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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-061

APPROVAL LETTER

ANDA 76-061

NOV 27 2002

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/NDA 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,

/S/

Gary Buehler 11/27/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-061

Final Printed Labeling

76-001

AP 4/27/02

NDC 0093-7161-01

PERGOLIDE MESYLATE Tablets 1 mg*

*Each tablet contains: pergolide mesylate equivalent to 1 mg pergolide

℞ only

TEVA

Usual Dosage: See package insert for full prescribing information.
Store at controlled room temperature, between 15° to 30°C (59° to 86°F)[see USP].
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. TP Iss. 7/2001
Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-7161-01 1

NDC 0093-7160-01

PERGOLIDE MESYLATE Tablets 0.05 mg*

*Each tablet contains: pergolide mesylate equivalent to 0.05 mg pergolide

℞ only

TEVA

Usual Dosage: See package insert for full prescribing information.
Store at controlled room temperature, between 15° to 30°C (59° to 86°F)[see USP].
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. TP Iss. 7/2001
Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-7160-01 4

NDC 0093-7159-01

PERGOLIDE MESYLATE Tablets 0.25 mg*

*Each tablet contains: pergolide mesylate equivalent to 0.25 mg pergolide

℞ only

TEVA

Usual Dosage: See package insert for full prescribing information.
Store at controlled room temperature, between 15° to 30°C (59° to 86°F)[see USP].
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. TP Iss. 7/2001
Manufactured By:
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Jerusalem, 91010, Israel
Manufactured For
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-7159-01 8

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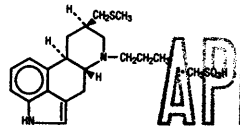
PERGOLIDE MESYLATE TABLETS

DESCRIPTION

Pergolide Mesylate is an ergot derivative dopamine receptor agonist at both D_1 and D_2 receptor sites. Pergolide mesylate is chemically designated as 8β-[(Methylthio)methyl]-6-propylergoline monomethanesulfonate; the structural formula is as follows:



$C_{16}H_{26}N_2S{\cdot}CH_4O_3S$ M.W. 410.60

The formula 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 0.05 mg (0.159 µmol), 0.25 mg (0.795 µmol) or 1 mg (3.18 µmol) pergolide as the base. The tablets also contain lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch and sodium starch glycolate. The 0.05 mg tablet also contains ferric oxide yellow. The 0.25 mg tablet also contains FD&C Blue No.2 aluminum lake and ferric oxide yellow. The 1 mg tablet also contains ferric oxide red.

CLINICAL PHARMACOLOGY

Pharmacodynamic Information

Pergolide mesylate is a potent dopamine receptor agonist. Pergolide is 10 to 1,000 times more potent than bromocriptine on a milligram per milligram basis in various *in vitro* and *in vivo* test systems. Pergolide mesylate inhibits the secretion of prolactin in humans; it causes a transient rise in serum concentrations of growth hormone and a decrease in serum concentrations of luteinizing hormone. In Parkinson's disease, pergolide mesylate is believed to exert its therapeutic effect by directly stimulating post-synaptic dopamine receptors in the nigrostriatal system.

Pharmacokinetic Information (Absorption, Distribution, Metabolism and Elimination)

Information on oral systemic 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 ^{14}C radiolabeled pergolide mesylate, approximately 55% of the administered radioactivity can be recovered from the urine and 5% from expired CO_2, suggesting that a significant fraction is absorbed. Nothing can be concluded about the extent of presystemic clearance, if any.

Data on postabsorption distribution of pergolide are unavailable.

At least 10 metabolites have been detected, including N-despropyl-pergolide, pergolide sulfoxide, and pergolide sulfone. Pergolide sulfoxide and pergolide sulfone are dopamine agonists in animals. The other detected metabolites have not been identified and it is not known whether any other metabolites are active pharmacologically.

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 antiparkinsonian adjunct was obtained in a multicenter study enrolling 376 patients with mild to moderate Parkinson's disease who were intolerant to *l*-dopa/carbidopa as manifested by moderate to severe dyskinesia and/or on-off phenomena. On average, the patients evaluated had been on *l*-dopa/carbidopa for 3.9 years (range, 2 days to 16.8 years). The administration of pergolide mesylate permitted a 5% to 30% reduction in the daily dose of *l*-dopa. On average, these patients treated with pergolide mesylate maintained an equivalent or better clinical status than they exhibited 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 *l*-dopa versus 7% taking placebo with *l*-dopa experienced symptomatic orthostatic and/or sustained hypotension, especially during initial treatment. With gradual dosage titration, tolerance to the hypotension usually develops. It is therefore important to warn patients of the risk, to begin therapy with low doses, and to increase the dosage in carefully adjusted increments over a period of 3 to 4 weeks (see **DOSAGE AND ADMINISTRATION**).

Hallucinosis

In controlled trials, pergolide mesylate with *l*-dopa caused hallucinosis in about 14% of patients as opposed to 3% taking placebo with *l*-dopa. This was of sufficient severity to cause discontinuation of treatment in about 3% of those enrolled; tolerance to this untoward effect was not observed.

Fatalities

In the placebo-controlled trial, 2 of 187 patients treated with placebo died as compared with 1 of 189 patients treated with pergolide mesylate. Of the 2,299 patients treated with pergolide mesylate in premarketing studies evaluated as of October 1988, 143 died while on the drug or shortly after discontinuing it. Because the patient population under evaluation was elderly, ill, 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 particular, a case-by-case review of the clinical course of the patients who died failed to disclose any unique set of signs, symptoms, or laboratory results that would suggest that treatment with pergolide caused their deaths. Sixty-eight percent (68%) of the patients who died were 65 years of age or older. No death (other than a suicide) occurred within the first month of treatment; most of the patients who died had been on pergolide for years. A relative frequency of the causes of death by organ system are: Pulmonary failure/Pneumonia, 35%; Cardiovascular, 30%; Cancer, 11%; Unknown, 8.4%; Infection, 3.5%; Extrapyramidal syndrome, 3.5%; Stroke, 2.1%; Dysphagia, 2.1%; Injury, 1.4%; Suicide, 1.4%; Dehydration, 0.7%; Glomerulonephritis, 0.7%.

Serious Inflammation and Fibrosis

There have been rare reports of pleuritis, pleural effusion, pleural fibrosis, pericarditis, pericardial effusion or retroperitoneal fibrosis in patients taking pergolide. Some patients had experienced similar events while taking the ergot derivative bromocriptine. Pergolide should be used with caution in patients with a history of these conditions, particularly those patients who experienced the events while taking ergot derivatives. 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 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.

The use of pergolide mesylate in patients on *l*-dopa may cause and/or exacerbate preexisting states of confusion and hallucinations (see **WARNINGS**) and preexisting dyskinesia. Also, the abrupt discontinuation of pergolide mesylate in patients receiving it chronically as an adjunct to *l*-dopa may precipitate the onset of hallucinations and confusion; these may occur within a span of several days. Discontinuation of pergolide should be undertaken gradually whenever possible, even if the patient is to remain on *l*-dopa.

A symptom complex resembling the neuroleptic 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 antiparkinsonian therapy, including pergolide.

Information for Patients

Patients and their families should be informed of the common adverse consequences of the use of pergolide mesylate (see **ADVERSE REACTIONS**) and the risk of hypotension (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 an infant.

Laboratory Tests

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

Drug Interactions

Dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthines) or metoclopramide, ordinarily should not be administered concurrently with pergolide mesylate (a dopamine agonist); these agents may diminish the effectiveness of pergolide mesylate.

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

A 2-year carcinogenicity study was conducted in mice using dietary levels of pergolide mesylate equivalent to oral doses of 0.6,

with *l*-dopa. This was of sufficient severity to cause discontinuation of treatment in about 3% of those enrolled; tolerance to this untoward effect was not observed.

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility
A 2-year carcinogenicity study was conducted in mice using dietary levels of pergolide mesylate equivalent to oral doses of 0.6, 3.7, and 36.4 mg/kg/day in males and 0.6, 4.4, and 40.8 mg/kg/day in females. A 2-year study in rats was conducted using dietary levels equivalent to oral doses of 0.04, 0.18, and 0.88 mg/kg/day in males and 0.05, 0.28, and 1.42 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 (6 mg/day equivalent to 0.12 mg/kg/day).

A low incidence of uterine neoplasms occurred in both rats and mice. Endometrial adenomas and carcinomas were observed in rats. Endometrial sarcomas were observed in mice. The occurrence of these neoplasms is probably attributable to the high estrogen/progesterone ratio that would occur in rodents as a result of the prolactin-inhibiting action of pergolide mesylate. The endocrine mechanisms believed to be involved in the rodents are not present in humans. However, even though there is a known correlation between uterine malignancies occurring in pergolide-treated rodents and human risk, there are no human data to substantiate this conclusion.

Pergolide mesylate was evaluated for mutagenic potential in a battery of tests that included an Ames bacterial mutation assay, a DNA repair assay in cultured rat hepatocytes, an *in vitro* mammalian cell-point-mutation assay in cultured L5178Y cells, and a determination of chromosome alteration in bone marrow cells of Chinese hamsters. A weak mutagenic response was noted in the mammalian cell-point-mutation assay only after metabolic activation with rat liver microsomes. No mutagenic effects were obtained in the 2 other *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. Prolactin has been reported to be involved in stimulating and maintaining progesterone levels required for implantation in mice and, therefore, the impaired fertility at the high dose may have occurred because of decreased prolactin levels.

Usage in Pregnancy – Pregnancy Category B
Reproduction studies were conducted in mice at doses of 5, 16, and 45 mg/kg/day and in rabbits at doses of 2, 6, and 16 mg/kg/day. The highest doses tested in mice and rabbits were 375 and 133 times the 6 mg/day maximum human dose administered in controlled clinical trials. In these studies, there was no evidence of harm to the fetus due to pergolide mesylate.

There are, however, no adequate and well-controlled studies in pregnant women. Among women who received pergolide mesylate for endocrine disorders in premarketing studies, there were 33 pregnancies that resulted in healthy babies and 6 pregnancies that resulted in congenital abnormalities (3 major, 3 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 mesylate 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 mesylate 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 mesylate which were not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including dyskinesia, hallucinations, somnolence, insomnia; digestive complaints, including nausea, constipation, diarrhea, dyspepsia; and respiratory system complaints, including rhinitis.

