

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-385/S030/S031/S035

Trade Name: Permax

Generic Name: Peroglide mesylate

Sponsor: Eli Lilly and Company

Approval Date: October 2, 3004

Indications: Indicated for adjunctive treatment to levodopa/carbidopa in management of the signs and symptoms of Parkinson's disease.

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APPLICATION NUMBER:
19-385/S030/S031/S035

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APPLICATION NUMBER:
19-385/S030/S031/S035

APPROVAL LETTER



NDA 19-385/S-030/ S-031/S-035

Eli Lilly and Company
Attention: Elizabeth C. Sloan, Pharm.D.
Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46185

Dear Dr. Sloan:

Please refer to your supplemental new drug applications dated November 30, 2002 (S-030), December 5, 2000 (S-031), and February 10, 2003 (S-035), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Permax (pergolide mesylate) tablets, and to your amendments dated February 10, 2003 (S-031 and S-035), and February 13, 2003 (S-030).

We also refer to (a) an Agency letter dated November 9, 2002, which requests revision of labeling and issuance of a "Dear Healthcare Practitioner" letter (S-035), and (b) an Agency letter dated December 19, 2002, which states that supplemental applications S-030 and S-031 are approvable.

Additional reference is made to a September 3, 2003 email from Ms. Bryn Bright to Dr. John Feeney of this Division. In that email Ms. Bright states that Lilly will agree to the wording for the Warning regarding falling asleep during activities of daily living, as discussed during several recent telephone conversations, beginning August 11.

Supplemental Application S-030

Originally this "Changes Being Effected" supplemental new drug application provided for the inclusion of two new sentences in the **PRECAUTIONS - Information for Patients** subsection of labeling. The February 13, 2003 amendment provided alternative proposed language to the **WARNINGS - Falling Asleep During Activities of Daily Living** subsection, and to the **PRECAUTIONS - Information for Patients** subsection in response to an Agency December 19, 2002 letter. The September 3, 2003 email communication agrees to accept the Agency's originally proposed language for **WARNINGS -Falling Asleep During Activities of Daily Living** subsection.

Supplemental Application S-031

This "Prior Approval" supplemental new drug application proposes the addition of a new subsection, **PRECAUTIONS - Geriatric Use**.

Supplemental Application S-035

This "Changes Being Effected" supplemental new drug application proposes changes to the **WARNINGS -Serous Inflammation and Fibrosis** subsection of labeling.

Your submissions of February 10, 2003 (S-031 & S-035) and February 13, 2003 (S-030), constitute a complete response to our approvable letter dated December 19, 2002 (S-030 and S-031), and our labeling change request letter dated November 9, 2002 (S-035). The September 3, 2003 email communication provides agreed upon labeling (Code 5.02 PV 2271-A UCP).

We have completed our review of supplemental new drug applications S-030, S-031, and S-035, as amended, and they are approved effective on the date of this letter, for use as recommended in the agreed upon labeling text provided.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert)

We remind you that the **WARNINGS – Falling Asleep During Activities of Daily Living** subsection should be a Bold warning and should be the first warning in labeling. Also, we remind you that a Dear Health Care Professional letter should issue, advising practitioners about this new warning.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Management Officer, at (301) 594-2850.

Sincerely Yours

Russell Katz, M.D.
Division Director
Division of Neuropharmacology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:

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

/s/

Russell Katz
10/2/03 08:48:12 AM

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APPLICATION NUMBER:
19-385/S030/S031/S035

APPROVABLE LETTER



NDA 19-385/S-030/S-031

Lilly Research Laboratories
Attention: Bryn Bright, Pharm.D.
Senior Regulatory Associate, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Bright:

Please refer to your supplemental new drug applications dated November 30, 2000 (S-030), and December 5, 2000 (S-031) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Permax (pergolide mesylate) tablets.

We additionally refer to an Agency letter dated April 6, 2000, requesting that you research your adverse event safety database regarding sudden attacks of sleep occurring to patients taking Permax as well as an Agency letter dated August 29, 2002, requesting revisions to the labeling.

These supplemental applications provide for the following revisions to product labeling:

S-030

- This "Changes Being Effected" supplemental new drug application proposes the inclusion of two new sentences in the **PRECAUTIONS-Information for Patients** subsection. This new information was added after your review of your safety database and in response to the aforementioned Agency letter dated April 6, 2000. These sentences describe: 1) the potential for somnolence and, therefore, the need for caution in operating hazardous machinery, and 2) the possible additive sedative effects when used in combination with other CNS depressants.

S-031

- This "Prior Approval" supplemental new drug application proposes the addition of a new subsection under **PRECAUTIONS** entitled **Geriatric Use** to add information on geriatric use and to comply with a Federal Register notice dated August 27, 1997.

We have completed the review of these applications, and they are approvable. Before these applications may be approved, however, it will be necessary for you to make revisions, as outlined below, to the product labeling.

In regard to the revisions made under S-030, we concur with your assessment that it is difficult to assess a causal association between Parkinson's Disease patients treated with pergolide and sleep attacks due to the background incidence of sleep disorders in this population. However, based upon the pergolide associated cases summarized in your November 30, 2000 submission and those cases published in the medical literature, we believe that these sleep related adverse events resemble the cases described in the Requip (ropinirole) and Mirapex (pramipexole) warning statements in their respective prescriber labelings. Therefore, we are requesting that you insert the following similar language as that found in the Requip and Mirapex prescriber labelings:

[The following new subsection should be placed in the **WARNINGS** section of labeling.]

Falling Asleep During Activities of Daily Living:

Patients treated with PERMAX have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles which sometimes resulted in accidents. Although many of these patients reported somnolence while on PERMAX, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events had been reported as late as one year after the initiation of treatment.

Somnolence is a common occurrence in patients receiving PERMAX. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with PERMAX, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with PERMAX such as concomitant sedating medications or the presence of sleep disorders. If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), PERMAX should ordinarily be discontinued. If a decision is made to continue PERMAX, patients should be advised to not drive and to avoid other potentially dangerous activities. While dose reduction clearly reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

We are additionally requesting that you propose alternative language for the **PRECAUTIONS-Information for Patients** subsection so that it is compatible with the

new language in the **WARNINGS-Falling Asleep During Activities of Daily Living** subsection.

In regard to the changes made under S+031, we believe that your proposed statement _____ is misleading since it de-emphasizes the increased incidence of these events. Therefore, we are requesting the following revisions to this subsection of labeling:

Under **PRECAUTIONS-Geriatric Use**

[The following paragraph should be inserted to replace your proposed language in this subsection.]

