Mexazil® XR

Memantine HCl Extended Release and Donepezil HCl

FORMS AND PRESENTATION

Mexazil® XR 14/10: Capsules: Box of 30.
Mexazil® XR 28/10: Capsules: Box of 30.

COMPOSITION

Mexazil® XR 14/10: Each capsule contains Memantine HCl Extended Release 14mg and Donepezil HCl 10mg.
Mexazil® XR 28/10: Each capsule contains Memantine HCl Extended Release 28mg and Donepezil HCl 10mg.
Excipients: sugar spheres, ethylcellulose, hydroxypropylmethyl cellulose, talc, lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide, titanium dioxide, gelatin, sodium lauryl sulphate, iron oxide red (Mexazil® XR 28/10).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Mexazil® XR is a combination of memantine extended-release, an N-methyl-D-aspartate (NMDA) receptor antagonist, and donepezil, an acetylcholinesterase inhibitor.

Mechanism of Action

Mexazil® XR capsules contain two approved medications: memantine hydrochloride and donepezil hydrochloride. Each of those medications is postulated to have a different mechanism in Alzheimer's disease.

Memantine

Persistent activation of central nervous system 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.

Donepezil

Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's disease attribute some of them to a deficiency of cholinergic neurotransmission. Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine in the central nervous system through reversible inhibition of its hydrolysis by acetylcholinesterase. There is no evidence that donepezil prevents or slows neurodegeneration in patients with Alzheimer's disease.

Pharmacokinetic properties

Mexazil® XR was bioequivalent to co-administration of individual memantine hydrochloride extended-release and donepezil hydrochloride.

Exposure (AUC and Cmax) of memantine and donepezil following Mexazil® XR administration in the fed or fasted state was similar. Further, exposure of memantine and donepezil following Mexazil® XR administration as intact capsule or capsule contents sprinkled on applesauce was similar in healthy subjects.

Memantine Hydrochloride

Memantine is well absorbed after oral administration and has linear pharmacokinetics over the therapeutic dose range. It is excreted predominantly unchanged in urine and has a terminal elimination half-life of about 60-80 hours. In a study comparing 28 mg once-daily memantine hydrochloride extended-release to 10 mg twice-daily memantine hydrochloride, Cmax and AUC 0-24 values were 48% and 33% higher for the memantine hydrochloride extended-release dosage regimen, respectively.

Absorption

After multiple dose administration of memantine hydrochloride extended-release, memantine peak concentrations occur around 9-12 hours postdose. There is no difference in the absorption of memantine hydrochloride extended-release when the capsule is taken intact or when the contents are sprinkled on applesauce.

After single-dose administration, there is no difference in memantine exposure, based on Cmax or AUC, for memantine hydrochloride extended-release when the drug product is administered with food or on an empty stomach. However, peak plasma concentrations are achieved about 18 hours after administration with food versus approximately 25 hours after administration on an empty stomach.

Distribution

The mean volume of distribution of memantine is 9-11 L/kg and the plasma protein binding is low (45%).

Metabolism

Memantine undergoes partial hepatic metabolism. The hepatic microsomal CYP450 enzyme system does not play a significant role in the metabolism of memantine.

Elimination

Memantine is excreted predominantly in the urine, unchanged, and has a terminal elimination half-life of about 60-80 hours. 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. Renal clearance involves active tubular secretion moderated by pH dependent tubular reabsorption.

INDICATIONS

Mexazil® XR is indicated for the treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on 10 mg of donepezil hydrochloride once daily.

CONTRAINDICATIONS

Mexazil® XR is contraindicated in patients with known hypersensitivity to memantine hydrochloride, donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation.

PRECAUTIONS

Anesthesia

Donepezil hydrochloride, an active ingredient in Mexazil® XR, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Cardiovascular Conditions

Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of donepezil hydrochloride, an active ingredient in Mexazil® XR.