Associated with Discontinuation of Treatment
Twenty-seven percent (27%) of approximately 1,200 patients receiving pergolide mesylate for treatment of Parkinson's disease in premarketing clinical trials in the U.S. and Canada discontinued treatment due to adverse events. The events most commonly causing discontinuation were related to the nervous system (15.5%), primarily hallucinations (7.8%) and confusion (1.8%).

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 mesylate who participated in the premarketing controlled clinical trials comparing pergolide mesylate with placebo. In a double-blind, controlled study of 6 months' duration, patients with Parkinson's disease were continued on *l*-dopa/carbidopa and were randomly assigned to receive either pergolide mesylate or placebo as additional therapy.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial

Body System/ Adverse Event*	Percentage of Patients Reporting Events: Pergolide Mesylate N = 189	Placebo N = 187
Body as a Whole		
Pain	7.0	2.1
Abdominal pain	5.8	2.1
Injury, accident	5.8	7.0
Headache	5.3	6.4
Asthenia	4.2	4.8

Body as a Whole cont...		
Chest pain	3.7	2.1
Flu syndrome	3.2	2.1
Neck pain	2.7	1.6
Back pain	1.6	2.1
Surgical procedure	1.6	<1
Chills	1.1	0
Face edema	1.1	0
Infection	1.1	0
Cardiovascular		
Postural hypotension	9.0	7.0
Vasodilation	3.2	<1
Palpitation	2.1	<1
Hypotension	2.1	<1
Syncope	2.1	1.1
Hypertension	1.6	1.1
Arrhythmia	1.1	<1
Myocardial infarction	1.1	<1
Digestive		
Nausea	24.3	12.8
Constipation	10.6	5.9
Diarrhea	6.4	2.7
Dyspepsia	6.4	2.1
Anorexia	4.8	2.7
Dry Mouth	3.7	<1
Vomiting	2.7	1.6
Hemic and Lymphatic		
Anemia	1.1	<1
Metabolic and Nutritional		
Peripheral edema	7.4	4.3
Edema	1.6	0
Weight gain	1.6	0
Musculoskeletal		
Arthralgia	1.6	2.1
Bursitis	1.6	<1
Myalgia	1.1	<1
Twitching	1.1	0
Nervous System		
Dyskinesia	62.4	24.6
Dizziness	19.1	13.9
Hallucinations	13.8	3.2
Dystonia	11.6	8.0
Confusion	11.1	9.6
Somnolence	10.1	3.7
Insomnia	7.9	3.2
Anxiety	6.4	4.3
Tremor	4.2	7.5
Depression	3.2	5.4
Abnormal dreams	2.7	4.3
Personality disorder	2.1	<1
Psychosis	2.1	0
Abnormal gait	1.6	1.6
Akathisia	1.6	0
Extrapyramidal syndrome	1.6	1.1
Incoordination	1.6	<1
Paresthesia	1.6	3.2
Akinesia	1.1	1.1
Hypertonia	1.1	0
Neuralgia	1.1	<1
Speech Disorder	1.1	1.6
Respiratory System		
Rhinitis	12.2	5.4
Dyspnea	4.8	1.1
Epistaxis	1.6	<1
Hiccup	1.1	0
Skin and Appendages		
Rash	3.2	2.1
Sweating	2.1	2.7
Special Senses		
Abnormal vision	5.8	5.4
Diplopia	2.1	0
Taste perversion	1.6	0
Eye disorder	1.1	0
Urogenital System		
Urinary frequency	2.7	6.4
Urinary tract infection	2.7	3.7
Hematuria	1.1	<1

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

Events Observed During the Premarketing Evaluation of Pergolide Mesylate

This section reports event frequencies evaluated as of October 1988 for adverse events occurring in a group of approximately 1,800 patients who took multiple doses of pergolide mesylate. The conditions and duration of exposure to pergolide mesylate varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. In the absence of appropriate controls in some of the studies, a causal relationship between these events and treatment with pergolide mesylate cannot be determined.

The following enumeration by organ system describes 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** sections.

The following definitions of frequency are used: **frequent adverse events are defined as those occurring in at least 1/100 patients;** infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Body as a Whole – *Frequent:* headache, asthenia, accidental injury, pain, abdominal pain, chest pain, back pain, flu syndrome, neck pain, fever; *Infrequent:* facial edema, chills, enlarged abdomen, malaise, neoplasm, hernia, pelvic pain, sepsis, cellulitis, moniliasis, abscess, jaw pain, hypothermia; *Rare:* acute abdominal syndrome, LE syndrome.

Cardiovascular System – *Frequent:* postural hypotension, syncope, hypertension, palpitations, vasodilatations, congestive heart failure; *Infrequent:* myocardial infarction, tachycardia, heart arrest, abnormal electrocardiogram, angina pectoris, thrombophlebitis, bradycardia, ventricular extrasystoles, cerebrovascular accident, ventricular tachycardia, cerebral ischemia, atrial fibrillation, varicose vein, pulmonary embolus, AV block, shock; *Rare:* vasculitis, pulmonary hypertension, pericarditis, migraine, heart block, cerebral hemorrhage.

Digestive System – *Frequent:* nausea, vomiting, dyspepsia, diarrhea, constipation, dry mouth, dysphagia; *Infrequent:* flatulence, abnormal liver function tests, increased appetite, salivary gland enlargement, thirst, gastroenteritis, gastritis, periodontal abscess, intestinal obstruction, nausea and vomiting, gingivitis, esophagitis, cholelithiasis, tooth caries, hepatitis, stomach ulcer, melena, hepatomegaly, hematemesis, eructation; *Rare:* sialadenitis, peptic ulcer, pancreatitis, jaundice, glossitis, fecal incontinence, duodenitis, colitis, cholecystitis, aphthous stomatitis, esophageal ulcer.

Endocrine System – *Infrequent:* hypothyroidism, adenoma, diabetes mellitus, ADH inappropriate; *Rare:* endocrine disorder, thyroid adenoma.

Hemic and Lymphatic System – *Frequent:* anemia; *Infrequent:* leukopenia, lymphadenopathy, leukocytosis, thrombocytopenia, petechia, megaloblastic anemia, cyanosis; *Rare:* purpura, lymphocytosis, eosinophilia, thrombocythemia, acute lymphoblastic leukemia, polycythemia, splenomegaly.

Metabolic and Nutritional System – *Frequent:* peripheral edema, weight loss, weight gain; *Infrequent:* dehydration, hypokalemia, hypoglycemia, iron deficiency anemia, hyperglycemia, gout, hypercholesteremia; *Rare:* electrolyte imbalance, cachexia, acidosis, hyperuricemia.

Musculoskeletal System – *Frequent:* twitching, myalgia, arthralgia; *Infrequent:* bone pain, tenosynovitis, myositis, bone sarcoma, arthritis; *Rare:* osteoporosis, muscle atrophy, osteomyelitis.

Nervous System – *Frequent:* dyskinesia, dizziness, hallucinations, confusion, somnolence, insomnia, dystonia, paresthesia, depression, anxiety, tremor, akinesia, extrapyramidal syndrome, abnormal gait, abnormal dreams, incoordination, psychosis, personality disorder, nervousness, choreoathetosis, amnesia, paranoid reaction, abnormal thinking; *Infrequent:* akathisia, neuropathy, neuralgia, hypertonia, delusions, convulsion, libido increased, euphoria, emotional lability, libido decreased, vertigo, myoclonus, coma, apathy, paralysis, neurosis, hyperkinesia, ataxia, acute brain syndrome, torticollis, meningitis, manic reaction, hypokinesia, hostility, agitation, hypotonia; *Rare:* stupor, neuritis, intracranial hypertension, hemiplegia, facial paralysis, brain edema, myelitis, hallucinations and confusion after abrupt discontinuation.

Respiratory System – *Frequent:* rhinitis, dyspnea, pneumonia, pharyngitis, cough increased; *Infrequent:* epistaxis, hiccup, sinusitis, bronchitis, voice alteration, hemoptysis, asthma, lung edema, pleural effusion, laryngitis, emphysema, apnea, hyperventilation; *Rare:* pneumothorax, lung fibrosis, larynx edema, hypoxia, hypoventilation, hemothorax, carcinoma of lung.

Skin and Appendages System – *Frequent:* sweating, rash; *Infrequent:* skin discoloration, pruritus, acne, skin ulcer, alopecia, dry skin, skin carcinoma, seborrhea, hirsutism, herpes simplex, eczema, fungal dermatitis, herpes zoster; *Rare:* vesiculobullous rash, subcutaneous nodule, skin nodule, skin benign neoplasm, lichenoid dermatitis.

Special Senses System – *Frequent:* abnormal vision, diplopia; *Infrequent:* otitis media, conjunctivitis, tinnitus, deafness, taste perversion, ear pain, eye pain, glaucoma, eye hemorrhage, photophobia, visual field defect; *Rare:* blindness, cataract, retinal detachment, retinal vascular disorder.

Urogenital System – *Frequent:* urinary tract infection, urinary frequency, urinary incontinence, hematuria, dysmenorrhea:

This section reports event frequencies evaluated as of October 1998 for adverse events occurring in a group of approximately 1,800 patients who took multiple doses of pergolide mesylate. The conditions and duration of exposure to pergolide mesylate varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. In the absence of appropriate controls in some of the studies, a causal relationship between these events and treatment with pergolide mesylate cannot be determined.

The following enumeration by organ system describes 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** sections.

The following definitions of frequency are used: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Body as a Whole – *Frequent:* headache, asthenia, accidental injury, pain, abdominal pain, chest pain, back pain, flu syndrome, neck pain, fever; *Infrequent:* facial edema, chills, enlarged abdomen, malaise, neoplasm, hernia, pelvic pain, sepsis, cellulitis, moniliasis, abscess, jaw pain, hypothermia; *Rare:* acute abdominal syndrome, LE syndrome.

Cardiovascular System – *Frequent:* postural hypotension, syncope, hypertension, palpitations, vasodilatations, congestive heart failure; *Infrequent:* myocardial infarction, tachycardia, heart arrest, abnormal electrocardiogram, angina pectoris, thrombophlebitis, bradycardia, ventricular extrasystoles, cerebrovascular accident, ventricular tachycardia, cerebral ischemia, atrial fibrillation, varicose vein, pulmonary embolus, AV block, shock; *Rare:* vasculitis, pulmonary hypertension, pericarditis, migraine, heart block, cerebral hemorrhage.

