3.2.2.3.2.20 Pergolide for sexual enhancement

Permax (generic name: pergolide mesylate) is ergot-derived medication with similarity to Parlodel (generic name: bromocriptine) and cabergoline (brand name: Dostinex). Like bromocriptine and cabergoline, pergolide can be used for sexual enhancement, or, more specifically, as support for sexual excitement, orgasm, and ejaculation.

(The following is pharmacological data from the Permax package insert. Please be aware that the dosage information applies to the treatment of Parkinson's disease, not for sexual enhancement. Dosages for sexual enhancement are much lower than those for the treatment of Parkinson's disease.)

Permax (pergolide mesylate) is an ergot derivative dopamine receptor agonist at both D1 and D2receptor sites. Permax is provided for oral administration in tablets containing 0.05 m, 0.25 mg, or 1 mg pergolide as the base.

Pergolide mesylate is a potent dopamine receptor agonist. Pergolide is 10 to 1,000 times more potent than bromocriptine on a milligram per milligram basis in various in vitro and in vivotest 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.

The major route of excretion is the kidney.

Permax is indicated as adjunctive treatment to levodopa/carbidopa in the management of the signs and symptoms of Parkinson's disease.

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.

Store at controlled room temperature, 59 to 86 F (15degree celsius to 30degree celsius).

US law prohibits dispensing without prescription.

Side effects

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 systemcomplaints, including rhinitis.

Twenty-seven percent (27%) of approximately 1,200 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%). 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 month,s 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.

Incidence of Treatment-Emergent Adverse Experiences in the

Placebo-Controlled Clinical Trial Percentage of Patients Reporting Events

Body System/Adverse Event*

Pergolide Mesylate

Placebo

N= 189

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

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

Confusion

11.1

9.6

Somnolence

10.1

3.7

Insomnia

7.9

nxiety

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 Svstem

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.

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.

Hallucinosis

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

Fatalities

In the placebo-controlled trial, 2 of 187 patients treated with placebo died as compared with 1 of 189 patients treated with pergolide mesylate. Of the 2,299 patients treated with pergolide mesylate in premarketing studies evaluated as of October 1988, 143 died while on the drug or shortly after discontinuing it. Because the patient population under evaluation was elderly, ill, and at high risk death, it seems unlikely that pergolide mesylate played any role in these

deaths, but the possibility that pergolide shortens survival of patients cannot be excluded with absolute certainty.

In particular, a case-by-case review of the clinical course of the patients who died failed to disclose any unique set of signs, symptoms, or laboratory results that would suggest that treatment with pergolide caused their deaths. Sixty-eight percent (68%) of the patients who died were 65 years of age or older. No death (other than a suicide) occurred within the first month of treatment; most of the patients who died had been on pergolide for years. A relative frequency of the causes of death by organ system are:

Pulmonary failure/Pneumonia, 35%;
Cardiovascular, 30%;
Cancer, 11%;
Unknown, 8.4%;
Infection, 3.5%;
Extrapyramidal syndrome, 3.5%;
Stroke, 2.1%;
Dysphagia, 2.1%;
Injury, 1 .4 %;
Suicide, 1.4%;
Dehydration, 0.7%;
Glomerulonephritis, 0.7%.

Serious Inflammation and Fibrosis

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

Precautions

Caution should be exercised when administering pergolide mesylate to patients proneto cardiac dysrhythmias.

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

The use of pergolide mesylate in patients on l-dopa may cause and/or exacerbate preexisting states of confusion and hallucinations 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.

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.

Animal studies indicate that the manifestations of over-dosage 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.