Peptic Ulcer Disease and Gastrointestinal Bleeding

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Patients treated with Mexazil® XR should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs).

Nausea and Vomiting

Donepezil hydrochloride, an active ingredient in Mexazil® XR, when initiated, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea, and vomiting. Although in most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of donepezil hydrochloride, patients should be observed closely at the initiation of treatment.

Genitourinary Conditions

Although not observed in clinical trials of donepezil hydrochloride, an active ingredient in Mexazil® XR, cholinomimetics may cause bladder outflow obstruction. Conditions that raise urine pH may decrease the urinary elimination of memantine, an active ingredient in Mexazil® XR, resulting in increased plasma levels of memantine.

Seizures

Cholinomimetics, including donepezil hydrochloride, an active ingredient in Mexazil® XR, are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's disease.

Pulmonary Conditions

Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

PREGNANCY AND LACTATION

Pregnancy

There are no adequate data on the developmental risk associated with the use of Mexazil® XR or its active ingredients (memantine hydrochloride and donepezil hydrochloride) in pregnant women. Adverse developmental effects (mortality and decreased body weight and skeletal ossification) were observed in the offspring of rats administered memantine or donepezil during pregnancy at doses associated with minimal maternal toxicity. These doses are higher than those used in humans at the recommended daily dose of Mexazil® XR.

Lactation

There are no data on the presence of memantine or donepezil in human milk, the effects on the breastfed infant, or the effects of Mexazil® XR or its metabolites on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Mexazil® XR and any potential adverse effects on the breastfed infant from Mexazil® XR or from the underlying maternal condition.

DRUG INTERACTIONS

Use of Memantine with 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 reactions. 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.

Use of Memantine with Other N-methyl-D-aspartate (NMDA) Antagonists

The combined use of memantine hydrochloride with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

Effect of Other Drugs on the Metabolism of Donepezil

Inhibitors of CYP3A4 (e.g., ketoconazole) and CYP2D6 (e.g., quinidine), inhibit donepezil metabolism in vitro. Whether there is a clinical effect of quinidine is not known. Inducers of CYP3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of donepezil.

Use of Donepezil with Anticholinergics

Because of their mechanism of action, cholinesterase inhibitors, including donepezil hydrochloride, have the potential to interfere with the activity of anticholinergic medications.

Use of Donepezil with Cholinomimetics and Other Cholinesterase Inhibitors

A synergistic effect may be expected when cholinesterase inhibitors, including

donepezil hydrochloride, are given concurrently with succinylcholine, similar neuromuscular blocking agents, or cholinergic agonists such as bethanechol.

ADVERSE EFFECTS

The most common adverse reactions, occurring at a frequency of at least 5% in patients taking memantine hydrochloride extended-release 28 mg/day, and greater than placebo, were headache (6% vs 5%), diarrhea (5% vs 4%), and dizziness (5% vs 1%).

The most common adverse reactions, occurring at a frequency of at least 5% in patients taking donepezil, and at twice or more the rate of placebo, were diarrhea (10% vs 4%), anorexia (8% vs 4%), vomiting (8% vs 4%), nausea (6% vs 2%), and ecchymosis (5% vs 2%).

DOSAGE AND ADMINISTRATION

Recommended Dosing

The recommended dose of Mexazil® XR is 28 mg/10 mg once daily.

For patients stabilized on donepezil and not currently on memantine:

For patients stabilized on donepezil hydrochloride 10 mg and not currently on memantine hydrochloride, the recommended starting dose of Mexazil® XR is 7 mg/10 mg, taken once a day in the evening. The dose should be increased in 7 mg increments of the memantine hydrochloride component to the recommended maintenance dose of 28 mg/10 mg once daily. The minimum recommended interval between dose increases is one week. The dose should only be increased if the previous dose has been well tolerated. The maximum dose is 28 mg/10 mg once daily.