Digestive System – *Frequent:* nausea, vomiting, dyspepsia, diarrhea, constipation, dry mouth, dysphagia; *Infrequent:* flatulence, abnormal liver function tests, increased appetite, salivary gland enlargement, thirst, gastroenteritis, gastritis, periodontal abscess, intestinal obstruction, nausea and vomiting, gingivitis, esophagitis, cholelithiasis, tooth caries, hepatitis, stomach ulcer, melena, hepatomegaly, hematemesis, eructation; *Rare:* sialadenitis, peptic ulcer, pancreatitis, jaundice, glossitis, fecal incontinence, duodenitis, colitis, cholecystitis, aphthous stomatitis, esophageal ulcer.

Endocrine System – *Infrequent:* hypothyroidism, adenoma, diabetes mellitus, ADH inappropriate; *Rare:* endocrine disorder, thyroid adenoma.

Hemic and Lymphatic System – *Frequent:* anemia; *Infrequent:* leukopenia, lymphadenopathy, leukocytosis, thrombocytopenia, petechia, megaloblastic anemia, cyanosis; *Rare:* purpura, lymphocytosis, eosinophilia, thrombocythemia, acute lymphoblastic leukemia, polycythemia, splenomegaly.

Metabolic and Nutritional System – *Frequent:* peripheral edema, weight loss, weight gain; *Infrequent:* dehydration, hypokalemia, hypoglycemia, iron deficiency anemia, hyperglycemia, gout, hypercholesteremia; *Rare:* electrolyte imbalance, cachexia, acidosis, hyperuricemia.

Musculoskeletal System – *Frequent:* twitching, myalgia, arthralgia; *Infrequent:* bone pain, tenosynovitis, myositis, bone sarcoma, arthritis; *Rare:* osteoporosis, muscle atrophy, osteomyelitis.

Nervous System – *Frequent:* dyskinesia, dizziness, hallucinations, confusion, somnolence, insomnia, dystonia, paresthesia, depression, anxiety, tremor, akinesia, extrapyramidal syndrome, abnormal gait, abnormal dreams, incoordination, psychosis, personality disorder, nervousness, choreoathetosis, amnesia, paranoid reaction, abnormal thinking; *Infrequent:* akathisia, neuropathy, neuralgia, hypertonia, delusions, convulsion, libido increased, euphoria, emotional lability, libido decreased, vertigo, myoclonus, coma, apathy, paralysis, neurosis, hyperkinesia, ataxia, acute brain syndrome, torticollis, meningitis, manic reaction, hypokinesia, hostility, agitation, hypotonia; *Rare:* stupor, neuritis, intracranial hypertension, hemiplegia, facial paralysis, brain edema, myelitis, hallucinations and confusion after abrupt discontinuation.

Respiratory System – *Frequent:* rhinitis, dyspnea, pneumonia, pharyngitis, cough increased; *Infrequent:* epistaxis, hiccup, sinusitis, bronchitis, voice alteration, hemoptysis, asthma, lung edema, pleural effusion, laryngitis, emphysema, apnea, hyperventilation; *Rare:* pneumothorax, lung fibrosis, larynx edema, hypoxia, hypoventilation, hemothorax, carcinoma of lung.

Skin and Appendages System – *Frequent:* sweating, rash; *Infrequent:* skin discoloration, pruritus, acne, skin ulcer, alopecia, dry skin, skin carcinoma, seborrhea, hirsutism, herpes simplex, eczema, fungal dermatitis, herpes zoster; *Rare:* vesiculobullous rash, subcutaneous nodule, skin nodule, skin benign neoplasm, lichenoid dermatitis.

Special Senses System – *Frequent:* abnormal vision, diplopia; *Infrequent:* otitis media, conjunctivitis, tinnitus, deafness, taste perversion, ear pain, eye pain, glaucoma, eye hemorrhage, photophobia, visual field defect; *Rare:* blindness, cataract, retinal detachment, retinal vascular disorder.

Urogenital System – *Frequent:* urinary tract infection, urinary frequency, urinary incontinence, hematuria, dysmenorrhea; *Infrequent:* dysuria, breast pain, menorrhagia, impotence, cystitis, urinary retention, abortion, vaginal hemorrhage, vaginitis, priapism, kidney calculus, fibrocystic breast, lactation, uterine hemorrhage, urolithiasis, salpingitis, pyuria, metrorrhagia, menopause, kidney failure, breast carcinoma, cervical carcinoma; *Rare:* amenorrhea, bladder carcinoma, breast engorgement, epididymitis, hypogonadism, leukorrhea, nephrosis, pyelonephritis, urethral pain, uricaciduria, withdrawal bleeding.

Postintroduction Reports - Voluntary reports of adverse events temporally associated with pergolide that have been received since market introduction and which may have no causal relationship with the drug, include the following: neuroleptic malignant syndrome.

OVERDOSAGE

There is no clinical experience with massive overdosage. The largest overdose involved a young hospitalized adult patient who was not being treated with pergolide mesylate but who intentionally took 60 mg of the drug. He experienced vomiting, hypotension, and agitation. Another patient receiving a daily dosage of 7 mg of pergolide mesylate unintentionally took 19 mg/day for 3 days, after which his vital signs were normal but he experienced severe hallucinations. Within 36 hours of resumption of the prescribed dosage level, the hallucinations stopped. One patient unintentionally took 14 mg/day for 23 days instead of her prescribed 1.4 mg/day dosage. She experienced severe involuntary movements and tingling in her arms and legs. Another patient who inadvertently received 7 mg instead of the prescribed 0.7 mg experienced palpitations, hypotension, and ventricular extrasystoles. The highest total daily dose (prescribed for several patients with refractory Parkinson's disease) has exceeded 30 mg.

Symptoms

Animal studies indicate that the manifestations of overdosage in man might include nausea, vomiting, convulsions, decreased blood pressure, and CNS stimulation. The oral median lethal doses in mice and rats were 54 and 15 mg/kg respectively.

Treatment

To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Management of overdosage may require supportive measures to maintain arterial blood pressure. Cardiac function should be monitored; an antiarrhythmic agent may be necessary. If signs of CNS stimulation are present, a phenothiazine or other butyrophenone neuroleptic agent may be indicated; the efficacy of such drugs in reversing the effects of overdose has not been assessed.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

There is no experience with dialysis or hemoperfusion, and these procedures are unlikely to be of benefit.

DOSAGE AND ADMINISTRATION

Administration of Pergolide Mesylate Tablets should be initiated with a daily dosage of 0.05 mg for the first 2 days. The dosage should then be gradually increased by 0.1 or 0.15 mg/day every third day over the next 12 days of therapy. The dosage may then be increased by 0.25 mg/day every third day until an optimal therapeutic dosage is achieved.

Pergolide Mesylate Tablets are usually administered in divided doses 3 times per day. During dosage titration, the dosage of concurrent *l*-dopa/carbidopa may be cautiously decreased.

In clinical studies, the mean therapeutic daily dosage of Pergolide Mesylate Tablets was 3 mg/day. The average concurrent daily dosage of *l*-dopa/carbidopa (expressed as *l*-dopa) was approximately 650 mg/day. The efficacy of Pergolide Mesylate Tablets at doses above 5 mg/day has not been systematically evaluated.

HOW SUPPLIED

Pergolide Mesylate Tablets, equivalent to 0.05 mg pergolide, are available as ivory, capsule shaped tablets, scored on one side and debossed with "9" on the left side of the score and "3" on the right side of the score. The other side is debossed with "7160". They are available in bottles of 100.

Pergolide Mesylate Tablets, equivalent to 0.25 mg pergolide, are available as mottled green, capsule shaped tablets, scored on one side and debossed with "9" on the left side of the score and "3" on the right side of the score. The other side is debossed with "7159". They are available in bottles of 100.

Pergolide Mesylate Tablets, equivalent to 1 mg pergolide, are available as mottled pink, capsule shaped tablets, scored on one side and debossed with "9" on the left side of the score and "3" on the right side of the score. The other side is debossed with "7161". They are available in bottles of 100.

Storage Conditions

Store at controlled room temperature, between 15° to 30°C (59° to 86°F) [see USP].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 7/2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-061

CHEMISTRY REVIEW(S)

MINOR AMENDMENT

ANDA 76-061

JAN 16 2002

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

TEL: 215-591-3000

ATTN: Philip Erickson, R.Ph.

FAX 215-591-8812

FROM: Kassandra Sherrod

PROJECT MANAGER: 301-827-5849

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 (1 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 deficiency

JAN 16 200

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,

/s/

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:

Submission date	Submission type
12/21/2000	Original
01/18/2001	Acknowledgement Letter
02/15/2001	Labeling Review

10. PHARMACOLOGICAL CATEGORY
Dopamine receptor agonist

11. Rx or OTC
Rx

12. RELATED DMFs:

DMF —	DMF —	DMF —
DMF —	DMF —	DMF —
DMF —	DMF —	DMF —

13. DOSAGE FORM
Tablet; Oral

14. POTENCIES
0.05, 0.25, and 1 mg

15. CHEMICAL NAME
8β-[(Metylthio)methyl]-6-propylergoline monomethanesulfonate
Molecular weight: ~~~
Chemical Formula: $C_{19}H_{26}N_2S \bullet CH_4O_3S$

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:

Submission date	Submission type
12/21/2000	Original
01/18/2001	Acknowledgement Letter
02/15/2001	Labeling Review
04/18/2001	Bio Review
05/25/2001	Chem Review #1
08/22/2001	Amendment

10. PHARMACOLOGICAL CATEGORY
Dopamine receptor agonist

11. Rx or OTC
Rx

12. RELATED DMFs:
DMF [redacted] DMF [redacted] DMF [redacted]

DMF —— DMF —— DMF ——
DMF —— DMF —— DMF ——

13. DOSAGE FORM
Tablet; Oral

14. POTENCIES
0.05, 0.25, and 1 mg

15. CHEMICAL NAME
8β-[(Metylthio)methyl]-6-propylergoline monomethanesulfonate
Molecular weight: ——
Chemical Formula: $C_{19}H_{26}N_2S \bullet CH_4O_3S$

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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ON ORIGINAL

