

PERMAX[®]

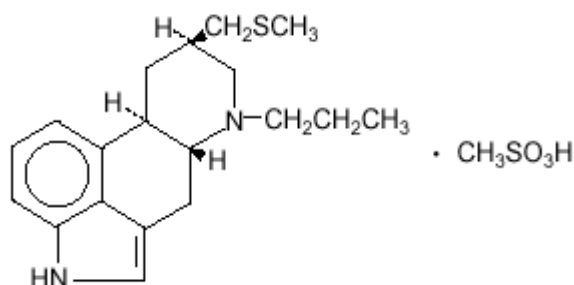
(pergolide mesylate).

PERMAX can cause fibrotic reactions and cardiac valvulopathy. Ongoing treatment will require continued monitoring for these adverse events.

Pergolide mesylate is an ergot derivative dopamine receptor agonist at D₁, D₂ and D₃ receptor sites. Pergolide mesylate is chemically designated as 8 β-[(Methylthio)methyl]-6-propylergoline monomethanesulfonate.

The formula weight of the base is 314.5; 1 mg of base corresponds to 3.18 micromol. The CAS number for pergolide is 66104-22-1.

Pergolide mesylate has the following structural formula:



Description

Pergolide mesylate is provided for oral administration in tablets containing 0.05, 0.25, and 1 mg pergolide as the base. The pharmaceutical excipients are lactose, croscarmellose sodium, povidone, magnesium stearate, iron oxide yellow (0.05 and 0.25 mg tablets), methionine (0.05 mg tablet), iron oxide red (1 mg tablet), and indigo carmine - aluminium lake (0.25 mg tablet).

Clinical Pharmacology

Pharmacodynamic Information

Pergolide is a dopamine receptor agonist which exhibited high *in vitro* binding affinities for the D₁, D₂ and D₃ receptors (respective K_i values of 180, 33 and 4.2 nM). Pergolide has been shown to be 20 to 200 times more potent than bromocriptine on a milligram for milligram basis *in vivo*. 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 luteinising 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 single doses. However, following oral administration of ¹⁴C radiolabelled pergolide mesylate, approximately 55% of the administered radioactivity can be recovered from the urine, 40% from the faeces 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 post absorption 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 via 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.

PERMAX has not been systematically assessed as sole treatment for Parkinson's disease or as therapy in newly diagnosed patients. Limited data are available on the efficacy and safety of pergolide when used with levodopa-benserazide combinations.

Indications

Pergolide mesylate is indicated as second line therapy in patients who are intolerant or fail treatment with a non-ergot compound, as adjunctive treatment with levodopa in combination with decarboxylase inhibitors in the treatment of Parkinson's disease.

Treatment should be initiated under specialist supervision. The benefit of continued treatment should be regularly reassessed taking into account the risk of fibrotic reactions and valvulopathy (see "Contraindications", "Precautions" and "Adverse Effects").

Contraindications

Pergolide mesylate is contraindicated in patients who:

- are hypersensitive to this drug or other ergot derivatives, or any of its pharmaceutical excipients (see DESCRIPTION).
- Have a history of pulmonary, pericardial, or retroperitoneal fibrotic disorders
- Have anatomical evidence of cardiac valvulopathy of any valve (e.g. echocardiogram showing valve leaflet thickening, valve restriction, valve mixed restriction-stenosis).

Precautions

Valvulopathy and respiratory disorders linked to fibrotic tissue degeneration

Fibrotic and serosal inflammatory disorders such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving one or more valves (aortic, mitral, and tricuspid) or retroperitoneal fibrosis have occurred after prolonged usage of ergot derivatives such as pergolide. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of pergolide.

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

Before Initiating Treatment

Before initiating treatment with PERMAX, all patients should undergo a cardiovascular examination, including an echocardiogram, to assess potential presences of symptomatic valvular disease. It may also be appropriate to perform baseline investigations of ESR or other inflammatory markers, lung function/chest X-ray, and renal function prior to initiation of therapy. If fibrotic valvular disease is detected, the patient should not be treated with PERMAX (see “Contraindications”).

During Treatment

Fibrotic disorders can have an insidious onset and patients should be regularly monitored for the symptoms and signs of progressive fibrosis. These include:

- Pleuropulmonary disease – dyspnoea, shortness of breath, persistent cough, or chest pain
- Renal insufficiency, or ureteral obstruction or abdominal valvular obstruction that may occur with pain in the loin and/or flank, and lower limb oedema, as well as any possible abdominal masses or tenderness that may indicate retroperitoneal fibrosis
- Cardiac failure, as cases of pericardial fibrosis have often presented as cardiac failure; constrictive pericarditis should be excluded if such symptoms appear.
- Cardiac failure, as cases of valvular fibrosis have often presented as cardiac failure; valvular fibrosis should be excluded if such symptoms appear.

Clinical diagnostic monitoring for the development cardiac valvular disease or fibrosis, as appropriate, is recommended. Following the initial echocardiogram prior to initiation of treatment, the next echocardiogram should occur within the first 3-6 months of treatment. Thereafter, the frequency of echocardiogram monitoring should be determined by appropriate individual clinical assessment with particular emphasis on the above mentioned signs and symptoms, but should occur every 6 to 12 months.

