DEMSER®
(METYROSINE)
Capsules

DESCRIPTION

DEMSER® (Metyrosine) is (α–)-α-methyl-L-tyrosine or (α-MPT). It has the following structural formula:

Metyrosine is a white, crystalline compound of molecular weight 195. It is very slightly soluble in water, acetone, and methanol, and insoluble in chloroform and benzene. It is soluble in alkaline aqueous solutions. It is also soluble in alkaline aqueous solutions, but is subject to oxidative degradation under these conditions.

DEMSER is supplied as capsules, for oral administration. Each capsule contains 250 mg metyrosine.

Inactive ingredients are colloidal silicon dioxide, gelatin, hydroxypropyl cellulose, magnesium stearate, titanium dioxide, and FD&C Blue 2.

CLINICAL PHARMACOLOGY

DEMSER inhibits tyrosine hydroxylase, which catalyzes the first transformation in catecholamine biosynthesis, i.e., the conversion of tyrosine to dihydroxyphenylalanine (DOPA). Because the first step is also the rate-limiting step, blockade of tyrosine hydroxylase activity results in decreased endogenous levels of catecholamines, usually measured as decreased urinary excretion of catecholamines and their metabolites.

In patients with pheochromocytoma, who produce excessive amounts of norepinephrine and epinephrine, administration of one to four grams of DEMSER per day has reduced catecholamine biosynthesis from about 35 to 80 percent as measured by the total excretion of catecholamines and their metabolites (metanephrine and vanillylmandelic acid). The maximum biochemical effect usually occurs within two to three days, and the urinary concentration of catecholamines and their metabolites usually returns to pretreatment levels within three to four days after DEMSER is discontinued. In some patients the total excretion of catecholamines and catecholamine metabolites may be lowered to normal or near normal levels (less than 10 mg/24 hours). In most patients the duration of treatment has been two to eight weeks, but several patients have received DEMSER for periods of one to 10 years.

Most patients with pheochromocytoma treated with DEMSER experience decreased frequency and severity of hypertensive attacks with their associated headache, nausea, sweating, and tachycardia. In patients who respond, blood pressure decreases progressively during the first two days of therapy with DEMSER; after withdrawal, blood pressure usually increases gradually to pretreatment values within two to three days.

Metyrosine is well absorbed from the gastrointestinal tract. From 53 to 88 percent (mean 69 percent) was recovered in the urine as unchanged metyrosine. Plasma concentrations of metyrosine do not increase significantly during long-term administration of doses of 2 g/day or less, but increase proportionately with doses greater than 2 g per day are given. Routine examination of the urine should be carried out. Metyrosine will crystallize as needles or rods. If metyrosine crystalluria occurs, fluid intake should be increased further. If crystalluria persists, the dosage should be reduced or the drug discontinued.

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Plasma half-life of metyrosine determined over an 8-hour period after single oral doses was 3-3.7 hours in three patients.


INDICATIONS AND USAGE

DEMSER is indicated in the treatment of patients with pheochromocytoma for:
1. Preoperative preparation of patients for surgery
2. Management of patients when surgery is contraindicated
3. Chronic treatment of patients with malignant pheochromocytoma

DEMSER is not recommended for the control of essential hypertension.

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CONTRAINDICATIONS

DEMSER is contraindicated in persons known to be hypersensitive to this compound.

WARNINGS

Maintain Fluid Volume During and After Surgery

When DEMSER is used preoperatively, alone or especially in combination with alpha-adrenergic blocking drugs, adequate intravascular volume must be maintained preoperatively (especially after tumor removal) and postoperatively to avoid hypotension and decreased perfusion of vital organs resulting from vasodilatation and expanded volume capacity. Following tumor removal, large volumes of plasma may be needed to maintain blood pressure and central venous pressure within the normal range.