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MINOR AMENDMENT

OCT 17 2001

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 TEL: 215-591-3000

ATTN: Philip Erickson, R.Ph. FAX: 215-591-8812

FROM: Kassandra Sherrod PROJECT MANAGER: 301-827-5849

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 (1 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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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
N/A

7. NONPROPRIETARY NAME
Pergolide Mesylate

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

9. AMENDMENTS AND OTHER DATES:

Submission date	Submission type
12/21/2000	Original
01/18/2001	Acknowledgement Letter
02/15/2001	Labeling Review
04/18/2001	Bio Review
05/25/2001	Chem Review #1
08/22/2001	Amendment
11/30/2001	Amendment

10. PHARMACOLOGICAL CATEGORY
Dopamine receptor agonist

11. Rx or OTC
℞

12. RELATED DMFs:

DMF	DMF	DMF
DMF	DMF	DMF
DMF	DMF	DMF

13. DOSAGE FORM
Tablet; Oral

14. POTENCIES
0.05, 0.25, and 1 mg

15. CHEMICAL NAME
8β-[(Metylthio)methyl]-6-propylergoline monomethanesulfonate
Molecular weight:
Chemical Formula: $C_{19}H_{26}N_2S \bullet CH_4O_3S$

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:
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 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:

Submission date	Submission type
12/21/2000	Original
01/18/2001	Acknowledgement Letter
02/15/2001	Labeling Review
04/18/2001	Bio Review
05/25/2001	Chem Review #1
08/22/2001	Amendment
11/30/2001	Amendment

01/28/2002 amendment DMF

10. PHARMACOLOGICAL CATEGORY
Dopamine receptor agonist

11. Rx or OTC
Rx

12. RELATED DMFs:

DMF [redacted] DMF [redacted] DMF [redacted]
DMF [redacted] DMF [redacted] DMF [redacted]
DMF [redacted] DMF [redacted] DMF [redacted]

13. DOSAGE FORM
Tablet; Oral

14. POTENCIES
0.05, 0.25, and 1 mg

15. CHEMICAL NAME
8β-[(Metylthio)methyl]-6-propylergoline monomethanesulfonate
Molecular weight: [redacted]
Chemical Formula: $C_{19}H_{26}N_2S \bullet CH_4O_3S$

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:
02/03/02

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MINOR AMENDMENT

ANDA 76-061

FEB 26 2002

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 TEL: 215-591-3000

ATTN: Philip Erickson, R.Ph. FAX: 215-591-8812

FROM: Kassandra Sherrod PROJECT MANAGER: 301-827-5849

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 (1 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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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:

Submission date	Submission type
12/21/2000	Original
01/18/2001	Acknowledgement Letter
02/15/2001	Labeling Review
04/18/2001	Bio Review
05/25/2001	Chem Review #1
08/22/2001	Amendment
01/28/2002	Amendment
11/30/2001	Amendment
02/01/2002	Tel Amendment
03/14/2002	Amendment

5/17/2002 Tel Amendment BT

10. PHARMACOLOGICAL CATEGORY
Dopamine receptor agonist

11. Rx or OTC
Rx

12. RELATED DMFs:

DMF [redacted]	DMF [redacted]	DMF [redacted]
DMF [redacted]	DMF [redacted]	DMF [redacted]
DMF [redacted]	DMF [redacted]	DMF [redacted]

13. DOSAGE FORM
Tablet; Oral

14. POTENCIES
0.05, 0.25, and 1 mg

15. CHEMICAL NAME
8β-[(Metylthio)methyl]-6-propylergoline monomethanesulfonate
Molecular weight: [redacted]
Chemical Formula: $C_{19}H_{26}N_2S \bullet CH_4O_3S$

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

17. COMMENTS
See review

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable
(BT)

19. REVIEWER:
Damaris Maldonado

DATE COMPLETED:
03/28/02

APPEARS THIS WAY
ON ORIGINAL

Redacted 20

pages of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

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
V:\firmsnz\teva\ltrs&rev\76061sta.501

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:

[redacted]

Firm's response #1:

[redacted]

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

Pergolide Mesylate Tablets, 0.05 mg Test Lot # K-26417				Permax® Tablets, 0.05 mg Reference Lot #: 3MN75M		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
10	91	[redacted]	5.4	96	[redacted]	3.1
20	94	[redacted]	3.1	99	[redacted]	1.5
30	96	[redacted]	2.8	99	[redacted]	1.8

Pergolide Mesylate Tablets, 0.25 mg Test Lot # K-26483				Permax® Tablets, 0.25 mg Reference Lot #: 2MX08M		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
10	95	[redacted]	3.9	94	[redacted]	5.1
20	97	[redacted]	2.3	98	[redacted]	1.2
30	97	[redacted]	1.5	97	[redacted]	1.4

Pergolide Mesylate Tablets, 1 mg Test Lot # K-26484				Permax® Tablets, 1 mg Reference Lot #: 2MT07M		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
10	91	[redacted]	3.7	96	[redacted]	2.6
20	93	[redacted]	3.4	100	[redacted]	1.5
30	94	[redacted]	2.7	101	[redacted]	1.7

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 [redacted] (Q) of the labeled amount of pergolide in 30 minutes.

DBE comment #5:

[redacted]

Firm's response #5:

[redacted]

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 Permax[R] 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. [ ]

   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.

/S/

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

/S/ 5/30/01

/S/

RD INITIALLED BY BDAVIT
FT INITIALLED BY BDAVIT

Date: 5/31/01

Concur: /S/

Date: 6/19/2001

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

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 bioequivalency 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\ltrs&rev\76061sta.501

Endorsements: (Final with Dates)
HFD-658/ Reviewer C. Kim /S/ 5/31/01 /S/ 5/31/01
HFD-658/ Bio team Leader B. Davit
HFD-658/ Reviewer N. Tran
HFD-650/ S. Mazzella
HFD-650/ D. Conner for 6/26/2001

BIOEQUIVALENCY - Acceptable

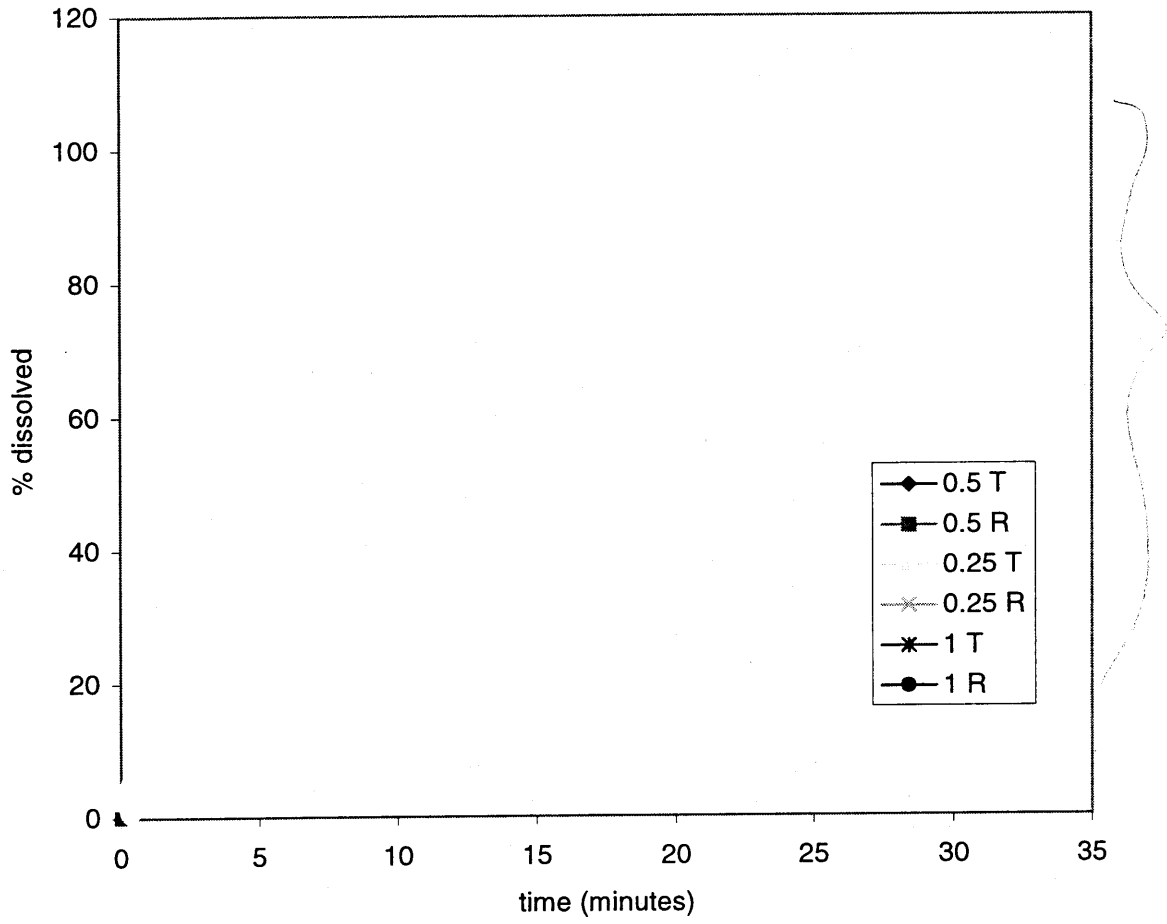
Submission date: 5/11/01

OK **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



Attachment

-----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; Arnwine, 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[R] Tablets, 0.05 mg. The waivers for 0.25 mg and 1 mg strengths are granted.

Formulation is acceptable.

DISSOLUTION : acceptable

DSI INSPECTION STATUS

Inspection needed. YES / (NO)	Inspection status:	Inspection results:
First Generic ____ New facility ____ For cause ____ other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Carol Y. Kim BRANCH : 3

INITIAL : /S/ DATE : 5/31/01

TEAM LEADER : Barbara M. Davit BRANCH : 3

INITIAL : /S/ DATE : 5/31/01

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

INITIAL : /S/ DATE : 6/22/2001

6-19
3S

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)

APR 18 '01

TO: APPLICANT: TEVA Pharmaceuticals USA

TEL: 215-591-3000

ATTN: Phillip Erickson

FAX: 215-591-8812

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:

APR 18

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.