Of the total number of subjects in clinical studies of pergolide mesylate, 78 were 65 and over. There were no apparent differences in efficacy between these subjects and younger subjects. There was an increased incidence of confusion, somnolence, and peripheral edema in patients 65 and over. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

We additionally remind you of our requested revisions to the **DESCRIPTION** and **HOW SUPPLIED** sections of labeling conveyed in our letter dated August 29, 2002. These requested revisions should be incorporated into your response to this letter.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling (to each application) ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz
12/19/02 10:21:58 AM

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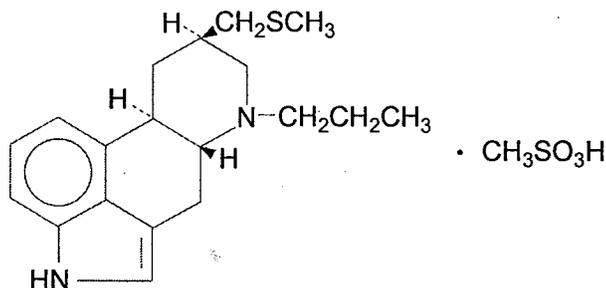
APPLICATION NUMBER:
19-385/S030/S031/S035

LABELING

PERMAX[®]
PERGOLIDE MESYLATE

DESCRIPTION

Permax[®] (Pergolide Mesylate) is an ergot derivative dopamine receptor agonist at both D₁ and D₂ receptor sites. Pergolide mesylate is chemically designated as 8β-[(Methylthio)methyl]-6-propylergoline monomethanesulfonate; the structural formula is as follows:



The empirical formula is C₁₉H₂₆N₂S•CH₄O₃S, representing a molecular weight of 410.60.

Permax 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 croscarmellose sodium, iron oxide, lactose, magnesium stearate, and povidone. The 0.05 mg tablet also contains L-methionine, and the 0.25 mg tablet also contains FD&C Blue No. 2.

CLINICAL PHARMACOLOGY**Pharmacodynamic Information**

Pergolide mesylate is a potent dopamine receptor agonist. Pergolide is 10 to 1000 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 postsynaptic 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 ¹⁴C radiolabeled pergolide mesylate, approximately 55% of the administered radioactivity can be recovered from the urine and 5% from expired CO₂, 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-despropylpergolide, 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

Permax 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

Falling Asleep During Activities of Daily Living — Patients treated with PERMAX have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles which sometimes resulted in accidents. Although many of these patients reported somnolence while on PERMAX, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events had been reported as late as 1 year after the initiation of treatment.

Somnolence is a common occurrence in patients receiving PERMAX. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with PERMAX, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with PERMAX such as concomitant sedating medications or the presence of sleep disorders. If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require participation (e.g., conversations, eating, etc.), PERMAX should ordinarily be discontinued. If a decision is made to continue PERMAX, patients should be advised to not drive and to avoid other potentially dangerous activities.

While dose reduction may reduce the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

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 2299 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%; Extrapyrarnidal syndrome, 3.5%; Stroke, 2.1%; Dysphagia, 2.1%; Injury, 1.4%; Suicide, 1.4%; Dehydration, 0.7%; Glomerulonephritis, 0.7%.

Serous Inflammation and Fibrosis — There have been rare reports of pleuritis, pleural effusion, pleural fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving one or more valves, or retroperitoneal fibrosis in patients taking pergolide. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of pergolide. 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

Because pergolide mesylate may cause somnolence and the possibility of falling asleep during activities of daily living, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that pergolide mesylate therapy does not affect them adversely. Patients should be advised that if increased somnolence or new episodes

of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Due to the possible additive sedative effects, caution should also be used when patients are taking other CNS depressants in combination with pergolide mesylate.

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 Permax. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions

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

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 no 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 gene 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 gene 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 depressed 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 pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in clinical studies of pergolide mesylate, 78 were 65 and over. There were no apparent differences in efficacy between these subjects and younger subjects. There was an increased incidence of confusion, somnolence, and peripheral edema in patients 65 and over. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

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 1200 patients receiving pergolide mesylate for treatment of Parkinson's disease in premarketing clinical trials in the US 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%).

Fatalities — 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
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
Vasodilatation	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 Permax — This section reports event frequencies evaluated as of October 1988 for adverse events occurring in a group of approximately 1800 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 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole — *Frequent*: headache, asthenia, accidental injury, pain, abdominal pain, chest pain, back pain, flu syndrome, neck pain, fever; *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 overdose 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 overdose, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Management of overdose 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 Permax 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.

Permax is 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 Permax 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 Permax at doses above 5 mg/day has not been systematically evaluated.

HOW SUPPLIED

Tablets (modified rectangle shape, scored):

0.05 mg, ivory, debossed with A 024, in bottles of 30 (UC5336) — NDC 65234-024-30

0.25 mg, green, debossed with A 025, in bottles of 100 (UC5337) — NDC 65234-025-10

1 mg, pink, debossed with A 026, in bottles of 100 (UC5338) — NDC 65234-026-10

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

PERMAX is a registered trademark of Eli Lilly and Company, and licensed in the US to Amarin Pharmaceuticals, Inc.

Literature revised

NDA 19-385 /S-030/ S-031/ S-035

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**Manufactured by:
Eli Lilly and Company
Indianapolis, IN 46285, USA**

**Distributed by:
Amarin Pharmaceuticals, Inc.
Mill Valley, CA 94941**

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-385/S030/S031/S035

MEDICAL REVIEW

Review and Evaluation of Clinical Data

NDA (Serial Number)	19385 (SLR-031)
Sponsor:	Lilly
Drug:	Permax
Proposed Indication:	Parkinson's disease
Material Submitted:	Geriatric labeling supplement
Correspondence Date:	12/5/00
Date Received / Agency:	12/6/00
Date Review Completed	11/12/02
Reviewer:	Eric P. Bastings, MD

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1. Introduction

The sponsor is submitting a geriatric labeling supplement, pursuant to the geriatric rule. The changes relate to 21 CFR 201.57 (f)(10)(ii)(B). The sponsor also submitted a report entitled "Use of Pergolide Mesylate in Geriatric Patients." This report summarizes information taken from the clinical trial B40-MC-LAAR, which was submitted in the original NDA, and also summarizes information from spontaneous reporting.

2. Geriatric use subsection

The sponsor is proposing to add the geriatric use subsection in the "Precautions" section of labeling. The proposed subsection is as follows: "**Geriatric Use—Of the total number of subjects in clinical studies of pergolide mesylate, 78 were 65 and over. There were no apparent differences**....."

..... Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function."