In addition, life-threatening arrhythmias may occur during anesthesia and surgery, and may require treatment with a beta-blocker or lidocaine. During surgery, patients should have continuous monitoring of blood pressure and electrocardiogram.

Intraoperative Effects

While the preoperative use of DEMSER in patients with pheochromocytoma is thought to decrease intraoperative problems with blood pressure control, DEMSER does not eliminate the danger of hypertensive crises or arrhythmias during manipulation of the tumor, and the alpha-adrenergic blocking drug, phentolamine, may be needed.

Interaction with Alcohol

DEMSER may add to the sedative effects of alcohol and other CNS depressants, e.g., hypnotics, sedatives, and tranquilizers. (See PRECAUTIONS, Information for Patients and Drug Interactions.)

PRECAUTIONS

General

Metyrosine Crystalluria: Crystalluria and urolithiasis have been found in dogs treated with DEMSER (Metyrosine) at doses similar to those used in humans, and crystalluria has also been observed in a few patients. To minimize the risk of crystalluria, patients should be urged to maintain fluid intake sufficient to achieve a daily urine volume of 2000 mL or more, particularly when doses greater than 2 g per day are given. Routine examination of the urine should be carried out. Metyrosine will crystallize as needles or rods. If metyrosine crystalluria occurs, fluid intake should be increased further. If crystalluria persists, the dosage should be reduced or the drug discontinued.

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Chronic animal studies have not been carried out. Therefore, suitable laboratory tests should be carried out periodically in patients requiring prolonged use of DEMSER and caution should be observed in patients with impaired hepatic or renal function.

Information for Patients

When receiving DEMSER, patients should be warned about engaging in activities requiring mental alertness and motor coordination, such as driving a motor vehicle or operating machinery. DEMSER may have additive sedative effects with alcohol and other CNS depressants, e.g., hypnotics, sedatives, and tranquilizers.

Patients should be advised to maintain a liberal fluid intake. (See PRECAUTIONS, General.)

Drug Interactions

Caution should be observed in administering DEMSER to patients receiving phenothiazines or haloperidol because the extrapyramidal effects of these drugs can be expected to be potentiated by inhibition of catecholamine synthesis.

Concurrent use of DEMSER with alcohol or other CNS depressants can increase their sedative effects. (See PRECAUTIONS, Information for Patients and Drug Interactions.)

Laboratory Test Interference

Spurious increases in urinary catecholamines may be observed in patients receiving DEMSER due to the presence of metabolites of the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenic studies in animals and studies on mutagenesis and impairment of fertility have not been performed with metyrosine.

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The acute toxicity of metyrosine was 442 mg/kg and 752 mg/kg in the female mouse and rat respectively.

Reduction of drug dose or cessation of treatment results in the disappearance of these symptoms. Diarrhea, and decreased salivation with dry mouth.

Agitated depression, neuromuscular effects (including fine tremor of the hands, gross tremor of the trunk, tightening of the jaw with trismus), and SGOT levels, peripheral edema, and hypersensitivity reactions such as urticaria and pharyngeal edema have been reported rarely.

Hematologic disorders (including eosinophilia, anemia, thrombocytopenia, and thrombocytosis), increased abdominal pain, and impotence or failure of ejaculation may occur. Crystalluria (see PRECAUTIONS) and transient dysuria and hematuria have been observed in a few patients. Hematologic disorders (including eosinophilia, anemia, thrombocytopenia, and thrombocytosis), increased SGOT levels, peripheral edema, and hypersensitivity reactions such as urticaria and pharyngeal edema have been reported rarely.

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

Signs of metyrosine overdosage include those central nervous system effects observed in some patients even at low dosages.

At doses exceeding 2000 mg/day, some degree of sedation or feeling of fatigue may persist. Doses of 2000-4000 mg/day can result in anxiety or agitated depression, neuromuscular effects (including fine tremor of the hands, gross tremor of the trunk, tightening of the jaw with trismus), diarrhea, and decreased salivation with dry mouth.

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