5. [ ]

Sincerely yours,

/S/

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

Pergolide Mesylate Tablets
0.05, 0.25 and 1 mg
ANDA 76-061
Reviewer: Carol Y. Kim
V:\firmsnz\teva\ltrs&rev\76061stf.D00

Teva Pharmaceuticals, USA
Sellersville, PA
Submission Date: 12/21/00

Review of a Bioequivalence Study and Dissolution Data

I. Introduction

First Generic: Yes

Indication: For adjunct treatment with levodopa/carbiodpa 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^{R} (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 prochloroperazine
   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] labeling 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:	[redacted]
Principal Investigator:	[redacted]
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:	[redacted]
Analytical Director:	[redacted]
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:	[redacted]	-
Full Batch Size:	[redacted]	-
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 4 hours post-dosing	Overnight pre-dosing 4 hours post-dosing

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

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Washout Period:**	28 days
No. of Treatments:	2	**Center**	single

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	74
Route of Administration:	oral	**No. of Subjects Completing:**	49
		No. of Subjects Plasma Analyzed:	48
		No. of Dropouts:	1
		Sex(es) Included:	Males
		Age:	18-55 years
		Healthy Volunteers Only:	Y
		No. of Adverse Events:	306

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.

	Group 1	Group 2
Subject no*.	#1-48 (except #38)	#50-76
Dosing dates	8/12/00 and 9/9/00	10/21/00 and 11/18/00

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

	Subjects (total= 48)
Samples analyzed in the final report	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

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:

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

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=Permax^{R} Tablets, 0.05 mg, Dose Administered=2 tablets (2 X 0.05 mg), fasting

Time (hours)	Test	%CV	Reference	%CV	Ratio (T/R)*
0	0	-	0.0	-	-
0.5	4.75	102.61	4.94	91.98	0.96
1	13.80	59.73	16.33	82.58	0.85
1.33	18.00	56.95	20.52	74.36	0.88
1.67	21.77	53.44	22.98	64.85	0.95
2	24.30	49.86	25.83	50.66	0.94
2.5	24.69	45.43	27.11	45.17	0.91
3	27.53	49.14	28.03	40.58	0.98
4	28.05	47.60	29.41	42.48	0.95
5	25.92	44.54	26.50	40.99	0.98
6	24.71	51.23	25.23	42.43	0.98
8	20.56	52.17	20.75	45.77	0.99
12	12.00	55.60	12.19	49.58	0.98
24	4.42	82.85	4.81	67.88	0.92
36	1.07	166.15	1.05	181.07	1.02

*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

Parameter*	Test Mean	Test %CV	Ref Mean	Ref %CV	T/R Ratio
AUCT	356.11	57.04	368.90	47.77	0.97
AUCI	405.67	51.00	425.06	43.30	0.95
CMAX	30.87	45.11	33.41	47.77	0.92
TMAX	3.78	36.25	3.87	37.70	0.98
KEL	0.10	36.65	0.10	34.82	1.00
THALF	7.60	29.97	7.97	29.58	0.95

*AUCT=pg*hr/ml, AUCI=pg*hr/ml, TMAX=hr, CMAX=pg/ml

Table 3
Geometric Mean ratios and 90% confidence intervals for pergolide

	Geometric Means		Geometric Mean	90%CI	
Parameter*	Test	Reference	Ratio (T/R)	Lower 90% CI	Upper 90% CI
LAUC0-inf	352.95	382.51	0.92	87.95	98.46
LAUC0-t	285.80	315.15	0.91	84.54	99.15
LCmax	27.37	29.74	0.92	84.29	101.19

*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) AUC_T/AUC_I 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 ln-transformed AUCT, 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 ln-transformed AUCT and Cmax

Pergolide	fasting	
	ln AUCT	ln CMAX
MSE, Test & Reference	0.2274781	0.2682702

V. Dissolution (Not to be released under FOI)

Specification	NLT % — Q) of labeled amount of pergolide in 30 minutes
Reference Products	Permax® Tablets, 0.05, 0.25, and 1 mg

Results of In Vitro Dissolution Profile Summary for Pergolide Mesylate Tablets

Pergolide Mesylate Tablets, 0.05 mg Test Lot # K-26417				Permax® Tablets, 0.05 mg Reference Lot #: 3MN75M Exp: 7/19/00		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
10	95		2.4	96		3.7
20	97		1.3	101		2.3
30	97		0.8	101		1.8

Pergolide Mesylate Tablets, 0.25 mg Test Lot # K-26483				Permax® Tablets, 0.25 mg Reference Lot #: 2MX08M Exp: 11/01		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
10	93		2.7	91		5.2
20	96		1.7	98		1.5
30	97		1.3	98		1.6

Pergolide Mesylate Tablets, 1 mg Test Lot # K-26484				Permax® Tablets, 1 mg Reference Lot #: 2MT07M Exp: 11/01		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
10	91		3.4	94		5.1
20	94		1.8	99		2.2
30	95		1.6	98		2.4

Dissolution testing site: not reported

Comments

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

	Each tablet (mg)			Each tablet (%)		
Ingredients	0.05 mg strength	0.25 mg strength	1 mg strength	0.05 mg strength	0.25 mg strength	1 mg strength
Pergolide Mesylate	0.065*	0.325**	1.300***	0.03	0.14	0.54
Lactose Monohydrate NF (						
Lactose Monohydrate NF (						
Pregelatinized Starch NF						
Sodium Starch Glycolate NF						
Microcrystalline Cellulose NF						
Magnesium Stearate NF						
Color FD&C Blue No. 2 Aluminium						
Color Ferric Oxide NF Yellow						
or Ferric Oxide NF Red						
otal						

*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

Product	Assay %	Content Uniformity % (RSD%)
Test, Pergolide Mesylate Tablets 0.05 mg Lot # K-26417		96.6 (0.6)
Reference, Permax® Tablets, 0.05 mg Lot # 3MN75M		100.0 (1.2)
Test, Pergolide Mesylate Tablets 0.25 mg Lot # K-26483		95.7 (0.9)
Reference, Permax® Tablets, 0.25 mg Lot # 2MX08M		99.3 (1.3)
Test, Pergolide Mesylate Tablets 1 mg Lot # K-26484		98.0 (1.1)
Reference, Permax® Tablets, 1 mg Lot # 2MT07M		100.8 (2.7)

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.

5. [redacted]

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 Permax^{R} 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.

/S/

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

3/20/01
3/21/01

/S/

RD INITIALLED BY BDAVIT
FT INITIALLED BY BDAVIT

/S/

Date: 3/22/01

Concur: /S/

Date: 4/3/2001

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

CC: ANDA #76061
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer C. Kim
HFD-658/ Bio team leader B. Davit

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Endorsements: (Final with Dates)
HFD-658/ Reviewer C. Kim 3/21/01
HFD-658/ Bio team Leader B. Davit 3/22/01
HFD-617/ Project Manager
HFD-650/ D. Conner for 4/3/2001

BIOEQUIVALENCY - Incomplete Submission date: 12/21/00

OK **1. Fasting Study (STF)** **Strength: 0.05 mg**
Clinical: ———— **Outcome: IC**
Analytical: ————

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

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

Outcome Decisions: IC - incomplete

Fig. 1: Dissolution Comparision for ANDA#76061 Pergolide Mesylate Tablet

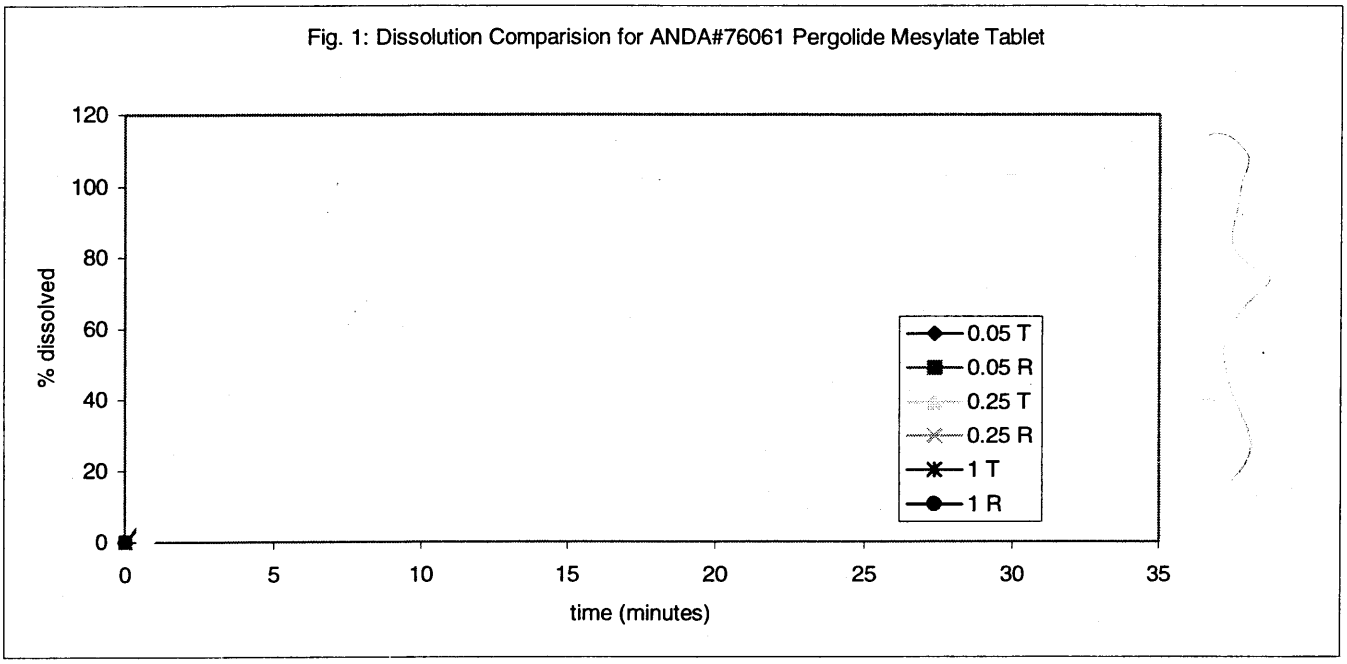
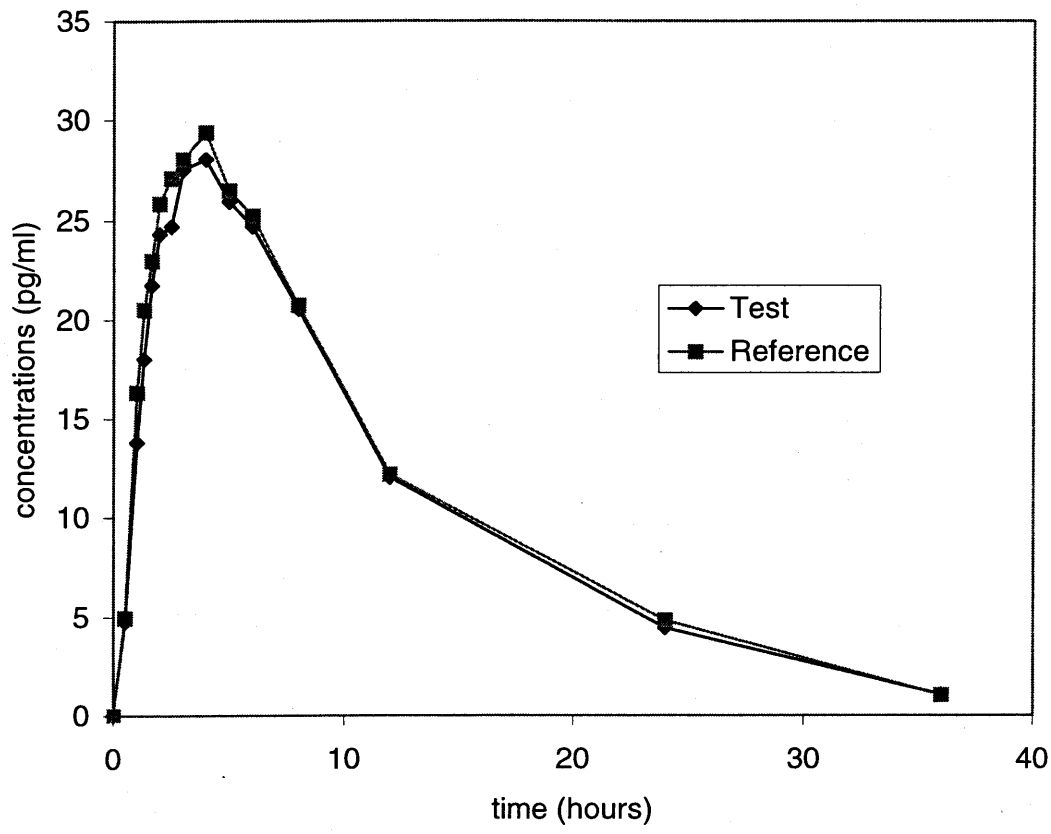