3. Sponsor's report: "Use of Pergolide Mesylate in Geriatric Patients."

The New Drug Application for pergolide was submitted to the FDA in 1985 and approval was obtained in 1988. Approval was based on a single double-blind randomized controlled trial (Lilly study B40-MC-LAAR referred to as LAAR for the remainder of this document). This study is the only source of double-blind, placebo-controlled data available. Other sources of material used in this analysis include open label clinical trials and data obtained from spontaneous reports in the pharmacovigilance database.

The LAAR study had a total population of 376 patients (189 pergolide and 187 placebo). Of the 189 patients treated with pergolide, 78 were 65 years old or older. Because of this small sample size, the sponsor modified the criteria defining the geriatric population in order to obtain a sample size of 100 or more. COMMENT: the geriatric rule states that a number of patient inferior to 100 in adequate and well controlled studies is considered insufficient to determine whether elderly respond differently, and recommends in that case the following standard labeling: "Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."

The sponsor used "63 years old or older" as the criteria for "geriatric" population. This resulted in a sample size of 103 geriatric patients taking pergolide. The sponsor analyzed the data both with the 63 years old cut-off age and with the 65 years old cut-off age. The sponsor did not identify any relevant difference when comparing both cohorts.

The geriatric population in the LARR study had nominally more severe disease at baseline based on the Total Disability Rating Score (DRS), one the four primary outcome measures used in that study. The DRS scale is somewhat similar but not identical to the UPDRS. Part A of the DRS scale provides information regarding activities of daily living. Part B provides information from the neurological examination. Part C contains questions related to complications of therapy. The other three outcomes measures used in the LARR study were the Hoehn and Yahr rating, the "off time," and a therapeutic index (without further details provided). The Hoehn and Yahr rating was not different between geriatric and younger subjects at baseline.

Using the total DRS (first of four primary outcomes in the LARR Study), the treatment effect with pergolide in geriatric patients was not different from the treatment effect in non-geriatric patients (Table 1).

Table 1: Total DRS change from baseline to endpoint

Treatment	Age group	N	Mean change	Within treatment p-value	Treatment p-value	Age group p-value	Treatment age group interaction
Pergolide	<63	86	-64.3	<0.001	<0.001	.005	.259
	≥63	102	-42.3	<0.001			
Placebo	<63	76	-24.2	<0.001			
	≥63	107	-20.6	<0.001			

However, using categorical assessments of 25% (Table 2) or 50% (Table 3) improvement in total DRS, nominally significant treatment by age group interaction was seen.

Table 2: 25% decrease in total DRS

Treatment	Age group	n	25% Decrease	n	%	Age group p-value	Treatment age group interaction
Pergolide	<63	86	No	25	29.1	<0.001	<0.001
			Yes	61	70.9		
	≥63	102	No	58	56.9		
			Yes	44	43.1		
Placebo	<63	76	No	54	71.1	.3888	
			Yes	22	29		
	≥63	107	No	83	77.6		
			Yes	24	22.4		

Table 3: 50% decrease in total DRS

Treatment	Age group	n	50% Decrease	n	%	Age group p-value	Treatment age group interaction
Pergolide	<63	86	No	54	62.8	<0.001	<0.001
			Yes	32	37.2		
	≥63	102	No	89	87.3		
			Yes	13	12.8		
Placebo	<63	76	No	69	90.8	0.035	
			Yes	7	9.2		
	≥63	107	No	105	98.1		
			Yes	2	1.9		

Table 2 and Table 3 suggest that the effect size was smaller in older subjects. In my opinion, the critical element is that the change in total DRS (Table 1) was not different between younger and older subjects.

Table 4 and Table 5 show that there was no significant difference nor a trend for a significant difference for the other primary outcome measures “Off time” and the “Hoehn and Yahr” score.

Table 4: Off time

Treatment	Age group	N	Mean change (hour)	Within-treatment p-value	Treatment p-value	Age group p-value	Treatment by age group interaction
Pergolide	<63	86	-2.3	<0.001	<0.001	0.105	0.434
	≥63	102	-1.4	<0.001			
Placebo	<63	76	-0.3	0.325			
	≥63	107	-0.1	0.659			

Table 5: Hoehn and Yahr (Stage of disease)

Treatment	Age group	N	Mean change	Within-treatment p-value	Treatment p-value	Age group p-value	Treatment by age group interaction
Pergolide	<63	86	-0.6	<0.001	<0.001	0.015	0.237
	≥63	102	-0.2	<0.001			
Placebo	<63	76	-0.1	0.058			
	≥63	107	-0.1	0.184			

For adverse events in the LARR Study, a treatment by age group nominally significant interaction was seen for peripheral edema, confusion, and somnolence. The only trend ($p \leq 0.1$) for a higher AE incidence in patients age 63 and higher than in younger patients was for chest pain ($p=0.08$). There also was nominally less constipation, dystonia, and dyskinesia in older patients.

Table 6: Significant differences and trends in adverse event differences between the geriatric and non-geriatric population.

	Pergolide age ≥ 63 (n=103)	Pergolide age < 63 (n=86)	Placebo age ≥ 63 (n=110)	Placebo age < 63 (n=77)	Treatment by age group interaction
Peripheral edema	13 (12.6%)	1 (1.2%)	7 (6.4%)	1 (1.3%)	<0.001
Confusion	18 (17.5%)	3 (3.5%)	12 (10.9%)	6 (7.8%)	0.007
Somnolence	17 (16.5%)	2 (2.3%)	3 (2.7%)	4 (5.2%)	0.023
Chest pain	7 (6.8%)	0 (0%)	2 (2.6%)	2 (1.8%)	0.08

The sponsor also analyzed spontaneously reported data. The sponsor utilized its own database (CLINTRACE) as well as the AERS database. A total of 2362 adverse events (AEs) were reported in 996 geriatric patients (compared to only 673 patients with AEs in the non-geriatric patients). The sponsor looked at reporting ratios¹ of adverse events. There were fourteen types of AEs where the proportional reporting ratio (PRR, defined as reporting ratio in geriatric patients/reporting ratio in non-geriatric patients) was two or more (Table 7). Urinary incontinence, heart failure, and hypokinesia were reported at

¹ Defined as number of spontaneous cases reported for that event divided by the total number of spontaneous cases for all adverse events in the same age group.

least four times relatively more frequently in geriatric patients than in non-geriatric patients.

