

Reminyl

NAME OF THE MEDICINAL PRODUCT

REMINYL (galantamine hydrobromide) Tablets and Oral Solution

QUALITATIVE AND QUANTITATIVE COMPOSITION

REMINYL tablets contain galantamine hydrobromide, equivalent to respectively 4, 8 and 12 mg galantamine base.

REMINYL oral solution contains galantamine hydrobromide, equivalent to 4 mg/ml galantamine base. For excipients, see List of Excipients.

PHARMACEUTICAL FORM

Film-Coated Tablets for Oral Use

- 4 mg galantamine as off-white, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G4" on the other side;
- 8 mg galantamine as pink, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G8" on the other side;
- 12 mg galantamine as orange-brown, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G12" on the other side.

Oral Solution 4 mg/ml

Clear, colourless solution.

CLINICAL PARTICULARS

Therapeutic Indications

REMINYL is indicated for the treatment of mild to moderately severe dementia of the Alzheimer type.

Posology and Method of Administration

Adults

REMINYL should be administered twice a day, preferably with morning and evening meals. Ensure adequate fluid intake during treatment.

Starting Dose

The recommended starting dose is 8 mg/day (4 mg twice a day) for 4 weeks.

Maintenance Dose

- The initial maintenance dose is 16 mg/day (8 mg twice a day) and patients should be maintained on 16 mg/day for at least 4 weeks.
- An increase to the maximum recommended maintenance dose of 24 mg/day (12 mg twice a day) should be considered after appropriate assessment including evaluation of clinical benefit and tolerability.
- There is no rebound effect after abrupt discontinuation of treatment (e.g. in preparation for surgery).

Children

Use of REMINYL in children is not recommended. No data on the use of REMINYL in pediatric patients are available.

Hepatic and Renal Impairment

Galantamine plasma levels may be increased in patients with moderate to severe hepatic or renal impairment. In patients with moderately impaired hepatic function, based on pharmacokinetic modeling, dosing could begin with 4 mg once daily, preferably taken in the morning for at least one week. Thereafter, patients should proceed with 4 mg b.i.d. for at least four weeks. In these patients, daily doses should not exceed 8 mg b.i.d. In patients with severe hepatic impairment, the use of REMINYL is not recommended.

For patients with a creatinine clearance greater than 9 ml/min, no dosage adjustment is required.

In patients with severe renal impairment (creatinine clearance less than 9 ml/min), the use of REMINYL is not recommended since no data are available.

Concomitant Treatment

In patients treated with potent CYP2D6 or CYP3A4 inhibitors, dose reductions can be considered (see: Interactions with Other Medicinal Products and Other Forms of Interaction).

Contraindications

REMINYL should not be administered to patients with a known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulations.

Special Warnings and Special Precautions for Use

REMINYL is indicated for patients with mild to moderately severe dementia of the Alzheimer's type. The benefit of REMINYL in patients with other types of dementia or other types of memory impairment has not been demonstrated.

Patients with Alzheimer's disease lose weight. Treatment with cholinesterase inhibitors, including galantamine, has been associated with weight loss in these patients. During therapy, patient's weight should be monitored. As with other cholinesterases, REMINYL should be given with caution in the following conditions:

Cardiovascular Conditions: because of their pharmacological action, cholinesterases may have vagotonic effects on heart rate (e.g. bradycardia). The potential for this action may be particularly important to patients with 'sick sinus syndrome' or other supraventricular cardiac conduction disturbances or who use drugs that significantly reduce heart rate concomitantly, such as digoxin and beta-blockers. In clinical trials, use of REMINYL has been associated with syncope and rarely with severe bradycardia.

Gastrointestinal Conditions: patients at increased risk of developing peptic ulcers, e.g. those with a history of ulcer disease or those predisposed to these conditions, including those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs), should be monitored for symptoms. However, clinical studies with REMINYL showed no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. The use of REMINYL is not recommended in patients with gastrointestinal obstruction or recovering from gastrointestinal surgery.

Neurological Conditions: Although cholinesterases are believed to have some potential to cause seizures, seizure activity may also be a manifestation of Alzheimer's disease.