Fig 2: Mean plasma concentrations of Pergolide Mesylate, ANDA # 76061, under fasting conditions



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.

Subject No.	Trt	Pd	Description	Onset time	Severity	Relationship to study drug	Resolution
1	A	1	nausea	1 h 13 min	mild	possibly	with treatment
1	***A***	***1***	***vomiting***	***1 h 16 min***	***moderate***	***possibly***	***with treatment***
1	A	1	dizziness	5 h 49 min	moderate	possibly	spontaneous
1	A	1	hot flushes	7 h 50 min	moderate	possibly	spontaneous
2	A	1	drowsiness	21 min	mild	probably	spontaneous
2	B	1	drowsiness	38 min	mild	probably	spontaneous
2	B	2	nausea	43 min	mild	possibly	with treatment
2	B	2	headache	1 h 28 min	mild	possibly	spontaneous
2	B	2	dizziness	1 h 31 min	moderate	possibly	spontaneous
3	B	1	drowsiness	51 min	mild	possibly	spontaneous
3	B	1	headache	1 h 41 min	mild	possibly	spontaneous
3	B	1	difficult bowel movement	2 h 20 min	mild	possibly	spontaneous
3	B	1	heartburn	3 h 52 min	mild	probably	spontaneous
3	A	2	abdominal pain	1 h 56 min	mild	probably	spontaneous
4	B	2	drowsiness	54 min	mild	possibly	spontaneous
4	B	2	hot flushes	1 h 9 min	mild	possibly	spontaneous
5	B	1	nausea	22 min	mild	possibly	spontaneous
5	B	1	dizziness	27 min	mild	possibly	spontaneous
5	B	1	stuffy nose	40 min	mild	possibly	spontaneous
5	B	1	heartburn	50 min	mild	possibly	spontaneous
5	***B***	***1***	***vomiting***	***51 min***	***moderate***	***possibly***	***with treatment***
5	B	1	cold sweat	51 min	moderate	possibly	spontaneous
5	B	1	feels cold	1 h 10 min	mild	possibly	spontaneous
5	B	1	tremors	1 h 12 min	mild	possibly	spontaneous
5	B	1	weakness	1 h 12 min	moderate	possibly	spontaneous
6	B	1	pain in left thigh	30 min	mild	possibly	spontaneous
6	***B***	***1***	***vomiting***	***48 min***	***moderate***	***possibly***	***with treatment***
6	B	1	nausea	48 min	mild	possibly	with treatment
7	A	1	hot flushes	32 min	mild	possibly	spontaneous
7	***A***	***1***	***vomiting***	***1 h 13 min***	***moderate***	***possibly***	***with treatment***
8	B	1	blurred vision	45 min	moderate	probably	spontaneous
8	B	1	weakness	48 min	moderate	possibly	spontaneous
8	A	2	nausea	50 min	mild	possibly	with treatment
8	A	2	dizziness	50 min	mild	possibly	spontaneous
8	A	2	blurred vision	1 h 15 min	mild	probably	spontaneous
8	A	2	nausea	1 h 15 min	mild	possibly	with treatment
8	A	2	feels sleepy	1 h 28 min	mild	possibly	spontaneous
8	A	2	blurred vision	1 h 44 min	moderate	probably	spontaneous
8	A	2	blurred vision	5 h 46 min	mild	probably	spontaneous
9	***B***	***1***	***vomiting***	***1 h 6 min***	***moderate***	***possibly***	***with treatment***
10	B	2	dizziness	57 min	mild	possibly	spontaneous
10	B	2	headache	1 h 2 min	mild	possibly	spontaneous
12	B	1	drowsiness	33 min	mild	probably	spontaneous
12	B	1	cold sweat	36 min	mild	probably	spontaneous
12	B	2	cold sweat	1 h 4 min	mild	probably	spontaneous
12	B	2	drowsiness	1 h 8 min	mild	probably	spontaneous
12	B	2	stuffy nose	1 h 18 min	mild	possibly	spontaneous
13	A	1	nausea	36 min	mild	probably	with treatment
13	A	1	shivers	37 min	mild	possibly	spontaneous
13	A	1	weakness	1 h 21 min	mild	possibly	spontaneous
13	B	2	dizziness	48 min	mild	possibly	spontaneous
13	B	2	shaking	56 min	mild	possibly	spontaneous
13	B	2	nausea	1 h 26 min	mild	probably	with treatment
13	B	2	headache	1 h 41 min	mild	possibly	spontaneous
14	B	2	stuffy nose	1 h 34 min	mild	possibly	spontaneous

Subject No.	Trt	Pd	Description	Onset time	Severity	Relationship to study drug	Resolution
14	B	2	fatigue	1 h 49 min	mild	possibly	Spontaneous
15	B	1	dizziness	54 min	moderate	possibly	spontaneous
15	B	1	nausea	54 min	moderate	possibly	with treatment
15	B	1	weakness	1 h 6 min	moderate	possibly	spontaneous
15	***B***	***1***	***vomiting***	***1 h 37 min***	***moderate***	***possibly***	***with treatment***
15	B	1	vomiting	2 h 58 min	moderate	possibly	with treatment
15	B	1	vomiting	5 h 2 min	moderate	possibly	with treatment
16	B	1	nausea	26 min	mild	possibly	with treatment
16	***B***	***1***	***vomiting***	***30 min***	***moderate***	***possibly***	***with treatment***
16	B	1	vomiting	1 h 16 min	moderate	possibly	with treatment
16	B	1	vomiting	1 h 50 min	moderate	possibly	with treatment
17	B	1	dizziness	52 min	moderate	probably	spontaneous
17	B	1	dizziness	1 h 11 min	moderate	probably	spontaneous
17	B	1	dizziness	2 h 36 min	severe	probably	spontaneous
17	A	2	dizziness	1 h 1 min	mild	probably	spontaneous
17	A	2	dizziness	1 h 47 min	mild	probably	spontaneous
18	A	1	shivers	59 min	mild	possibly	spontaneous
18	A	1	nausea	1 h 4 min	mild	possibly	with treatment
18	***A***	***1***	***vomiting***	***2 h 18 min***	***moderate***	***possibly***	***with treatment***
18	A	1	sore throat	2 h 18 min	mild	possibly	spontaneous
19	A	1	nausea	59 min	moderate	possibly	with treatment
19	A	1	nausea	7 h 50 min	moderate	possibly	with treatment
19	A	1	hot flushes	7 h 50 min	moderate	possibly	spontaneous
19	B	2	drowsiness	24 min	mild	possibly	spontaneous
19	B	2	dizziness	7 h 49 min	mild	possibly	spontaneous
20	B	2	drowsiness	1 h 37 min	mild	possibly	spontaneous
21	A	1	nausea	1 h 12 min	moderate	possibly	with treatment
23	B	1	dizziness	48 min	mild	probably	spontaneous
23	B	1	hot flushes	48 min	mild	possibly	spontaneous
23	A	2	dizziness	1 h 2 min	moderate	probably	spontaneous
24	B	2	hot flushes	54 min	mild	possibly	spontaneous
24	B	2	nausea	54 min	moderate	possibly	with treatment
24	B	2	dizziness	54 min	moderate	possibly	spontaneous
25	B	1	nausea	1 h 4 min	mild	possibly	with treatment
25	B	1	blurred vision	1 h 4 min	mild	possibly	spontaneous
25	B	1	headache	4 h 2 min	mild	possibly	spontaneous
25	B	1	difficulty sleeping	1 day 15 hours 12 min	mild	possibly	spontaneous
27	B	1	weakness	51 min	moderate	probably	spontaneous
27	B	1	dizziness	2 h 36 min	moderate	possibly	spontaneous
27	B	1	dizziness	4 h	moderate	possibly	spontaneous
27	B	1	nausea	4 h 34 min	moderate	possibly	with treatment
27	***B***	***1***	***vomiting***	***4 h 34 min***	***moderate***	***possibly***	***with treatment***
27	B	1	headache	6 h 8 min	mild	possibly	spontaneous
27	A	2	hot flushes	38 min	mild	possibly	spontaneous
27	A	2	blurred vision	49 min	mild	possibly	spontaneous
27	A	2	weakness	2 h 16 min	moderate	probably	spontaneous
28	A	2	drowsiness	1 h 6 min	mild	possibly	spontaneous
30	A	1	nausea	1 h 1 min	moderate	possibly	with treatment
31	B	1	abdominal pain	20 min	mild	possibly	spontaneous
31	B	1	dizziness	35 min	mild	possibly	spontaneous
31	B	1	headache	5 h	mild	possibly	with treatment
32	A	1	blurred vision	39 min	moderate	possibly	spontaneous
32	A	1	abdominal pain	39 min	moderate	possibly	spontaneous
32	A	1	dizziness	39 min	moderate	possibly	spontaneous
32	A	1	hot flushes	40 min	moderate	possibly	spontaneous
32	A	1	dizziness	1 h 4 min	mild	possibly	spontaneous
33	B	1	nausea	18 min	moderate	possibly	with treatment
33	B	1	dizziness	24 min	moderate	possibly	spontaneous
33	B	1	stomachache	30 min	mild	possibly	spontaneous
33	B	1	feels sleepy	31 min	mild	possibly	spontaneous
33	***B***	***1***	***vomiting***	***58 min***	***moderate***	***possibly***	***with treatment***
33	B	1	headache	5 h 8 min	mild	possibly	with treatment