Table 7: Adverse Drug Experience reported at least two times more commonly in geriatric than in non-geriatric patients (from sponsor table 43)

Co-start term	% Reports (geriatric patient)	% Reports (non-geriatric patient)	Geriatric/non-geriatric	Pergolide/other Lilly drugs (geriatric)
Urinary incontinence	1.7	0.1	17.0	4.28
Heart failure	2.6	0.6	4.33	6.14
Hypokinesia	1.2	0.3	4.0	12.31
Infection	1.0	0.3	3.33	1.27
Myocardial infarction	1.0	0.3	3.33	1.09
Abnormal gait	2.6	0.9	2.89	3.58
Psychosis	1.1	0.4	2.75	4.89
Cardiovascular disorder	1.0	0.4	2.5	2.67
Coma	1.0	0.4	2.5	1.42
Apnea	1.4	0.6	2.33	4.85
Weight loss	1.4	0.6	2.33	0.96
Death	1.3	0.6	2.17	1.58
Delirium	1.4	0.7	2.0	3.81
Convulsion	1.2	0.6	2.0	0.99

The increased ratios may be due either to an increase in susceptibility of geriatric patients to develop such an event from exposure to pergolide or to the fact that such an event occurs more frequently in geriatric patients regardless of drug exposure. In order to differentiate these two possibilities, the same group of adverse events were compared between geriatric patients who received pergolide and geriatric patients receiving any other Lilly drug in the CLINTRACE database. This is shown in the last column of Table 7. Eight adverse events were reported at least two times more often in the geriatric patients who took pergolide than in geriatric patients who took other Lilly drugs: heart failure, psychosis, urinary incontinence, abnormal gait, delirium, apnea, hypokinesia, and cardiovascular disorder. The sponsor argues that the majority of these adverse events is in the present USPI or would be consistent with manifestations of PD, with the exception of heart failure (and cardiovascular disorder).

The sponsor reviewed reports of heart failure in patients on pergolide in the CLINTRACE database. The sponsor identified 57 geriatric cases, and 17 non-geriatric cases. Two geriatric cases involved constrictive pericarditis (with right-sided heart failure), compared to one case constrictive pericarditis and one case of right-sided heart failure in the non geriatric population.

The sponsor also looked in the AERS database for heart failure reports in geriatric patients (using several relevant MEDDRA terms), and found a modestly elevated reporting ratio in geriatric patients / reporting ratio in non-geriatric patients for heart failure and pergolide (2.7) compared to other drugs (cabergolide = 2.7; bromocriptine = 1.9; levodopa/carbidopa = 1.1). The sponsor argues that is not indicative of causality. Pericarditis appears in the warning section, and congestive heart failure is listed in the

adverse reactions section. For that reason, the sponsor proposes no modification regarding pericarditis and heart failure. The sponsor emphasizes that the adverse events identified in the controlled trial are different from those identified in the pharmacovigilance. COMMENT: This discrepancy can be also explained by a longer duration of administration in the pharmacovigilance database, and by the small sample size of the controlled trial which may have easily missed infrequent adverse events.

4. Comments

1. Since the geriatric population studied in the only pergolide controlled study was under 100 subjects, this sample size, according to the Guidance For Industry on the Content and Format for Geriatric Labeling (October 2001) can be considered as insufficient to determine whether elderly patients respond differently.
2. However, the target number of 100 is reached when patients age 63 and over are considered. Since some important safety information was identified in that slightly modified geriatric population, I propose to allow the sponsor to use paragraph (ii)(B) for the geriatric labeling.
3. I concur with the sponsor identification of a higher incidence of confusion, somnolence, and peripheral edema in the geriatric population. The sponsor statement "There were no apparent differences in safety or efficacy between these subjects and younger subjects" ~~_____~~
~~_____~~
4. The higher incidence of heart failure seen in the pharmacovigilance database for geriatric patients on pergolide may be related by the higher incidence of peripheral edema seen in the controlled trial. Even though the relative ratio (see section 3) is relatively small (2.7), ~~_____~~
~~_____~~
5. I concur with the statement on kidney excretion. It is standard language for renally excreted drugs.
6. I recommend the following text for the geriatric subsection:
"Geriatric Use—Of the total number of subjects in clinical studies of pergolide mesylate, 78 were 65 and over. There were no apparent differences in efficacy between these subjects and younger subjects. There was an increased incidence of confusion, somnolence, and peripheral edema in patients 65 and over. Other reported clinical experience has identified evidence for a higher incidence of heart failure in patients 65 and over. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function."

5. Recommendation

I recommend an approvable action.

6. Comments to sponsor

Please refer to your supplemental new drug application dated December 5, 2000, received December 6, 200, for Permax tablets. This supplement proposes a labeling change (addition of a geriatric subsection). We have completed the review of this application and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

- Your statement that "There were no apparent differences between these subjects and younger subjects, _____ is misleading, since it de-emphasizes the increased incidence of these events.
- The higher incidence of heart failure seen in the pharmacovigilance database for geriatric patients on pergolide may be related by the higher incidence of peripheral edema seen in the controlled trial. It represents a safety signal which should be reported in labeling.

We propose the following text for the geriatric subsection:

"Geriatric Use—Of the total number of subjects in clinical studies of pergolide mesylate, 78 were 65 and over. There were no apparent differences in efficacy between these subjects and younger subjects. There was an increased incidence of confusion, somnolence, and peripheral edema in patients 65 and over. Other reported clinical experience : _____

_____ This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function."

Eric P. Bastings, M.D.

Medical Reviewer

J. Feeney, MD _____

epb 11/12/02

cc:

HFD-120

NDA 19385 (SLR-031)

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

/s/

Eric Bastings
12/10/02 05:11:42 PM
MEDICAL OFFICER

John Feeney
12/18/02 03:31:08 PM
MEDICAL OFFICER

Concur, but after discussing the nature of the evidence for increased incidence of heart failure, I do not believe this merits mention in labeling. Therefore, that sentence in Dr Bastings proposed labeling should revert to the standard language.

Review and Evaluation of Clinical Data

NDA	19385
Sponsor:	Eli Lilly
Drug:	pergolide
Proposed Indication:	Parkinson's disease
Material Submitted:	CBE Labeling Supplements SLR 030, 031, and 035, Response to Approvable Letter
Correspondence Date:	2/10/03, 2/13/03
Date Received / Agency:	2/11/03, 2/14/03
Date Review Completed	8/5/03
Reviewer:	Leonard Peter Kapcala, MD

This medical officer review and evaluation of 3 labeling supplements for pergolide summarizes information submitted and provides recommendations and comments for the DNDP Director and Team Leader. The DNDP Director and Team Leader will use this information to decide whether the proposed labeling changes are acceptable.

