explained.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
## REVIEW OF PROFESSIONAL LABELING CHECK LIST

<table>
<thead>
<tr>
<th>Established Name</th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different name than on acceptance to file letter?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Is this product a USP item? If so, USP supplement in which verification was assured: USP ?/</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Is this name different than that used in the Orange Book?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>If not USP, has the product name been proposed in the PFR?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Error Prevention Analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the firm proposed a proprietary name? If yes, complete this subsection.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you find the name objectionable? List reasons in PFR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Packaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in PFR.</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Because of proposed packaging configuration or for any other reason, does this applicant meet fall to meet all of the unstructured conditions of use of reference for the NDA?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Does the package proposed have any safety and/or regulatory concerns?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>If IV product packaged in syrups, could there be adverse patient outcome if given by direct IV injection?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Is the strength and/or concentration of the product unsuppressed by the insert labeling?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Is the color of the container (i.e., the color of the cap of a mydriatic ophthalmic) or cap incorrect?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Individual cartons required? Issues for PFR: innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Are there any other safety concerns?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Labeling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label.)</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Has applicant failed to clearly differentiate multiple product strengths?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Labeling (continued)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Is the Manufacturer by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is &quot;Jointly Manufactured by...&quot;, statement needed?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemists should confirm the data has been adequately supported.</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Scoring: Describe scoring configuration of RLD and applicant (page #) in the PFR</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Is the scoring configuration different than the RLD?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Has the firm failed to describe the scoring in the HOW SUPPLIED section?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Inactive Ingredients: (PFR: List page # in application where inactives are listed)</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Do any of the inactives differ in concentration for this route of administration?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Is there a discrepancy in inactives between DESCRIPTION and the composition statement?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Has the term &quot;other ingredients&quot; been used to protect a trade secret? If so, in claim supported?</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Failure to list the coloring agents if the composition statement lists e.g., Opaque, Opaque subscription?</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to list gelatin, coloring agents, antimicrobial for capsules in DESCRIPTION?</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does USP have labeling recommendations? If any, does ANDA meet them?</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the product light sensitive? If yes, is NDA and/or ANDA in a light resistant container?</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure of DESCRIPTION to meet USP Description and Stability information? If so, USP information should be used. However, only include solvents appearing in innovator labeling</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioequivalence issues: (Compare bioequivalence values: Insert to study. List CASA, Texas, T 1/2 and date study acceptable)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insert labeling references a food effect or a no-effect? If so, was a food study done?</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail interchange</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTES/QUESTIONS TO THE CHEMIST:**

**FOR THE RECORD:**

1. **MODEL LABELING:** Permax®, NDA 19-385/S-026; approved October 6, 1999.
2. **INACTIVE INGREDIENTS:** Consistent with application. See page 96, vol. 1.1.
3. **PATENTS/EXCLUSIVITIES:** 4797405 expires 10/26/07 & 5114948 expires 10/19/09. Firm submits PIV certification to both patents. No unexpired exclusivity.
4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
   - NDA: Store at controlled room temperature, 59°F to 86°F (15°C to 30°C).
   - ANDA: Store at controlled room temperature, between 15°C to 30°C (59°F to 86°F).
5. **DISPENSING STATEMENT COMPARISON**
   - NDA: none
   - ANDA: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
6. **PACKAGE CONFIGURATION**
   - NDA: Bottles of 30's for the 0.05 mg and bottles of 100's for the 0.25 and 1 mg.
   - ANDA: Bottles of 100's for all three strengths.
7. **CONTAINER/CLOSURE** (see page 541, vol. B1.2)
   - Container: 
   - Closure: CRC
8. **FINISHED DOSAGE FORM**
   - NDA: Scored Tablets
   - ANDA: Scored Tablets (see page 674, vol. B1.2)

**Date of Review:** February 9, 2001  
**Date of Submission:** December 21, 2000

**Primary Reviewer:** Koungh Lee  
**Date:** 02/14/01

**Team Leader:** Charlie Hoppes  
**Date:** 04/15/01

**cc:**
- ANDA: 76-061
- DUP/DIVISION FILE
- HFD-613/KLee/CHoppes (no cc)
- V:\FIRMSNZ\TEVALTRS&REV\76061.na1.labeling

Review
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-061

CORRESPONDENCE
August 8, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA 76-061
PERGOLIDE MESYLATE TABLETS, eq. to 0.05 mg, 0.25 mg, and 1 mg base
TELEPHONE AMENDMENT

Dear Mr. Buehler:

We submit herewith an amendment to the above referenced pending ANDA in response to a telephone conversation with Frank Holcombe of your office on August 5, 2002. Specifically, Dr. Holcombe expressed concern regarding the granting of a 24 month tentative expiration dating for both the 0.05 mg and 0.25 mg tablet strengths. His evaluation was based upon the review of 18 month room temperature stability data. As of August 6, 2002, full term 24 month room temperature data became available. This additional data point and the calculated 95% confidence interval using these data were evaluated. The data project acceptable stability results for the 0.25 mg strength beyond 24 months. Therefore, based on these data, which are enclosed for your review as Attachment 1, we maintain our proposal of a 24 month tentative expiration dating for the 0.25 mg tablet strength. The data do however suggest that the 0.05 mg tablet strength be limited to an 18 month dating. Please find enclosed, as Attachment 2, a revised protocol for the 0.05 mg tablet which reflects our proposal of an 18 month tentative expiration dating. This protocol also reflects the addition of 15 and 21 month test stations per Dr. Holcombe’s recommendation. The original data for the 1 mg tablet fully supports a tentative dating of 24 months and therefore has not come into question. We have enclosed the 24 month room temperature data for the 1 mg in Attachment 1. These data are provided solely to complete our file.

This information is provided for your review and final approval of ANDA 76-061. Should you have additional comments or questions please do not hesitate to contact me via telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

[Signature]

Enclosures

TELEPHONE AMENDMENT

ORIG AMENDMENT

N/A

RECEIVED
AUG 09 2002
OGD/CDER
May 17, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA #76-061
PERGOLIDE MESYLATE TABLETS, 0.05 mg, 0.25 mg and 1 mg
TELEPHONE AMENDMENT- RESPONSE TO MAY 13, 2002 REQUEST

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced ANDA in response to a telephone conversation between Damaris Maldonado of the Office of Generic Drugs and Philip Erickson of TEVA Pharmaceuticals USA on May 13, 2002. Specifically, Ms. Maldonado requested updated stability data for Pergolide Mesylate Tablets.

As requested, stability data for the demonstration batches, stored for 18 months at controlled room temperature (25°C ± 2°C/ 60% RH ± 5% RH) conditions are provided in Attachment 1. Please note that the 24 month station (completed stability study) is not due out of the chamber until July 2002.

It is TEVA’s belief that the information contained herein represents a complete response to FDA’s May 13, 2002 telephone request. This information is submitted for your continued review and approval of ANDA #76-061. Should you have any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

[Signature]

PE/cj
Enclosures

RECEIVED
MAY 2002
OGD/CDER
March 14, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA # 76-061
PERGOLIDE MESYLATE TABLETS, 0.05 mg, 0.25 mg and 1.0 mg
MINOR AMENDMENT - RESPONSE TO FEBRUARY 26, 2002 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated February 26, 2002. For ease of review, please find attached a copy of this letter (Attachment 1). We have addressed your comments in the order in which they were presented in your letter.

A. Deficiencies

1. Please find attached the cover letter from the DMF holder which was submitted to the FDA on March 4, 2002 (Attachment 2).

2. Based on the supplier’s drug substance specifications, Teva has added limits for the known impurities of . Attached please find the amended QC monograph for release (RM-0243/Ed. 04 March 11, 2002) and the drug substance summary of specifications in Attachment 3.

3. Teva has included the declared content of the tablets to the formula for percent pergolide dissolved of labeled claim. The updated dissolution method was sent to the FDA on February 1, 2002 in response to a direct Methods Validation question. Please find attached the revised dissolution method (SI-11317/Ed. 03) and the revised monograph for release (PR-0095/Ed. 03) in Attachment 4.

RECEIVED
MAR 15 2002
OGD/CDER
It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. This information is submitted for your continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

[Signature]

PE/cw

Enclosures
TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road, P.O. Box 1090
North Wales, PA 19454-1090

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.

NAME OF DRUG: Pergolide Mesylate Tablets, 0.05 mg(base), 0.25 mg(base), 1.0 mg(base)

DATE OF APPLICATION: December 21, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 21, 2000

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;
2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day
period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregory Davis, Chief, Regulatory Support Branch, at (301)827-5862.

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

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

Should you have questions concerning this application, contact:

Kassandra Sherrod  
Project Manager  
(301) 827-5848

Sincerely yours,

Wm Peter Rickman  
Acting Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research
December 21, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD  20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
PERGOLIDE MESYLATE TABLETS, eq. to 0.05 mg, 0.25 mg, and 1 mg base

Dear Mr. Buehler:

We submit herewith an abbreviated new drug application for the drug product Pergolide Mesylate Tablets, 0.05 mg, 0.25 mg, and 1 mg.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs February 1999 Guidance for Industry: Organization of an ANDA (OGD #1, Rev. 1). These copies are presented in a total of 21 volumes; 10 for the archival copy and 11 for the review copy.

The application contains a full report of one in vivo bioequivalence study. This study compared Pergolide Mesylate Tablets, 0.05 mg manufactured by TEVA Pharmaceutical Industries, Ltd. to the reference listed drug, Permax® Tablets, 0.05 mg each administered as a 0.1 mg dose, under fasting conditions.

Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

[Signature]

PE/asg
Enclosures
February 1, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA #76-061
PERGOLIDE MESYLATE TABLETS, 0.05 mg, 0.25 mg and 1 mg
TELEPHONE AMENDMENT- RESPONSE TO JANUARY 23, 2002 REQUEST

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced ANDA in response to a telephone conversation between Damaris Maldonado of the Office of Generic Drugs and Jill Pastore of TEVA Pharmaceuticals USA on January 23, 2002. Specifically, Ms. Maldonado provided comments from the District Laboratory with regard to methods validation for Pergolide Mesylate Tablets. The comments are addressed below in the order they were presented by Ms. Maldonado.

1.
2. Per FDA’s comment regarding the formula used in the dissolution method, the calculation formula in the procedure has been revised to include as a factor the strength of product being tested in the denominator. A revised procedure for finished product release (PR-0095, edition 03) is provided in Attachment 3, and the revised stability method (SI-11317, edition 03) is provided in Attachment 4.

It is TEVA’s belief that the information contained herein represents a complete response to FDA’s January 23, 2002 telephone request. This information is submitted for your continued review and approval of ANDA #76-061. Should you have any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson, L.A.

PE/jbp
Enclosures
January 28, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA # 76-061
PERGOLIDE MESYLA TEABLETS, 0.05 mg, 0.25 mg and 1 mg
MINOR AMENDMENT - RESPONSE TO JANUARY 16, 2002 DEFICIENCY LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced pending Abbreviated New Drug Application in response to a review letter dated January 16, 2002. For ease of review, please find a copy of this letter in Attachment 1. The holder of drug master file No. responded to their deficiency letter from the FDA on January 25, 2002. Please find in Attachment 2 the cover letter that accompanied their response.

It is TEVA Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. This information is submitted for your continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

Phillip Erickson

Enclosures
September 12, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #76-061
PERGOLIDE MESYLATE TABLETS, 0.05 mg (base), 0.25 mg (base), 1 mg (base)
NOTIFICATION OF END OF 45 DAY CLOCK/STATUS OF SUIT

Dear Mr. Buehler:

In accord with 21 CFR 314.95, TEVA Pharmaceuticals USA hereby notifies the FDA that the 45 day period related to the notice of patent certification under section 505(j)(2)(A)(vii)(IV) of the Act for the above-referenced ANDA expired on April 27, 2001. This process was triggered on March 13, 2001, the day of receipt of notice by Eli Lilly and Company (hereafter "Lilly") as owner of NDA 19-385 for Permax® Tablets and owner of U.S. Patents 4,797,405 and 5,114,948. Please note that Lilly has granted Elan Pharmaceuticals, Inc., an exclusive license to market Permax® Tablets in the United States; Elan is also the exclusive licensee of the '405 and '948 patents.

Please note that Elan and Lilly dismissed their complaint against TEVA, and in fact never even served TEVA with respect to Pergolide Mesylate Tablets, as noted in the enclosed Notice of Voluntary Dismissal. As a result, Elan and Lilly have waived their right to pursue legal action under the scope of the Waxman-Hatch Act regarding TEVA's patent certification. Therefore, please note that TEVA anticipates final approval of Pergolide Mesylate Tablets, 0.05 mg, 0.25 mg and 1 mg upon completion of the Agency's satisfactory review of ANDA #76-061.

Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

[Signature]

PE/jhp
Enclosure
September 4, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA # 76-061
PERGOLIDE MESYLATED TABLETS, 0.05 mg, 0.25 mg and 1.0 mg
LABELING AMENDMENT

Dear Mr. Buehler:

We submit herewith a Labeling Amendment to the above-referenced pending ANDA in response to a September 4, 2001 telephone conversation between Kyoung Lee of the Labeling Review Branch and Philip Erickson of TEVA Pharmaceuticals USA. Per Mr. Lee’s request, please find enclosed 12 copies of the final print package insert as well as container labels. Please note that product strengths are differentiated by color on the container labels.

This information is submitted for your review and approval. If there are any questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

[Signature]
PE/dl
Enclosures
August 22, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA # 76-061
PERGOLIDE MESYLATE TABLETS, 0.05 mg, 0.25 mg and 1.0 mg
MINOR AMENDMENT - RESPONSE TO MAY 25, 2001 DEFICIENCY LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced, pending Abbreviated New Drug Application in response to a review letter dated May 25, 2001. For ease of review, please find attached a copy of this letter (Attachment 1). We have addressed your comments in the order in which they were presented in your letter.