Subject No.	Trt	Pd	Description	Onset time	Severity	Relationship to study drug	Resolution
34	B	1	dizziness	52 min	moderate	probably	spontaneous
34	B	1	nausea	54 min	moderate	probably	with treatment
34	B	1	heartburn	1 h 54 min	mild	probably	spontaneous
34	A	2	heartburn	44 min	mild	probably	spontaneous
34	A	2	dizziness	1 h	mild	probably	spontaneous
34	A	2	dizziness	1 h 21 min	mild	probably	spontaneous
34	A	2	nausea	1 h 59 min	mild	probably	with treatment
34	A	2	dizziness	1 h 59 min	moderate	probably	spontaneous
35	A	1	dizziness	1 h 3 min	mild	probably	spontaneous
35	B	2	dizziness	38 min	mild	probably	spontaneous
35	B	2	dizziness	55 min	moderate	probably	spontaneous
35	B	2	heartburn	56 min	mild	possibly	spontaneous
35	B	2	nausea	1 h 38 min	mild	possibly	with treatment
36	B	1	hot flushes	30 min	mild	possibly	spontaneous
36	B	1	nausea	35 min	moderate	possibly	with treatment
36	B	1	headache	45 min	mild	possibly	spontaneous
36	B	1	vom	3 h 1 min	moderate	possibly	with treatment
36	B	1	headache	3 h 45 min	mild	possibly	spontaneous
37	A	1	nausea	53 min	moderate	possibly	with treatment
37	***A***	***1***	***vomiting***	***54 min***	***moderate***	***possibly***	***with treatment***
37	A	1	stuffy nose	3 h 48 min	mild	possibly	spontaneous
39	A	1	muscular pain (ab area)	6 h 14 min	mild	possibly	spontaneous
39	B	2	nausea	1 h 22 min	mild	possibly	with treatment
40	A	1	nausea	33 min	mild	possibly	with treatment
40	A	1	hot flushes	33 min	mild	probably	spontaneous
40	B	2	dizziness	32 min	mild	possibly	spontaneous
40	B	2	hot flushes	41 min	mild	probably	spontaneous
41	A	1	hot flushes	1 h 5 min	mild	probably	spontaneous
41	B	2	nausea	1 h 21 min	moderate	possibly	with treatment
41	B	2	hot flushes	1 h 21 min	moderate	probably	spontaneous
42	A	1	dizziness	36 min	moderate	possibly	spontaneous
42	A	1	hot flushes	36 min	moderate	possibly	spontaneous
42	A	1	nausea	37 min	mild	possibly	with treatment
43	B	1	dizziness	36 min	mild	probably	spontaneous
43	A	2	dizziness	44 min	mild	probably	spontaneous
44	B	1	nausea	34 min	mild	possibly	with treatment
44	B	1	hot flushes	34 min	mild	possibly	spontaneous
45	B	2	stuffy nose	47 min	mild	possibly	spontaneous
47	A	1	nausea	26 min	mild	probably	with treatment
47	A	1	shaking in right leg	33 min	mild	possibly	spontaneous
47	A	1	shaking in left leg	33 min	mild	possibly	spontaneous
47	A	1	numbness, left hand	33 min	mild	possibly	spontaneous
47	A	1	cold sweat	33 min	moderate	possibly	spontaneous
47	A	1	numbness, right hand	33 min	mild	possibly	spontaneous
47	A	1	dizziness	1 h 43 min	moderate	probably	spontaneous
47	A	1	nose bleed	22 h 13 min	mild	possibly	spontaneous
47	B	2	dizziness	31 min	mild	probably	spontaneous
47	B	2	headache	56 min	mild	possibly	spontaneous
47	B	2	nausea	1 h	moderate	probably	with treatment
47	B	2	weakness	2 h 1 min	mild	possibly	spontaneous
47	B	2	nausea	2 h 3 min	mild	probably	with treatment
47	B	2	dizziness	4 h 19 min	moderate	possibly	spontaneous
48	B	1	blurred vision	49 min	moderate	possibly	spontaneous
48	B	1	nausea	50 min	mild	possibly	with treatment
48	***B***	***1***	***vomiting***	***55 min***	***moderate***	***possibly***	***with treatment***
48	B	1	stomachache	57 min	mild	possibly	spontaneous
50	B	1	nausea	28 min	moderate	possibly	with treatment
50	B	1	dizziness	28 min	moderate	possibly	spontaneous
50	B	1	fainting	29 min	severe	possibly	spontaneous
50	B	1	low blood pressure (82/48)	1 h 50 min	N/ap	possibly	spontaneous
50	B	1	feels tired	1 h 38 min	mild	possibly	spontaneous
50	B	1	dizziness	3 h 54 min	not recorded	possibly	spontaneous

Subject No.	Trt	Pd	Description	Onset time	Severity	Relationship to study drug	Resolution
50	A	2	hot flushes	30 min	mild	possibly	spontaneous
51	A	1	nausea	39 min	mild	possibly	with treatment
52	B	2	hot flushes	1 h 21 min	mild	possibly	spontaneous
52	B	2	high level of ALT (64 U/L)	1 d 12 h	N/ap	possibly	spontaneous
53	A	1	nausea	24 min	mild	possibly	with treatment
53	A	1	loose stools	27 min	moderate	possibly	spontaneous
53	A	1	nausea	37 min	moderate	possibly	with treatment
53	***A***	***1***	***vomiting***	***39 min***	***moderate***	***possibly***	***with treatment***
53	A	1	nausea	52 min	mild	possibly	with treatment
53	A	1	vomiting	1 h 13 min	moderate	possibly	with treatment
53	A	1	vomiting	2 h 24 min	severe	possibly	with treatment
54	A	1	hot flushes	17 min	mild	probably	spontaneous
54	A	1	nausea	17 min	moderate	probably	with treatment
54	B	2	hot flushes	52 min	mild	probably	spontaneous
54	B	2	feels nauseous	54 min	mild	probably	with treatment
55	B	1	dizziness	23 min	mild	possibly	spontaneous
55	B	1	fainting	36 min	severe	possibly	spontaneous
55	***B***	***1***	***vomiting***	***40 min***	***moderate***	***possibly***	***with treatment***
55	B	1	vomiting	58 min	moderate	possibly	with treatment
55	B	1	vomiting	1 h 4 min	severe	possibly	with treatment
55	B	1	vomiting	1 h 39 min	moderate	possibly	with treatment
55	B	1	vomiting	3 h 15 min	moderate	possibly	with treatment
55	B	1	nausea	7 h 40 min	mild	possibly	with treatment
55	B	1	vomiting	10 h 55 min	moderate	possibly	with treatment
56	B	1	dizziness	30 min	mild	probably	spontaneous
56	B	1	tachycardia (112 bpm)	5 h 51 min	N/ap	possibly	spontaneous
56	A	2	dizziness	1 h 5 min	mild	probably	spontaneous
57	A	1	nausea	26 in	mild	probably	with treatment
57	A	1	dizziness	26 min	mild	possibly	spontaneous
57	A	1	numbness, right and left forearm	37 min	mild	probably	spontaneous
57	B	2	headache	49 min	mild	possibly	spontaneous
57	B	2	nausea	49 min	moderate	probably	with treatment
57	B	2	numbness, right forearm	52 min	mild	probably	spontaneous
57	B	2	numbness, left forearm	52 min	mild	probably	spontaneous
57	B	2	numbness, abdomen	1 h 3 min	mild	probably	spontaneous
57	B	2	numbness, right leg	1 h 6 min	mild	probably	spontaneous
57	B	2	numbness, left leg	1 h 6 min	mild	probably	spontaneous
57	B	2	dry mouth	1 h 6 min	mild	possibly	spontaneous
57	B	2	drowsiness	1 h 16 min	mild	possibly	spontaneous
58	B	1	dizziness	45 min	moderate	possibly	spontaneous
58	B	1	dry mouth	46 min	mild	possibly	spontaneous
58	A	2	fatigue	44 min	mild	possibly	spontaneous
59	B	1	nausea	28 min	mild	possibly	with treatment
59	B	1	feels cold	28 min	mild	possibly	spontaneous
59	B	1	nausea	55 min	mild	possibly	with treatment
59	B	1	dizziness	55 min	moderate	possibly	spontaneous
59	B	1	shaking	58 min	mild	possibly	spontaneous
60	B	1	weakness	58 min	moderate	possibly	spontaneous
60	B	1	dizziness	58 min	moderate	possibly	spontaneous
60	B	1	Shaking, both legs	1 h 20 min	mild	possibly	spontaneous
60	A	2	headache	13 h 55 min	mild	possibly	with treatment
61	A	1	weakness	31 min	moderate	possibly	spontaneous
61	A	1	blurred vision	31 min	moderate	possibly	spontaneous
61	A	1	fainting	32 min	severe	possibly	spontaneous
62	B	1	dizziness	49 min	moderate	possibly	spontaneous
62	B	1	hot flushes	49 min	moderate	probably	spontaneous
62	B	1	numbness, left arm	49 min	mild	probably	spontaneous
62	B	1	numbness, right arm	49 min	mild	probably	spontaneous
62	A	2	numbness, right leg	1 h 1 min	mild	probably	spontaneous
62	A	2	numbness, left leg	1h 1 min	mild	probably	spontaneous
62	A	2	hot flushes	1h 1 min	mild	probably	spontaneous
62	A	2	hot flushes	1 h 13 min	mild	probably	spontaneous