Background / Introduction

Falling Asleep During Activities of Daily Living

In a letter (4/6/00) DNDP asked the sponsor to review all appropriate information related to pergolide and the possibility of sudden irresistible attacks of sleep (i.e. "sleep attacks") associated with the use of this dopaminergic agonist. Lilly, the sponsor, searched its clinical trials' and post-marketing databases and the literature for possible cases of sleep attacks associated with pergolide and submitted a response on 6/15/00 and a labeling supplement (SLR 030) on 11/30/00. Based upon a review (12/6/02, DFS) by Dr. Boehm, DNDP concluded that sleep attacks resembling those described in labeling for pramipexole and ropinirole had occurred and that the sponsor should revise the label accordingly. On 12/19/02 DNDP issued an approvable letter to the sponsor and requested that the sponsor revise the label according to language provided in the letter describing episodes of falling asleep during activities of daily living in the Warning section. The letter also requested that the sponsor propose alternative language for the Precautions section of the label that was compatible with the revised Warning section. The sponsor submitted (2/13/03) a Response to the Approvable letter which is one subject of this review.

Geriatric Labeling

The sponsor submitted a "Changes Being Effected" (CBE) labeling supplement (revised 12/5/2000; SLR 031) to add a new subsection under the Precautions section of the label on Geriatric Use to comply with the Federal Register notice (8/27/97). The sponsor's submission was reviewed by Dr. E. Bastings (12/18/02, DFS) and the approvable letter

12/19/02) from DNDP provided the sponsor with recommendations of specific language to include for geriatric labeling. The sponsor submitted (2/10/03) FPL for this revision according to DNDP recommendations and this is one subject of this review.

Cardiac Valvulopathy

Submission of post-marketing reports of cardiac valvulopathy associated with the use of pergolide prompted DNDP to examine this issue further. The Office of Drug Safety found several cases in which patients treated with pergolide developed cardiac valvulopathy of one or more valves. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of pergolide. DNDP concluded that pergolide may have been the cause of the cardiac valvulopathy, that was thought to be another fibrotic complication associated with the use of ergot drugs. DNDP notified (11/7/02 letter) the sponsor of these findings and recommended addition of these adverse reactions to the Warnings section of the label. After various discussions, the sponsor and DNDP came to an agreement on the wording of labeling regarding cardiac valvulopathy. In addition, the sponsor was to send a Dear Doctor/Health Care Professional letter informing of this new warning. The sponsor submitted a labeling supplement (SLR 035; 2/10/03) to add the warning on cardiac valvulopathy and this is also a subject of this review.

Submissions :

Falling Asleep During Activities of Daily Living (SLR 030)

- The sponsor has added most of the labeling recommended by DNDP in its letter (12/19/02). The sponsor has deleted some wording recommended by DNDP and has substituted other wording in a few places.
- Comparison of the Sponsor's Revised Label (Warnings) with wording recommended by DNDP is shown here.

4 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

Comments / Conclusions

Falling Asleep During Activities of Daily Living (SLR 030)

The sponsor has added and inserted the phrase _____ in describing the occurrence of reports of patients falling asleep during activities of daily living while being treated with pergolide. There does not appear to be any justification for this difference in wording for the pergolide label compared to the label for pramipexole and ropinirole that do not use this phrase. There is no reason to believe that the occurrence of this adverse reaction associated with pergolide use _____ of the same reaction with the use of pramipexole or ropinirole. Allowing the sponsor's proposed wording would seem to suggest to a prescriber _____ with pramipexole or ropinirole and would seem to confer an unfair advantage in the labeling of pergolide. The language recommended by DNDP is consistent with class labeling for this reaction that seems to be associated with drugs enhancing dopaminergic tone.

The sponsor has substituted language to note that sleep attacks occurring during pergolide use _____ in place of DNDP's wording "sometimes resulted in accidents." There is no justification for the sponsor's language that suggests that there is a _____ (after the conclusion has been drawn that pergolide use is associated with sudden onset of sleep, is a likely cause of at least some sleep attacks, and this association merits a Warning in labeling).

The sponsor has substituted wording indicating that "Somnolence is a _____ occurrence in patients receiving PERMAX." in place of DNDP's recommendation that "Somnolence is a common occurrence in patients receiving PERMAX." This change is not justified considering that the table (in the label) of the incidence of treatment-emergent adverse experiences in controlled trial experience shows that somnolence occurred in 10.1 % of patients treated with PERMAX and in 3.7 % of patients treated with PLACEBO. Somnolence does appear to be a common occurrence in patients treated with PERMAX based upon the controlled clinical trial experience.

_____ DNDP's recommended wording that many clinical experts believe that sudden sleep attacks during activities of daily living occurs in a setting or preexisting somnolence in the absence of such a patient history. _____

_____ DNDP's recommended wording that patients should be asked about factors that may increase the risk of drowsiness before initiating treatment with PERMAX. _____

The sponsor has substituted the word "may" in place of _____ regarding DNDP's recommended statement : "While dose reduction _____ reduces the degree of somnolence, ...". Although I might expect that reduction of the pergolide dose would

reduce somnolence, I'm not aware of evidence for noting that this reduction of somnolence ~~occurs~~ occurs merely by "dose reduction." Reduction of somnolence by decreasing the pergolide dose may depend on the level and amount of dose reduction and may vary from individual to individual. The sponsor's change may be more accurate and appropriate than our recommended wording/language.

The sponsor has proposed language for the Precautions section about operating hazardous machinery including automobiles. The sponsor's language is acceptable with the exception that ~~to~~ to include the word "new" in noting the type of sleep attack episodes that merit prohibition of activities while using pergolide until consulting a physician. The Precaution seems fine ~~the~~ the word "new" that may be ~~fine~~

Geriatric Labeling (SLR 031)

The sponsor has incorporated the language of DNDP's recommended labeling for Geriatric Use and this labeling is acceptable.

Cardiac Valvulopathy (SLR 035)

The sponsor has incorporated the language of DNDP's recommended labeling for the Warning about cardiac valvulopathy and this labeling is acceptable.

Recommendation

I recommend approval of SLR 031 and 035.

I recommend that SLR 030 is approvable and that the sponsor adopt the identical language for the Warnings section that DNDP recommended with the exception of altering the phrasing to "While dose reduction may reduce the degree of somnolence, ...".

Comments to Sponsor

1. SLR 031 and 035 are approved.
2. SLR 030 is approvable. We do not find justification for your deviation from the specific language recommended for the Warnings section of the labeling regarding falling asleep during activities of daily living. We recommend that you adopt our

specifically recommended language with the exception that it is acceptable to note that "While dose reduction **may reduce** the degree of somnolence, ...".