A. Chemistry

1. The manufacturer has responded to the FDA deficiencies for DMF # ___________.

Please find attached a copy of the cover letter from ___________ (Attachment 2).
Redacted

3

pages of trade

secret and /or

confidential

commercial

information
B. Additionally, we propose the following change:

\[
\text{[Diagram or text showing proposed change]}
\]

LABELING

As requested, all deficiencies related to the container and insert labeling have been addressed and the container and insert have been updated accordingly. Four copies of draft labels and insert labeling are provided (Attachment 13). Per an August 3, 2001 telephone discussion between Charlie Hoppes, Division of Labelling and Program Support, and Robert Vincent of Teva USA, comment 2.c regarding revision of the insert has been corrected. The deficiency comment was revised to read “see comment 1.c.” instead of “1.b.” Please find attached a side-by-side comparison of our current labeling vs. the labeling which we last submitted (Attachment 14).

It is TEVA Pharmaceuticals USA’s opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. This information is submitted for your continued review and approval of this ANDA. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

[Signature]

PE/jws
Enclosures
May 11, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA #76-061
PERGOLIDE MESYLATE TABLETS, equivalent to 0.05 mg, 0.25 mg, and 1 mg base
BIOEQUIVALENCY AMENDMENT - RESPONSE TO APRIL 18, 2001 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a bioequivalency amendment to the above referenced pending Abbreviated New Drug Application in response to a review letter dated April 18, 2001. A copy of the letter is provided as Attachment 1. The comments are addressed in the order in which they were presented:

1. Please find in Attachment 2 an amendment to the bioequivalency study report which contains data to support the long-term stability of pergolide in frozen study samples for a period of 244 days.

2. Because all medication is dispensed at least the day before dosing, pre-medication (prochlorperazine) was dispensed to both subjects #38 and #49.

Subject #38 was withdrawn from the study on the morning of the dosing, before receiving the pre-medication (prochlorperazine), because of abnormal vital signs as judged by the study physician. Please find in Attachment 3, a copy of page 1710 of the bioequivalency study report in which the exception of subject #38 was noted as well as the pre-dose vital signs of this subject. The vital signs page was not included in the report since this subject was not dosed.

Subject #49 withdrew voluntarily before receiving his study medication. Please see footnote 3 on page 1716 of the bioequivalency study report (copy provided in Attachment 3).
Neither subject is included in the study nor the study report because they did not receive any study medication. However, does have all information on these two subjects in their archive files.

3. Please find in Attachment 4, detailed SOP's (including SOP ANI 156) listing the criteria for acceptance of values due to pharmacokinetic repeats.

4. Per your request, please find in Attachment 5, the repeated dissolution testing results for all strengths of Pergolide Tablets versus Permax® using the following method:

5. 

It is Teva Pharmaceuticals USA’s opinion that the information presented herein represents a complete response to the comments set forth in the April 18, 2001 review letter. This information is submitted for your continued review and approval of ANDA #76-061. If there are any further questions, please do not hesitate to contact me directly at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

[Signature]

PE/asg
Enclosures
February 28, 2001

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #76-061
PERGOLIDE MESYLATE TABLETS, 0.05 mg, 0.25 mg and 1 mg

BIOEQUIVALENCE ELECTRONIC SUBMISSION DOCUMENT

Dear Mr. Buehler:

Reference is made to our original abbreviated new drug application #76-061 dated December 21, 2000 for Pergolide Mesylate Tablets, 0.05 mg, 0.25 mg and 1 mg.

We submit herewith a Bioequivalence Electronic Submission Document (Entry and Validation Application) for the above referenced original abbreviated new drug application. TEVA Pharmaceuticals USA hereby declares that the data contained in the electronic submission is identical to that included in the paper submission. Any differences have been noted in the accompanying companion document.

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

[Signature]

PE/va
Enclosures
April 6, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #76-061
PERGOLIDE MESYLATE TABLETS, 0.05 mg (base), 0.25 mg (base), 1.0 mg (base)
NOTICE OF CERTIFICATION OF NON-INFRINGEMENT AND RECEIPT OF NOTICE UNDER SECTION 505(j)(2)(B)(I) AND 21 CFR 314.95

Dear Mr. Buehler:

TEVA Pharmaceuticals USA hereby certifies that a Notice of Certification of Non-Infringement of U.S. Patent No. 4,797,405 and U.S. Patent No. 5,114,948 was provided to Eli Lilly & Co. as the holder of NDA #019385 for Permax® Tablets and owner of the patents in accord with 314.95(b). The notice dated March 7, 2001 contains the information as required under 314.95(c). A copy of the notice is provided herein.

Also provided, in accord with 21 CFR 314.95 (e), is documentation of the receipt of Notice of Certification for U.S. Patent No. 5,114,948. The Notice sent to the affected patent owner, application holder, or authorized representative had been received on March 13, 2001. This date is evidenced by the attached copies of the return receipt. In accord with 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is March 14, 2001, the first day after receipt of notice. The 45-day period will therefore end on April 27, 2001.

Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

[Signature]

PE/sg
Enclosures