For patients stabilized on both donepezil and memantine:

Patients stabilized on memantine hydrochloride (10 mg twice daily or 28 mg extended-release once daily) and donepezil hydrochloride 10 mg once daily can be switched to Mexazil® XR 28 mg/10 mg, taken once a day in the evening. Patients should start Mexazil® XR the day following the last dose of memantine hydrochloride and donepezil hydrochloride administered separately. If a patient misses a single dose of Mexazil® XR, the next dose should be taken as scheduled, without doubling up the dose.

Dosing in Patients with Severe Renal Impairment

For patients stabilized on donepezil and not currently on memantine:

For patients with severe renal impairment (creatinine clearance 5-29 mL/min, based on the Cockcroft-Gault equation) stabilized on donepezil hydrochloride 10 mg once daily and not currently on memantine hydrochloride, the recommended starting dose of Mexazil® XR is 7 mg/10 mg taken once a day in the evening. The dose should be increased to the recommended maintenance dose of 14 mg/10 mg once daily in the evening after a minimum of one week.

For patients stabilized on both donepezil and memantine:

Patients with severe renal impairment, stabilized on memantine hydrochloride (5 mg twice daily or 14 mg extended-release once daily) and donepezil hydrochloride 10 mg once daily, can be switched to Mexazil® XR 14 mg/10 mg, taken once daily in the evening.

Special polulations

Elderly patients

Memantine Hydrochloride

The majority of people with Alzheimer's disease are 65 years and older. In the clinical study of memantine hydrochloride extended-release, the mean age of patients was approximately 77 years; over 91% of patients were 65 years of age and older, 67% were 75 years of age and older, and 14% were 85 years of age and older. There were no clinically meaningful differences in most adverse events reported by patients ≥ 65 years old and < 65 years old.

Donepezil Hydrochloride

The mean age of patients enrolled in the clinical studies with donepezil hydrochloride was 73 years; 80% of these patients were between 65 and 84 years of age, and 49% of patients 75 years of age and older. There were no clinically significant differences in most adverse events reported by patients ≥ 65 years old and < 65 years old.

Renal Impairment

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

Hepatic Impairment

No dosage adjustment is needed in patients with mild or moderate hepatic impairment. Mexazil® XR has not been studied in patients with severe hepatic impairment .

Pediatric population

Safety and effectiveness of Mexazil® XR in pediatric patients have not been established.

Method of administration

Mexazil® XR can be taken with or without food. Mexazil® XR capsules can be taken intact or may be opened, sprinkled on applesauce, and swallowed without chewing. The entire contents of each Mexazil® XR capsule should be consumed; the dose should not be divided.

Except when opened and sprinkled on applesauce, as described above, Mexazil® XR capsules should be swallowed whole. Mexazil® XR capsules should not be divided, chewed, or crushed.

OVERDOSAGE

Memantine hydrochloride and donepezil hydrochloride are the two active ingredients of Mexazil® XR. No specific antidote for memantine hydrochloride overdose is known; however, elimination of memantine can be increased by acidification of the urine. Tertiary anticholinergics such as atropine may be used as an antidote for donepezil hydrochloride overdose.

In managing cases of overdose, consider the possibility of multiple drug involvement. In general, supportive measures should be utilized, and treatment should be symptomatic.

Memantine Hydrochloride Signs and symptoms most often accompanying overdosage with other formulations of memantine in clinical trials and from worldwide marketing experience, alone or in combination with other drugs and/or alcohol, include: agitation, asthenia, bradycardia, confusion, coma, dizziness, ECG changes, increased blood pressure, lethargy, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness.

Donepezil Hydrochloride Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse, and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for donepezil hydrochloride overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when coadministered with quaternary anticholinergics such as glycopyrrolate. It is not known whether donepezil hydrochloride and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation, and lower body surface temperature.

STORAGE CONDITIONS

Store below 30°C.

Dispense in a tight, light-resistant container.

Date of Revision: March 2023.

Marketing Authorization Holder and Manufacturer

Benta S.A.L. – Lebanon

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