Pulmonary Conditions: because of their cholinergic actions, cholinesterases should be prescribed with care for patients with a history of severe asthma or obstructive pulmonary disease.

Genitourinary: the use of REMINYL is not recommended in patients with urinary outflow obstruction or recovering from bladder surgery.

Safety in Subjects With Mild Cognitive Impairment (MCI)

REMINYL is not indicated for individuals with mild cognitive impairment (MCI), i.e., those who demonstrate isolated memory impairment greater than expected for their age and education, but do not meet criteria for Alzheimer's disease.

Two, 2-year controlled trials in subjects with MCI did not meet dual primary efficacy outcomes. Although mortality in both treatment arms was low, more deaths were initially recorded in subjects randomized to galantamine than to placebo, but the incidence of serious adverse events was identical between treatment groups. The deaths were due to various causes that are not unexpected in an elderly population. When data retrieved from the large proportion of patients who discontinued prior to completion of the double-blind period was included, there was no evidence of an increasing risk of death in REMINYL-treated subjects over time. More subjects from the placebo than the galantamine group discontinued prior to death, which may account for the difference in mortality initially recorded.

The MCI study results are discrepant from those observed in studies of Alzheimer's disease. In pooled studies in Alzheimer's disease (n=614), the mortality rate was numerically higher in the placebo than the REMINYL group.

Interactions with Other Medicinal Products and Other Forms of Interaction

Pharmacodynamic Interactions

Because of its mechanism of action, galantamine should not be given concomitantly with other cholinesterases. Galantamine antagonises the effect of anticholinergic medication. As expected with cholinesterases, a pharmacodynamic interaction is possible with drugs that significantly reduce the heart rate (e.g. digoxin and beta blockers).

Galantamine, as a cholinergic, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

Pharmacokinetic Interactions

Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine. Based on *in vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine.

Inhibition of gastric acid secretion will not impair the absorption of galantamine.

Other Drugs Affecting the Metabolism of Galantamine

Drugs that are potent inhibitors for CYP2D6 or CYP3A4 may increase the AUC of galantamine. Multiple dose pharmacokinetic studies demonstrated that the AUC of galantamine increased 30% and 40%, respectively, during co-administration of ketconazole and paroxetine. As co-administered with erythromycin, another CYP3A4 inhibitor, the galantamine AUC only increased approximately 10%. Population PK analysis for patients with Alzheimer's disease showed that the clearance of galantamine was decreased about 25-33% by concurrent administration of amitriptyline, fluoxetine, fluvoxamine, paroxetine and quinidine, known inhibitors of CYP2D6. Therefore, during initiation of treatment with potent inhibitors of CYP2D6 or CYP3A4 patients may experience an increased incidence of cholinergic side effects, predominantly nausea and vomiting. Under these circumstances, based on tolerability, a reduction of the galantamine maintenance dose can be considered (see: Posology and Method of Administration).

Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, at a dose of 10 mg/daily for 2 days followed by 10 mg BID for 12 days had no effect on the pharmacokinetics of galantamine 16 mg/day at steady state.

Effect of Galantamine on the Metabolism of Other Drugs

Therapeutic doses of galantamine (12 mg b.i.d.) had no effect on the kinetics of digoxin and warfarin. Galantamine did not affect the increased prothrombin time induced by warfarin.

In vitro studies indicated that the inhibition potential of galantamine with respect to the major forms of human cytochrome P450 is very low.

Pregnancy and Lactation

Use During Pregnancy

Reproduction studies conducted in pregnant rats at doses up to 16 mg/kg (or about 25 times the human therapeutic dose) and in pregnant rabbits up to 40 mg/kg (or about 63 times the human therapeutic dose) did not show any evidence of a teratogenic potential. A non-significant increase in the incidence of minor skeletal abnormalities was noted at a dose of 16 mg/kg in rats.

No studies are available on the use of REMINYL in pregnant women. REMINYL should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use During Lactation

It is not known whether REMINYL is excreted in human breast milk and there are no studies in lactating women. Therefore, women on REMINYL should not breast-feed.