Subject No.	Trt	Pd	Description	Onset time	Severity	Relationship to study drug	Resolution
62	A	2	nausea	1 h 13 min	moderate	possibly	with treatment
63	B	1	dizziness	26 min	mild	possibly	spontaneous
63	B	1	nausea	26 min	moderate	possibly	with treatment
63 B		***1***	***vomiting***	***52 min***	***moderate***	***possibly***	***with treatment***
64	A	1	dizziness	29 min	mild	possibly	spontaneous
64	A	1	hot flushes	29 min	mild	possibly	spontaneous
64	A	1	nausea	29 min	mild	possibly	with treatment
64 A		***1***	***vomiting***	***49 min***	***moderate***	***possibly***	***with treatment***
64	A	1	vomiting	1 h 2 min	moderate	possibly	with treatment
64	A	1	nausea	3 h 50 min	mild	possibly	with treatment
64	A	1	hot flushes	3 h 53 min	mild	possibly	spontaneous
64	A	1	headache	3 h 58 min	mild	possibly	spontaneous
65	A	1	dizziness	24 min	mild	possibly	spontaneous
65	A	1	hot flushes	24 min	mild	possibly	spontaneous
66	B	2	fatigue	1 h 18 min	mild	possibly	spontaneous
66	B	2	stuffy nose	1 h 18 min	mild	possibly	spontaneous
66	B	2	sore throat	1 h 41 min	mild	possibly	spontaneous
66	B	2	sore throat	2 h 5 min	mild	possibly	spontaneous
67	B	1	dizziness	32 min	moderate	possibly	spontaneous
67	B	1	coldness	40 min	moderate	possibly	spontaneous
67	B	1	nausea	43 min	moderate	possibly	with treatment
67	B	1	dizziness	1 h	moderate	possibly	spontaneous
67 B		***1***	***vomiting***	***1 h 16 min***	***moderate***	***possibly***	***with treatment***
67	B	1	stuffy nose	1 h 50 min	mild	possibly	spontaneous
67	B	1	weakness	2 h 33 min	mild	possibly	spontaneous
68	A	1	general numbness	27 min	mild	possibly	spontaneous
68	A	1	stuffy nose	1 h 44 min	mild	probably	spontaneous
68	B	2	hot flushes	33 min	mild	possibly	spontaneous
68	B	2	nausea	33 min	moderate	possibly	with treatment
68	B	2	dry mouth	36 min	mild	possibly	spontaneous
68	B	2	chills	54 min	mild	possibly	spontaneous
68	B	2	abdominal cramps	1 h 6 min	moderate	possibly	spontaneous
68	B	2	stuffy nose	1 h 34 min	mild	probably	spontaneous
68	B	2	dizziness	4 h 3 min	mild	possibly	spontaneous
70	B	1	dizziness	30 min	moderate	probably	spontaneous
70	B	1	coldness	1 h 42 min	moderate	possibly	spontaneous
70	B	1	dizziness	2h 32 min	mild	probably	spontaneous
70	A	2	dizziness	1 h 51 min	mild	probably	spontaneous
71	A	1	drowsiness	1 h 28 min	mild	possibly	spontaneous
71	A	1	hot flushes	1 h 42 min	moderate	possibly	spontaneous
72	B	1	feels like his heart rate increased	16 min	mild	possibly	spontaneous
72	B	1	hot flushes	1 h 5 min	mild	probably	spontaneous
72	B	1	dizziness	1 h 5 min	mild	possibly	spontaneous
72	B	1	drowsiness	1 h 26 min	mild	possibly	spontaneous
72	B	1	dizziness	3 h 1 min	mild	possibly	spontaneous
72	A	2	hot flushes	1 h 3 min	mild	probably	spontaneous
72	A	2	headache	3 h 31 min	mild	possibly	with treatment
73	B	1	fainting	1 h 2 min	severe	possibly	spontaneous
73 B		***1***	***vomiting***	***1 h 2 min***	***moderate***	***possibly***	***with treatment***
73	B	1	hot flushes	1 h 4 min	mild	possibly	spontaneous
73	B	1	stuffy nose	2 h 29 min	mild	possibly	spontaneous
73	B	1	dizziness	5 h 54 min	moderate	possibly	spontaneous
73	B	1	nausea	5 h 54 min	moderate	possibly	spontaneous
74	A	1	dizziness	1 h 7 min	moderate	possibly	spontaneous
74	A	1	headache	27 d 5 h 42 min	mild	possibly	spontaneous
74	B	2	nausea	not recorded	mild	possibly	with treatment
75	B	1	sensation of cold	12 min	mild	possibly	spontaneous
75	B	1	hot flushes	1 h 13 min	mild	possibly	spontaneous
75	B	1	stuffy nose	4 h 10 min	mild	probably	spontaneous
75	B	1	headache	9 d 3 h 10 min	mild	possibly	with treatment
75	A	2	nausea	41 min	moderate	possibly	with treatment
75	A	2	dizziness	55 min	mild	possibly	spontaneous

Subject No.	Trt	Pd	Description	Onset time	Severity	Relationship to study drug	Resolution
75	A	2	stuffy nose	1 h 40 min	mild	probably	spontaneous
76	A	1	nose bleeding	3 h 44 min	mild	possibly	spontaneous
76	B	2	dizziness	52 min	mild	possibly	spontaneous
76	B	2	hot flushes	52 min	mild	possibly	spontaneous

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-061

ADMINISTRATIVE DOCUMENTS

APPROVAL 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:

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, 59^0 to 86^0F (15^0 to 30^0C).
   - **ANDA:** Store at controlled room temperature, between 15^0 to 30^0C (59^0 to 86^0F).
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): CRC
8. **FINISHED DOSAGE FORM**
   - **NDA:** Scored Tablets
   - **ANDA:** Scored Tablets (see page 674, vol. B1.2)

Date of Review: September 13, 2001 /S/
Primary Reviewer: Koung Lee
Team Leader: Charlie Hoppes /S/

Date of Submission: Sept. 4 & Aug 22, 2001
Date: 9/18/01
Date: 9/18/01

cc: ANDA: 76-061
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\76061.AP.labeling Review

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.

/S/

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

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?	x		
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?	x		
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
		x	

Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			x
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

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.
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   - **NDA:** Store at controlled room temperature, 59^0 to 86^0F (15^0 to 30^0C).
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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:** [redacted]
   - **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: Koung Lee **Date:** 02/14/01

Team Leader: Charlie Hoppes **Date:** 4/5/01

cc:

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-061

CORRESPONDENCE

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

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

August 8, 2002

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/am

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,

PE
Enclosures

RECEIVED
AUG 0 9 2002
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

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

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

TELEPHONE AMENDMENT

ORIG AMENDMENT

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,

PE/cj
Enclosures

RECEIVED
MAY 2 0 2002
OGD / CDER

Mark 3/19/02 for

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

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

March 14, 2002

MINOR AMENDMENT

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 [redacted], 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 [redacted]. 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**.

3/19/02

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,

PE/cw
Enclosures

ANDA 76-061

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

MAR 16 2001

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,

/S/

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

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

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

50 (2)(1) OK
8-JAN-2001

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,

PE/asg
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

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

February 1, 2002

TELEPHONE AMENDMENT

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

ORIG AMENDMENT

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.

[redacted]

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 | U.A.

PE/jbp
Enclosures

mailed
1/29 2/1/02

TEVA

Administrative Offices:
TEVA PHARMACEUTICALS USA
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Phone: (215) 591 3000
FAX: (215) 591 8600

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

January 28, 2002

MINOR AMENDMENT

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

ORIG AMENDMENT
N/Am

ANDA # 76-061
PERGOLIDE MESYLATE TABLETS, 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**. [redacted] the holder of drug master file No [redacted] for [redacted] 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,

Philip Erickson, R.Ph.

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 29 2002

PE/asg
Enclosures

1/30/02

Pamela Mimms
DAI
Not sued on '948, '405
9/18/01

TEVA

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NEW CORRESP
NC

September 12, 2001

PATENT INFORMATION

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

PE/jbp
Enclosure

CENTER FOR DRUG
SEP 14 2001
EVALUATION AND RESEARCH

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

ORIG AMENDMENT
N/AF

September 4, 2001

LABELING AMENDMENT

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
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 Koung 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,

PE/dl
Enclosures

noted jg
8/27/01

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

ORIG AMENDMENT
N/AM

August 22, 2001

MINOR AMENDMENT

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 # [redacted]. Please find attached a copy of the cover letter from [redacted] (**Attachment 2**).

[redacted]

Redacted 3

pages of trade secret and /or confidential commercial information

B. Additionally, we propose the following change:

[redacted]

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,

PE/jws
Enclosures

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

BIOAVAILABILITY

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

BIOEQUIVALENCY AMENDMENT

ORIG AMENDMENT
N/AB

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 (prochloperazine), 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, [redacted] 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:

[redacted]

5. [redacted]

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,

PE/asg
Enclosures

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

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

BIOEQUIVALENCE ELECTRONIC SUBMISSION DOCUMENT
[TWO DISKETTES ENCLOSED:
1 ORIGINAL, 1 COPY]

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,

PE/va
Enclosures

N:\GENERICS\PENN\FDACORE\Pergolide\ANDA\Bio_EVA\Ltr_Comp_bio_EVA.wpd

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

April 6, 2001

NC

NEW CORRESP

PATENT INFORMATION

CENTER FOR DRUG EVALUATION AND RESEARCH
APR 0 9 2001
OGD

Gary Buehler, Director
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Food and Drug Administration
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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,

PE/asg
Enclosures