FRONT

MedChoice CNS

℞

Memantine Hydrochloride

Memandin

10 mg Film-Coated Tablet

ANTI-DEMENTIA

FORMULATION:

Each film-coated tablet contains:

Memantine Hydrochloride .....10 mg

Excipients ..... q.s.

Colour: Yellow Oxide of Iron, Indigo Carmine & Titanium Dioxide

PRODUCT DESCRIPTION:

Olive green coloured, round shape, biconvex, film-coated tablet, plain on both sides.

PHARMACEUTICAL DOSAGE FORM:

Tablet

PHARMACOLOGY:

Mechanism of Action and Pharmacodynamics

Persistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease. Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels. There is no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer's disease.

Memantine showed low to negligible affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine and glycine receptors and for voltage-dependent Ca2+, Na+ or K+ channels. Memantine also showed antagonistic effects at the 5HT3 receptor with a potency similar to that for the NMDA receptor and blocked nicotinic acetylcholine receptors with one-sixth to one-tenth the potency.

In vitro studies have shown that memantine does not affect the reversible inhibition of acetylcholinesterase by donepezil, galantamine, or tacrine.

Pharmacokinetics

Memantine is well absorbed after oral administration and has linear pharmacokinetics over the therapeutic dose range. It is excreted predominantly in the urine, unchanged, and has a terminal elimination half life of about 60-80 hours.

Absorption and Distribution

Following oral administration memantine is highly absorbed with peak concentrations reached in about 3-7 hours. Food has no effect on the absorption of memantine. The mean volume of distribution of memantine is 9-11 L/kg and the plasma protein binding is low (45%).

Metabolism and Elimination

Memantine undergoes partial hepatic metabolism. About 48% of administered drug is excreted unchanged in urine; the remainder is converted primarily to three polar metabolites which possess minimal NMDA receptor antagonistic activity: the N-glucuronide conjugate, 6-hydroxy memantine, and 1- nitroso-deaminated memantine. A total of 74% of the administered dose is excreted as the sum of the parent drug and the N-glucuronide conjugate. The hepatic microsomal CYP450 enzyme system does not play a significant role in the metabolism of memantine. Memantine has a terminal elimination half-life of about 60-80 hours. Renal clearance involves active tubular secretion moderated by pH dependent tubular reabsorption.

THERAPEUTIC INDICATIONS:

Memantine hydrochloride is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

DOSAGE AND ADMINISTRATION:

The recommended starting dose of memantine hydrochloride is 5 mg once daily. The recommended target dose is 20 mg/day. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses) and 20 mg/day (10 mg twice a day). The minimum recommended interval between dose increases is one week. Memantine hydrochloride can be taken with or without food.

Doses in Special Populations: A target dose of 5 mg BID is recommended in patients with severe renal impairment or as directed by the Physician.

CONTRAINDICATIONS:

Memantine hydrochloride is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

WARNING & PRECAUTIONS:

Information for Patients and Caregivers: Caregivers should be instructed in the recommended administration (twice per day for doses above 5 mg) and dose escalation (minimum interval of one week between dose increases).

Neurological Conditions

Seizures: Memantine has not been systematically evaluated in patients with a seizure disorder. In clinical trials of memantine, seizures occurred in 0.2% of patients treated with memantine and 0.5% of patients treated with placebo.

Genitourinary Conditions

Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine.

Special Populations

Hepatic Impairment:

Memantine undergoes partial hepatic metabolism, with about 48% of administered dose excreted in urine as unchanged drug or as the sum of parent drug and the N-glucuronide conjugate (74%). No dosage adjustment is needed in patients with mild or moderate hepatic impairment. Memantine should be administered with caution to patients with severe hepatic impairment.

Renal Impairment

No dosage adjustment is needed in patients with mild or moderate renal impairment. A dosage reduction is recommended in patients with severe renal impairment.

FERTILITY, PREGNANCY AND LACTATION:

Pregnancy

There are no or limited amount of data from the use of memantine in pregnant women. Animal studies indicate a potential for reducing intrauterine growth at exposure levels, which are identical or slightly higher than at human exposure. The potential risk for humans is unknown. Memantine should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is not known whether memantine is excreted in human breast milk but, taking into consideration the lipophilicity of the substance, this probably occurs. Women taking memantine should not breast-feed.

Fertility

No adverse reactions of memantine were noted on male and female fertility.

DRUG INTERACTIONS:

N-methyl-D-aspartate (NMDA) antagonists: The combined use of memantine with other NMDA antagonists (amantadine, ketamine and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

Effects of memantine on substrates of microsomal enzymes: In vitro studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. In addition, in vitro studies indicate that at concentrations exceeding those associated with efficacy, memantine does not induce the cytochrome P450 isozymes CYP1A2, CYP2C9, CYP2E1 and CYP3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Effects of inhibitors and/or substrates of microsomal enzymes on memantine: Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.

Acetylcholinesterase (AChE) inhibitors: Co-administration of memantine with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine and donepezil was similar to that of donepezil alone.

Drugs eliminated via renal mechanisms: Because memantine is eliminated in part by tubular secretion, co-administration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), metformin, cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of Memantine and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%.

Drugs that make the urine alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.

OVERDOSAGE AND TREATMENT:

Signs and symptoms associated with memantine overdosage in clinical trials and from worldwide marketing experience include agitation, confusion, ECG changes, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting and weakness. The largest known ingestion of memantine worldwide was 2.0 grams in a patient who took memantine in conjunction with unspecified antidiabetic medications. The patient experienced coma, diplopia, and agitation, but subsequently recovered.

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug.

As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic.

Elimination of memantine can be enhanced by acidification of urine.

ADVERSE EFFECTS:

Fatigue, pain, dizziness, headache, hypertension & joint pain may occur. Serious side effects: mental/mood changes (e.g., depression, agitation, anxiety), swelling of hands or feet, trouble breathing.

SHELF-LIFE:

36 months from the date of manufacturing.

CAUTION:

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

"For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction."

STORAGE CONDITION:

Store at a temperature not exceeding 30°C. Protect from light & moisture.

Keep out of the reach of children.

AVAILABILITY:

Alu/alu blister pack x 10's (Box of 30's).

DRP-6167

Date of First Authorization:

Date of Revision of Package Insert:

Manufactured by:
SYDLER REMEDIES PVT. LTD.
Plot No. C-7-8 (2), M.I.D.C., Bhosari,
Pune-411026, Maharashtra State, India

Imported by:
AMBICA INTERNATIONAL CORPORATION
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Distributed by:
MEDCHOICE CNS PHARMA CORPORATION
10F Unit 1001 88 Corporate Center Sedeño cor.
Valero Sts., Salcedo Village, Makati City, Makati, Metro Manila

170 mm

120 mm

120 mm