Effects on Ability to Drive and Use Machines

Alzheimer's disease may cause gradual impairment of driving performance or compromise the ability to use machinery. Furthermore, like other cholinesterases, REMINYL may cause dizziness and somnolence, which could affect the ability to drive or use machines, especially during the first weeks after initiation of treatment.

Undesirable Effects

Clinical Trial Data

Double-Blind Data - Adverse Drug Reactions Reported at $\geq 1\%$ Frequency

The safety of REMINYL was evaluated in 4457 subjects with mild to moderately severe dementia of the Alzheimer's type who participated in 7 placebo-controlled, double-blind clinical trials. The information presented in this section was derived from pooled data. Adverse Drug Reactions (ADRs) reported by $\geq 1\%$ of REMINYL-treated subjects in these trials are shown in Table 1.

System/Organ Class Adverse Reaction	REMINYL (n=2932) %	Placebo (n=1525) %
Metabolism and Nutrition Disorders		
Decreased appetite	5.2	1.4
Anorexia	3.8	1.0
Psychiatric Disorders		
Depression	4.2	2.9
Nervous System Disorders		
Dizziness	8.9	4.6
Headache	7.6	5.4
Tremor	2.0	0.8
Syncope	1.8	0.7
Lethargy	1.7	0.8
Somnolence	1.7	0.7
Cardiac Disorders		
Bradycardia	1.2	0.3
Gastrointestinal Disorders		
Nausea	25.0	7.6
Vomiting	12.8	3.1
Diarrhea	9.0	6.3
Abdominal pain	2.4	0.9
Abdominal pain upper	2.0	1.4
Dyspepsia	1.8	1.3
Stomach discomfort	1.6	0.6
Abdominal discomfort	1.0	0.4
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	1.2	0.7
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	1.5	0.8
General Disorders and Administration Site Conditions		
Fatigue	4.0	2.2
Asthenia	2.3	1.7
Malaise	1.4	0.7
Investigations		
Weight decreased	5.1	1.4

In a randomized, double-blind, placebo-controlled clinical trial, the safety profile of once-daily treatment with REMINYL prolonged release capsules was similar in frequency and nature to that seen with tablets. Nausea and vomiting, the most frequent adverse drug reactions, occurred mainly during titration periods, lasted less than a week in most cases and the majority of patients had one episode. Prescription of anti-emetics and ensuring adequate fluid intake may be useful in these instances.

Open-Label Data - Adverse Drug Reactions Reported at $\geq 1\%$ Frequency

The safety of REMINYL was evaluated in 1454 subjects with mild to moderately severe dementia of the Alzheimer's type who participated in 5 open-label clinical trials. The information presented in this section was derived from pooled data.

Adverse Drug Reactions (ADRs) reported by $\geq 1\%$ of REMINYL-treated subjects in these trials and not listed in Table 1 included Fall, which occurred at a rate of 6.5% in open-label trials.

Double Blind and Open-Label Data - Adverse Drug Reactions Reported at $< 1\%$ Frequency

Additional ADRs that occurred in $< 1\%$ of REMINYL-treated subjects in the double-blind and open-label clinical datasets are listed in Table 2.

System/Organ Class Adverse Reaction	REMINYL (n=2932) %	Placebo (n=1525) %
Metabolism and Nutrition Disorders		
Dehydration		
Nervous System Disorders		
Dysgeusia, Hypersomnia, Paresthesia		
Eye Disorders		
Vision blurred		
Cardiac Disorders		
Arrhythmias: first degree, Palpitations, Sinus bradycardia, Supraventricular extrasystoles		
Vascular Disorders		
Flushing, Hypotension		
Gastrointestinal Disorders		
Retching		
Musculoskeletal and Connective Tissue Disorders		
Muscular weakness		

In Table 3, ADRs are presented by frequency category based on spontaneous reporting rates. In Table 4, ADRs are presented by frequency category based on incidence in clinical trials, when known.

System/Organ Class Adverse Reaction	REMINYL (n=2932) %	Placebo (n=1525) %
Metabolism and Nutrition Disorders		
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