3. SLR 030 is approvable. Please ~~use~~ the word "new" in describing "new episodes of falling asleep" in the Precautions section. Any patient should avoid operating any hazardous machinery until consulting with a physician about any increase somnolence or any episode of falling asleep during activities of daily living while using PERMAX.

Leonard Peter Kapcala, M.D.
Medical Reviewer

John Feeney, M.D.
Neurology Team Leader, DNPDP

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

/s/

Leonard Kapcala
8/6/03 05:29:51 PM
MEDICAL OFFICER

John, Here i s my review of the 3
pergolide labeling supplements. Please let me know if
any questions. Thanx. Len

John Feeney
8/13/03 12:03:34 PM
MEDICAL OFFICER
concur; final labeling on sleep attacks will need to
be negotiated

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-385/S030/S031/S035

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF SUPPLEMENT

1. ORGANIZATION: HFD-120
2. NDA NUMBER: 19-385
4. SUPPLEMENT NUMBERS/DATES: SLR-030
letterdate: 30-NOV-00
stampdate: 01-DEC-00
5. AMMENDMENTS/REPORTS/DATES:
6. RECEIVED BY CHEMIST: 25-JAN-01

7. APPLICANT NAME AND ADDRESS: Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

8. NAME OF DRUG: PERMAX™ Tablets
9. NONPROPRIETARY NAME: Pergolide

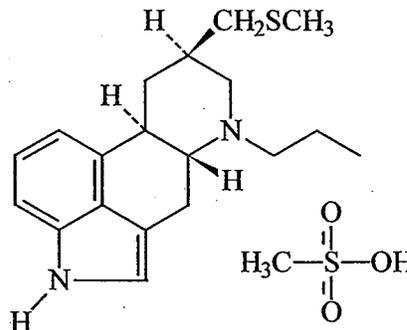
10. CHEMICAL NAME/STRUCTURE:
CA/IUPAC: 8β-[(methylthio)methyl]-6-propylergoline
monomethanesulfonate [66104-23-2]

11. DOSAGE FORM(S): Tablets
12. POTENCY: 0.05, 0.25, 1.0 mg

13. PHARMACOLOGICAL CATAGORY: dopamine agonist
Anti-Parkinson's

14. HOW DISPENSED: XXX (RX) (OTC)
15. RECORDS & REPORTS CURRENT: XXX (YES) (NO)

16. RELATED IND/NDA/DMF: IND 14,565



17. SUPPLEMENT PROVIDES FOR: revised package labeling for Permax®, pergolide mesylate.

18. COMMENTS: the provisions of packaging labeling in this submission appear to be identical to those of S-028. The reviewer recommends revisions for the product labeling to be considered adequate. Refer to the chemistry review of S-28.

19. CONCLUSIONS AND RECOMENDATIONS: Recommend APPROVAL of NDA 19-385 / SLR-030. Recommend additional changes in product labeling for the next printing. (Confer with CMC review S-028).

20. REVIEWER NAME

SIGNATURE

DATE COMPLETED

Thomas A. Broadbent, Ph.D.

01-FEB-01

cc: Orig. NDA 19-385
HFD-120/DivFile
HFD-120/TWheelous
HFD-120/TBroadbent
INT: MG

filename: N19385.030.doc

/s/

Thomas Broadbent
2/1/01 04:29:33 PM
CHEMIST

Maryla Guzewska
2/1/01 04:32:26 PM
CHEMIST

CHEMIST REVIEW
OF SUPPLEMENT

1. ORGANIZATION: HFD-120
2. NDA NUMBER: **19-385**
4. SUPPLEMENT NUMBERS/DATES: SLR-031
letterdate: 05-DEC-00
stampdate: 06-DEC-00
5. AMMENDMENTS/REPORTS/DATES:
6. RECEIVED BY CHEMIST: 25-JAN-01

7. APPLICANT NAME AND ADDRESS: Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

8. NAME OF DRUG: **PERMAX™** Tablets
9. NONPROPRIETARY NAME: Pergolide

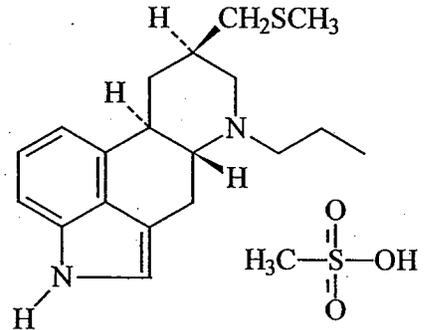
10. CHEMICAL NAME/STRUCTURE:
CA/IUPAC: 8β-[(methylthio)methyl]-6-propylergoline
monomethanesulfonate [66104-23-2]

11. DOSAGE FORM(S): Tablets
12. POTENCY: 0.05, 0.25, 1.0 mg

13. PHARMACOLOGICAL CATAGORY: dopamine agonist
Anti-Parkinson's

14. HOW DISPENSED: XXX (RX) (OTC)
15. RECORDS & REPORTS CURRENT: XXX (YES) (NO)

16. RELATED IND/NDA/DMF: IND 14,565



17. SUPPLEMENT PROVIDES FOR: revised package labeling for Permax®, pergolide mesylate.

18. COMMENTS: This supplement adds references to the product manufacturer and distributor to the product labeling in the HOW SUPPLIED section. This addition satisfies a recommendation made in the CMC review of S-28. See review notes and refer to the review of S-28.

19. CONCLUSIONS AND RECOMENDATIONS: Recommend APPROVAL of NDA 19-385 / SLR-031. Recommend additional changes in product labeling for the next printing. (Confer with CMC review S-028).

20. REVIEWER NAME SIGNATURE DATE COMPLETED

Thomas A. Broadbent, Ph.D.

01-FEB-01

cc: Orig. NDA 19-385
HFD-120/DivFile
HFD-120/TWheelous
HFD-120/TBroadbent
INT: MG

filename: N19385.031.doc

Review Notes – NDA 19-385 / S-031

F. Labeling (See submission, page 10)

The HOW SUPPLIED section adds reference to the product manufacturer and distributor.
It is shown as:

**Manufactured by:
Eli Lilly and Company
Indianapolis, IN 46285, USA**

**Distributed by:
Athena Neurosciences,
a business unit of
Elan Pharmaceuticals, Inc.
South San Francisco, CA 94080**

The statement is preceded by:

"Literature revised. _____"

Evaluation: Adequate. The addition of the manufacturer reference satisfies a recommendation made in the review of the labeling made in S-028. Refer to the CMC review of S-028.

The product labeling of PEMAX Tablets will be considered adequate upon the adoption of the labeling recommendations given in the CMC review of S-028.