PERMAX should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction or valvular leaflet thickening (see “Contraindications”). The need for other clinical monitoring (e.g. physical examination, cardiac auscultation, X-ray, echocardiogram, CT scans) should be determined on an individual basis.

Hypotension - Advice to Patients

Patients should be warned to begin therapy with low doses and to increase dosage in carefully adjusted increments over a period of 3 to 4 weeks (see DOSAGE AND ADMINISTRATION) to minimise the risk of symptomatic postural and/or sustained hypotension. With gradual dosage titration, tolerance to the hypotension usually develops (see PRECAUTIONS - Drug Interactions).

In clinical trials, approximately 10% of patients taking pergolide mesylate with *l*-dopa vs. 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.

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 pre-marketing studies, 6.2 per cent died while on the drug or shortly after discontinuation. The patient population under evaluation was elderly, ill and at high risk for death. A case-by-case review 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 these deaths.

Hallucinosi

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.

General

It is recommended that patients receiving pergolide for the first time undergo a detailed medical examination, to include monitoring of white cell counts and liver function tests. It is further suggested that this monitoring be continued on a yearly basis.

Use in patients on *L*-dopa may cause and/or exacerbate pre-existing states of confusion and hallucinations (see ADVERSE REACTIONS). Abrupt discontinuation of pergolide, 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, even if the patient is to remain on *L*-dopa.

A symptom complex resembling the neuroleptic malignant syndrome (NMS) (characterised 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.

Administration to patients receiving *L*-dopa may cause and/or exacerbate pre-existing dyskinesia.

Caution should be exercised when administering pergolide mesylate to patients prone to cardiac dysrhythmias. The safety of pergolide mesylate has not been established in the presence of hepatic or renal disease.

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.

Do not crush tablets. Caution is advised to minimize exposure risks when splitting tablets. In spontaneous cases, reports of eye irritation, irritating smell, or headache when pergolide mesylate tablets were split or crushed have been identified. In animal studies, pergolide mesylate was found to cause eye irritation and inhalation toxicity. In the event of pergolide mesylate powder exposure to the eye, the affected eye should be flushed immediately with water, and medical advice obtained. For nasal irritation, move to fresh air.

Somnolence / Sudden Sleep Onset

Pergolide has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported rarely.

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 PRECAUTIONS - Hypotension).

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's Disease. Health care professionals should

inform patients to seek help from their doctor if they, their family or their carer notice that their behaviour is unusual.

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

While no specific laboratory tests are deemed essential for the management of patients on pergolide mesylate, periodic routine evaluation is appropriate. Abnormalities in laboratory tests may include elevations of AST, ALT, alkaline phosphatase and urea nitrogen. Leucopenia has been reported.

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.

There are no clinical studies involving the concomitant administration of pergolide and warfarin. When these two drugs are co-prescribed, careful monitoring of anticoagulation should be performed, with adjustments of dosage as necessary.

Because of the risk of postural and/or sustained hypotension in patients taking pergolide, caution should be exercised if it is co-administered with antihypertensive agents.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

A 2-year carcinogenicity study was conducted in mice using dietary doses of pergolide mesylate 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, equivalent to approximately 0.5, 4 and 35 times the maximal recommended human dose on a body surface area basis. A 2-year study in rats was conducted using dietary 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, equivalent to approximately 0.1, 0.4 and 2 times the maximal recommended human dose on a body surface area basis.

A low incidence of uterine neoplasms occurred in both species. Endometrial adenomas and carcinomas were observed in rats and endometrial sarcomas were observed in mice. The occurrence of these neoplasms is probably attributable to the high oestrogen/progesterone ratio which 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 bacterial gene mutation assays, a point-mutation assay in cultured L5178Y mouse lymphoma cells, a chromosomal damage assay in Chinese hamster ovary cells, a DNA repair assay in cultured rat hepatocytes and an *in vivo* sister chromatid exchange assay in Chinese hamster bone marrow cells. A weak mutagenic response was noted in the *in vitro* mammalian cell-point-mutation assay in L5178Y cells only after metabolic activation with rat liver microsomes. The relevance of this finding to humans is unknown. No genotoxic effects

were observed in the other assays.

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, equivalent to approximately 0.5, 1.5 and 5 times the maximal recommended human dose on a body surface area basis, respectively. Prolactin has been reported to be involved in stimulating and maintaining progesterone levels required for implantation in mice and, therefore, the impaired fertility at high dose may occur because of depressed prolactin levels.

Usage in Pregnancy

Pregnancy Category C

Reproduction studies were conducted in mice at doses of 5, 16, and 45 mg/kg/day and in rabbits at doses of 2, 4, 8 and 16 mg/kg/day. These doses were equivalent to approximately 5, 15 and 41 times (mice) and 7, 13, 27 and 53 times (rabbits) the maximal recommended human dose on a body surface area basis, respectively. In these studies, there was no evidence of harm to the foetus 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.