/s/

Thomas Broadbent
2/1/01 04:35:05 PM
CHEMIST

Maryla Guzewska
2/1/01 04:36:44 PM
CHEMIST

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-385/S030/S031/S035

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

RMO REVIEW OF NDA FPL

NDA/Supp #: **19-385/ S-028;
S-030; S-031**

Date Review Completed: **01-09-01**

Date of Submission: **06-15-00; 11-30-00;
12-05-00**

Applicant's Name and Address:

**Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 45285**

Product Trade Name:
 Generic Name

**Permax
pergolide mesylate**

Dosage Form and Strength:

0.05, 0.25 & 1 mg Tablets

Pharmacological Category and/or
 Principal Indication:

**Adjunctive to levodopa/carbidopa in
management of Parkinson's Disease**

Material Reviewed:

1. S-020: FPL (PV 2275 UCP) approved on October 6, 1999.
2. An Agency letter dated October 6, 1999, approving S-020.
3. S-028: FPL (PV 2278 UCP) revised on March 20, 2000.
4. S-030: FPL (PV 2279 UCP) revised November 2000.
5. S-031: Annotated labeling (PV 2270UCP) revised November 2000.

Evaluation: (See Attached Review Notes)

VII. RECOMMENDATIONS:

With the concurrence of the review team, an approval letter should issue for S-028 and S-030. Additionally, we should recommend that the storage temperature statement be changed to conform to the draft Guidance document on stability. After agreement is reach on the text for S-031, a letter should issue approving S-031 based on draft labeling.

Merril J. Mille, R.Ph.

cc:ORIG NDA 19-385
HFD-120
HFD-120/MMille
DOC# C:\files\N19385.L031.doc

Concur:

John S. Purvis
Chief Project Manager

Review Notes

- I. COMPARATIVE LABELING:
Final printed labeling (PV 2275 UCP) for S-020 was approved on October 6, 1999. Therefore, this labeling was used as comparative labeling in this review.
- II. LABELING CHANGES
When the new FPL (PV 2279 UCP) was compared to FPL (PV 2275 UCP), the following changes to the labeling text were noted and are listed below by section:

SECTION NOTE #	PREVIOUS FPL S-020 PV 2275UCP	NEW FPL S-030 PV 2279UCP
-------------------	-------------------------------------	--------------------------------

SUPPLEMENT S-028

DESCRIPTION:

Note #1	methionine	L-methionine
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PRECAUTIONS:

Note #3 & 4	cell-point-mutation	cell gene mutation
-------------	---------------------	--------------------

HOW SUPPLIED:

Note #6	(UC5336)—(RxPak* of 30)	in bottles of 30 (UC5336)—
Note #7	(UC5337)—(RxPak* of 100)	in bottles of 100 (UC5337)—
Note #8	(UC5338)—(RxPak* of 100)	in bottles of 100 (UC5338)—
Note #9	*All RxPaks (prescription packages, Lilly) have safety closures.	[DELETION]
Note #10	59° to 86°F(15° to 30°C).	15° to 30°C (59° to 86°F).
Note #11	CAUTION—Federal (USA) law prohibits dispensing without prescription.	[DELETION]

Note #12

[ADDITION]

Permax is a registered trademark of Eli Lilly and Company, and licensed exclusively in the U.S. to Elan Pharmaceuticals, Inc.

SUPPLEMENT S-030

PRECAUTIONS:

Note #2 [ADDITION]

Because pergolide mesylate may cause somnolence, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that pergolide mesylate therapy does not affect them adversely. Due to the possible additive sedative effects, caution should also be used when patients are taking other CNS depressants in combination with pergolide mesylate.

III. **LABELING CHANGES**

When the annotated labeling (PV 2270 UCP) was compared to FPL (PV 2279 UCP) annotated labeling, the following changes to the labeling text were noted and are listed below by section:

SECTION	PREVIOUS FPL	ANNOTATED LABELING
NOTE #	S-030 PV 2279UCP	S-031 PV 2270UCP

SUPPLEMENT S-031

PRECAUTIONS:

Note #5 [ADDITION]

Geriatric use – Of the total number of subjects in clinical studies of pergolide mesylate, 78 were 65 and over. There were no apparent differences in _____ efficacy between these subjects and younger subjects. _____

_____ Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

IV. SUPPLEMENT S-028

Supplemental application S-028 provides revised FPL in response to an Agency letter dated October 6, 1999. Specifically, the revisions include: 1) the addition of "L" to L-methionine in the DESCRIPTION section, 2) a change in terminology from "mammalian cell point mutation assay" to the current terminology of mammalian cell gene assay in the PRECAUTIONS section, 3) the deletion of the RxPak terms, and 4) a change in the corporate signature of Athena Neurosciences in the HOW SUPPLIED section of labeling.

SUPPLEMENT S-030

Supplement application S-030 provides revised FPL that includes two new sentences in the *Information for Patients* subsection of PRECAUTIONS in response to an Agency letter dated April 6, 2000. These sentences describe: 1) the potential for somnolence and, therefore, the need for caution in operating hazardous machinery, and 2) the possible additive sedative effects when used in combination with other CNS depressants.

SUPPLEMENT S-031

Supplemental application S-031 provides revised draft labeling in response to the geriatric rule published in the Federal Register on August 27, 1997. Specifically, the revision includes the addition of a *Geriatric Use* subsection in the PRECAUTIONS section of labeling.

V. COMMENTS:A. S-028

1. FPL PV2278UCP was implemented as "Changes Being Effected" upon submission.
2. The chemist should review the changes in the DESCRIPTION and HOW SUPPLIED sections. [See Notes #1, 6, 7, 8, 9 & 10]
3. The revised storage statement is not consistent with the current recommendation in the draft Guidance Document: Stability Testing of Drug Substances and Drug Products (Issued 6/5/1998, Posted 6/8/1998). For solid dosage forms, the document recommends the following storage statement:
Store at 25° (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]
[See Note # 10]

4. The deletion of the Federal Caution statement is consistent with Section 126 of FDAMA – Elimination of Certain Labeling Requirements. Although the phrase “Rx Only” is intended to replace the Federal Caution statement, it is not required to be on the package insert labeling. [See Note # 11]
5. The pharmacologist should review the changes in the description of the mutagenicity studies in the *Carcinogenesis, Mutagenesis, and Impairment of Fertility* subsection of PRECAUTIONS. [See Notes # 3 & 4]
6. The references to the trademark ownership and licensure rights have been clarified at the end of the HOW SUPPLIED section. [See Note # 12]

B. S-030

1. An Agency letter dated April 6, 2000 requested the sponsor to assess the safety of Permax in relation to sleep or sudden onset of sleep. This was a result of reports of sudden irresistible attacks of sleep in dopamine agonists (high affinity to D3 receptor subtypes), such as Mirapex and Requip. On June 15, 2000, the sponsor submitted a safety report and a commitment to add a precautionary statement regarding somnolence in labeling.
2. In a fax dated July 11, 2000, the sponsor provided revised draft labeling incorporating a somnolence statement in the PRECAUTIONS section of labeling. [See Note # 2]
3. On July 28, 2000, the sponsor was notified that the draft text submitted on July 11, 2000 was acceptable.
4. FPL PV2279UCP was implemented as “Changes Being Effected” upon submission.