Paediatric Use

Safety and effectiveness in children have not been established.

Effects on the Ability to Drive and Use Machinery

Patients should be cautioned about operating hazardous machinery, including motor vehicles, while taking pergolide because pergolide may cause somnolence or rarely episodes of sudden onset of sleep.

Adverse Reactions

Side-effects

The following adverse events, which are listed in decreasing order of frequency under body system, were observed during placebo-controlled clinical trials at a frequency of one per cent or greater and at a significantly higher incidence than placebo (P value less than or equal to 0.05):

Body as a whole: pain, abdominal pain.

Digestive system: nausea, dyspepsia.

Nervous system: dyskinesia, hallucinations, somnolence, insomnia.

Respiratory system: rhinitis, dyspnoea.

Special senses: diplopia.

Cardiovascular system: atrial premature contractions.

Other events that have been reported include:

Nervous system: confusion, dizziness.

Digestive system: constipation, diarrhoea, vomiting.

Cardiovascular system: hypotension, sinus tachycardia, palpitation, syncope.

Skin and appendages: rash.

Other uncommon or rare undesirable effects include:

Fever, liver function tests abnormal, hiccups and erythromelalgia (warm, red, painful swelling of the extremities).

Twenty-seven percent of 1,200 patients receiving PERMAX for the treatment of Parkinson's disease in U.S. and Canadian trials discontinued due to adverse events. The more common events that caused discontinuation were related to the nervous system, primarily hallucinations and confusion.

Certain adverse experiences (e.g. dyskinesia, hallucinations) are frequently observed in patients receiving levodopa, pergolide and/or other dopamine agonists. These experiences are dose related and tend to improve with dosage reduction of levodopa or of pergolide.

Postural hypotension and nausea are most frequently reported during the initial titration phase.

Post Introduction 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 (with rapid de-titration of pergolide); sudden onset of sleep; Raynaud's phenomenon.

Following market introduction, there have been reports of cases of fibrotic and serosal inflammatory conditions such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, retroperitoneal fibrosis or cardiac valvulopathy in patients taking pergolide (see PRECAUTIONS).

Patients treated with dopamine agonists for treatment of Parkinson's Disease, including pergolide, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality. These effects are generally reversible upon reduction of the the dose or treatment discontinuation.

Dosage and Administration

Administration of pergolide mesylate should be initiated with a daily dosage of 50 micrograms for the first 2 days. The dosage should then be gradually increased by 100 or 150 micrograms/day every third day over the next 12 days of therapy. The dosage may then be increased by 250 micrograms/day every third day until an optimal therapeutic dosage is achieved.

Pergolide mesylate is usually administered in divided doses 3 times per day. During dosage titration, the dosage of concurrent *L*-dopa/decarboxylase inhibitor may be cautiously decreased.

In clinical studies, the mean therapeutic daily dosage of pergolide mesylate was 3 mg/day and the average concurrent daily dosage of *L*-dopa/carbidopa (expressed as *L*-dopa) was approximately 650 mg/day.

The risk of fibrosis is substantially increased at pergolide doses above 3 mg/day. A dose of 3

mg/day should not be exceeded (see Precautions – Valvulopathy and respiratory disorders linked to fibrotic tissue degeneration).

Overdosage

There is no clinical experience with massive overdosage. Overdoses of 60 mg on one day, 19 mg/day for 3 days, or 14 mg/day for 23 days have occurred. Symptoms and signs included vomiting, hypotension, agitation, severe hallucinations, severe involuntary movements and tingling sensations. Another patient who inadvertently received 7 mg, instead of the prescribed 0.7 mg (700 micrograms), experienced palpitations, hypotension and ventricular extrasystoles. The highest daily dose (prescribed for several patients with refractory Parkinson's disease) has exceeded 30 mg. (The safety and efficacy of doses above 5mg/day have not been systematically evaluated.)

In animals, manifestations of overdosage include vomiting, convulsions, decreased blood pressure and CNS stimulation.

Treatment

Symptomatic supportive therapy and cardiac monitoring is recommended. Arterial blood pressure should be maintained. An antiarrhythmic agent may be necessary. If signs of CNS stimulation are present, a phenothiazine, or other butyrophenone neuroleptic agent, may be indicated.

Activated charcoal may be considered. Dialysis or haemoperfusion are unlikely to be of benefit.

Presentation

Tablets No. 4131 PERMAX (ivory), containing pergolide mesylate equivalent to 0.05 mg pergolide in blister packs of 100.

Tablets No. 4133 PERMAX (green), containing pergolide mesylate equivalent to 0.25 mg pergolide in blister packs of 100.

Tablets No. 4135 PERMAX (pink), containing pergolide mesylate equivalent to 1.0 mg pergolide in blister packs of 100.

Pharmaceutical Precautions

Store below 25°C. Protect from light.

Shelf Life

Shelf life is 2 years.

Major Incompatibilities

None stated.

Medicine Classification

Prescription Medicine.

Name and Address

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