C. S-031

1. The text proposed for the Geriatric Use subsection requires a clinical review. [See Note #5]
2. The implementation of this labeling change is pending prior approval by FDA.

VI. CONCLUSIONS:

- A. Although the changes in S-028 and S-030 are acceptable from a regulatory standpoint, concurrence from the review team is necessary prior to action on these supplements.
- B. The implementation of FPL (PV2278UCP & PV2279UCP) prior to Agency approval is acceptable.
- C. Action on S-031 will be based on the clinical review.
- D. Our action letter should recommend revision of the new storage statement as described in the draft guidance document on stability.

END OF REVIEW

Division of Neuropharmacological Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: 20-658/S030/S031/S035

Name of Drug: Permax (pergolide mesylate)

Applicant: Lilly Research Laboratories

Material Reviewed:

Submission	Letter Date	Receipt Date	Action Letters
S-030	November 30, 2000	December 1, 2000	AE Letter December 19, 2002
	February 13, 2003	February 14, 2003	
S-031	December 5, 2000	February 11, 2003	AE Letter December 19, 2002
	February 10, 2003		
S-035	February 10, 2003	February 11, 2003	Agency Request Letter November 9, 2002

Background and Notes of Interest

An approvable letter for supplemental applications S-030 and S-031 issued on December 19, 2002. In this letter we also asked the sponsor to make the following revisions:

S-030

1. Add a new Falling Asleep During Activities of Daily Living subsection in **WARNINGS** section of labeling. The language provided was similar to the language in the Requip and Mirapex labels.
2. We requested that the sponsor propose alternative language for the **PRECAUTIONS – Information for Patients** subsection so that it is compatible with the new language in the **WARNINGS- Falling Asleep During Activities of Daily Living** subsection.

S-031

1. We provided alternative language for the **PRECAUTIONS-Geriatric Use** subsection.
2. We reminded the sponsor of previous requests provided in an Agency letter dated August 2, 2002, to make specific revisions to the **DESCRIPTION** and **HOW SUPPLIED** sections of labeling.

S-035

Based upon post-marketing adverse event reporting, the Division issued a letter dated November 7, 2002, in which the sponsor was asked to change the labeling of pergolide under the **WARNINGS - Serous Inflammation and Fibrosis** subsection to include valvulopathy. The language was negotiated and agreed upon on January 29, 2003. This negotiated language was disseminated in a Dear Health Care Professional Letter and was submitted to the Agency on February 10, 2003 as S-035.

Review

S-030 Label Code: 5.01 PV 2271-A UCP

Dates: November 30, 2000 amended February 13, 2003

CBE: Yes

Review: Medical Officer – (Needed)

- The November 30, 2000 submission provided for the inclusion of two new sentences in the **PRECAUTIONS – Information for Patients** subsection.
- The February 13, 2003 amendment responds to the Agency December 19, 2002 letter, by providing counter proposed language for the **WARNINGS – Falling Asleep During Activities of Daily Living** subsection and proposing alternative language for the **PRECAUTIONS – Information for Patients** subsection as requested in the Agency Dec. 19, 2002 letter.

S-031 Label Code: 4.03 PV 2271 UCP

Dates: December 5, 2000 amended February 10, 2003

CBE: No

Review Medical Officer (not needed since sponsor uses the proposed language)

- The December 5, 2000 supplement provides for addition of a Geriatric subsection under **PRECAUTIONS**.
- The February 10, 2003 amendment provides the requested language to the proposed Geriatric subsection exactly as requested in the Agency December 19, 2002 letter.

S-035 Label Code: 4.03 PV 2271 UCP

Dates: February 10, 2003

CBE: Yes

Review: Medical Officer (not needed since sponsor uses agreed upon language)

- In response to an Agency letter, dated November 7, 2002, and January 29, 2003 negotiations, the sponsor submitted this supplement which provides changes to the **WARNINGS - Serous Inflammation and Fibrosis** subsection as agreed upon and as distributed in a Dear Health Care Professional letter.

After comparing the last approved label, S-028 (PV 2278) to the most recent proposed label (5.01 PV 2271-A-UCP) dated February 13, 2003, the following differences were noted:

1. **DESCRIPTION** section – Agency recommended changes as described in an 8/29/02 letter. (S-028)
2. **WARNINGS – Serous Inflammation and Fibrosis** subsection, Agency recommended changes as described in an Agency letter dated November 7, 2002 and negotiated on January 29, 2003. (S-035)
3. **WARNINGS – Falling Asleep During Activities of Daily Living** subsection, counter-proposed language. In particular, there are changes throughout that lessen the degree of severity. (S-030)
4. **PRECAUTIONS – Information to Patients** subsection, new language provided in an effort to be compatible with the language provided in **WARNINGS – Falling Asleep During Activities of Daily Living** subsection. (S-030)
5. **PRECAUTIONS – Geriatric Use** subsection, the Agency December 19, 2002 recommended language was adopted. (S-031)
6. **HOW SUPPLIED** – the Agency August 29, 2002 requested changes to the tablet description and the storage conditions. (S-028)

Conclusions

Of the six changes noted above items #3 and #4 are not language provided by the Agency.

Therefore, if the medical officer finds all of the changes including the counter-proposed language (item #3) and the associated changes to the **PRECAUTIONS – Information to Patients** subsection (item #4) acceptable, then I recommend that an approval letter issue for S-030, S-031, and S-035.

If the medical reviewer finds item #3 and/or #4 unacceptable, then I recommend that an approval letter issue for S-031 and S035 and that another approvable letter issue for S-030.

CDR Teresa Wheelous
Sr. Regulatory Management Officer

Robbin Nighswander
Supervisory Regulatory Project Manager

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

/s/

Teresa Wheelous
8/5/03 11:10:18 AM
CSO

Robbin Nighswander
8/6/03 02:44:15 PM
CSO