PACKAGE INSERT

SCHEDULING STATUS

Schedule 4

PROPRIETARY NAME (and dosage form)

S4 REMINYL® CR 8 mg (Prolonged Release Capsules)

S4 REMINYL® CR 16 mg (Prolonged Release Capsules)

S4 REMINYL® CR 24 mg (Prolonged Release Capsules)

COMPOSITION

REMINYL prolonged release capsules contain galantamine hydrobromide, equivalent to respectively 8 mg, 16 mg and 24 mg galantamine base.

PHARMACOLOGICAL CLASSIFICATION

A. 5.3 - Cholinomimetics

PHARMACOLOGICAL ACTION

Pharmacodynamics

Galantamine, a tertiary alkaloid is a selective, competitive and reversible inhibitor of acetylcholinesterase. In addition, galantamine enhances the intrinsic action of acetylcholine on nicotinic receptors, probably through binding to an allosteric site of the receptor.

Pharmacokinetics

Absorption

After oral intake of a single dose 8 mg galantamine, a peak plasma concentration of 43 ± 13 ng/ml, is reached after 1,2 hours, with a mean AUC_{∞} of 427 ± 102 ng.h/ml. The absolute oral bioavailability of galantamine is 88,5 %. Oral intake of galantamine with food slows down its rate of absorption (C_{max} reduced by about 25 %), but does not affect the extent to which it is absorbed (AUC).

The prolonged release capsules are bioequivalent to the b.i.d. immediate release tablets with respect to AUC_{24h} and C_{min}. The C_{max} value is reached after 4.4 hours, was about 24 % lower than that of tablet. Food has no effect on AUC and C_{max} of the prolonged release capsules and slightly increases t_{max} by about 12 %.

Distribution

The plasma protein binding of galantamine is low: 17,7 ± 0,8 %. In whole blood, galantamine is mainly distributed to blood cells (52,7 %) and plasma water (39,0 %), whereas the fraction of galantamine bound to plasma proteins is only 8,4 %. The blood-to-plasma concentration ratio of galantamine is 1,17.

Metabolism

Major metabolic pathways were N-oxidation, N-demethylation, O-demethylation, glucuronidation and epimerization. *In vitro* studies confirmed that cytochrome P450 2D6 and 3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of galantamine. O-demethylation was far more important in extensive metabolisers of CYP2D6. The levels of excretion of total radioactivity in the urine and faeces were not different between poor and extensive metabolisers. In plasma from poor and extensive metabolisers, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity. In plasma from extensive metabolisers, the glucuronide of O-desmethylgalantamine was also important.

None of the active metabolites of galantamine (norgalantamine, O-desmethylgalantamine and O-desmethyl-norgalantamine) could be detected in their unconjugated form in plasma from poor or extensive metabolisers after single dosing. Norgalantamine was detectable in plasma from patients after multiple dosing, but did not represent more than 10 % of the galantamine levels.

Elimination

The elimination of galantamine is bi-exponential, with a terminal half-life in the order of 7-8 h. Galantamine has a plasma clearance of approximately 200 ml/min with a volume of distribution (average Vd_{ss} of 175 l). Seven days after a single oral dose of 4 mg ^{3}H-galantamine, 90 – 97 % of the radioactivity was recovered in the urine and 2,2 – 6,3 % in the faeces. After i.v. and oral administration,

18 – 22 % of the dose was excreted as unchanged galantamine in the urine in 24 hours, with a renal clearance of about 65 ml/min, which represents 20 – 25 % of the total plasma clearance.

Dose-linearity

After repeated oral dosing of 12 mg galantamine b.i.d., mean trough and peak plasma concentrations fluctuated between 30 and 90 ng/ml. The pharmacokinetics of galantamine is linear in the dose range 4 – 16 mg b.i.d.

Characteristics in patients

Data from clinical trials in patients indicate that the plasma concentrations of galantamine with Alzheimer's disease are 30 – 40 % higher than in healthy young subjects.

The pharmacokinetics of galantamine in subjects with mild hepatic impairment (CHILD score of 5 – 6) was comparable to those in healthy subjects. In patients with moderate hepatic impairment (CHILD score of 7 – 9), the AUC and half life of galantamine were increased by about 30 %.

The disposition of galantamine was studied in young subjects with varying degrees of renal function. Elimination of galantamine decreased with decreasing creatinine clearance. Plasma concentrations of galantamine increased in subjects with impaired renal function by 38% in moderate (Cl_{CR} = 52 – 104 ml/min) and by 67 % in severe impairment (Cl_{CR} = 9 – 51 ml/min), compared to age and weight-matched healthy subjects (Cl_{CR} > = 121 ml/min). A population pharmacokinetic analysis and simulations indicate that no dose-adjustments are needed in Alzheimer patients with renal impairment provided that the Cl_{CR} is at least 9 ml/min, as the galantamine renal clearance is lower in the Alzheimer population.

INDICATIONS

REMINYL is indicated for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer type. Efficacy data beyond 6 months has not been established (see Warnings).

CONTRA-INDICATIONS

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

Severe impaired hepatic and renal function, as safety has not been demonstrated.

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption, should not take this medicine.

WARNINGS

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.

Treatment with cholinesterase inhibitors, including REMINYL, has been associated with weight loss in patients with Alzheimer's disease. During therapy patient's weight should be monitored.

REMINYL should be given with caution in the following conditions:

Cardiovascular conditions

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 medicines that significantly reduce the heart rate concomitantly such as digoxin and beta blockers. In clinical trials, use of REMINYL has been associated with syncope and rarely with bradycardia.

Gastro-intestinal 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. The use of REMINYL is not recommended in

patients with gastro-intestinal obstruction or recovering from gastro-intestinal surgery.

Neurological conditions

Epilepsy: cholinomimetics are believed to lower the threshold for seizures in sensitive patients.

Pulmonary conditions

Because of their cholinomimetic actions, REMINYL should be prescribed with care for patients with a history of asthma or chronic, obstructive bronchitis.

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 treated with REMINYL or placebo did not meet dual primary efficacy outcomes. Although mortality in both treatment arms was low, more deaths were initially recorded in subjects randomized to REMINYL 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 a statistically significant increasing risk of death in REMINYL-treated subjects over time. More subjects from the placebo than the REMINYL group discontinued prior to death, which may account for the difference in mortality initially recorded.

INTERACTIONS

Interactions with other medicaments and other forms of interactions:

Pharmacodynamic interactions:

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

REMINYL as a cholinomimetic, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

Pharmacokinetic interactions:

Based on *in-vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of REMINYL.

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

Other medicines affecting the metabolism of REMINYL

Drugs that are potent inhibitors for CYP2D6 or CYP3A4 may increase the AUC of REMINYL. Multiple dose pharmacokinetic studies demonstrated that the AUC of REMINYL increased 30 – 40 %, respectively, during co-administration of ketoconazole and paroxetine. As co-administered with erythromycin, another CYP3A4 inhibitor, the REMINYL AUC only increased approximately 10 %. Population PK analysis for patients with Alzheimer's disease showed that the clearance of REMINYL 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 REMINYL maintenance dose can be considered.

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 REMINYL 16 mg/day at steady state.

Effect of REMINYL on the metabolism of other medicines

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

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

PREGNANCY AND LACTATION

No studies are available on the use of REMINYL in pregnant women. REMINYL should not be used during pregnancy.

It is not known whether REMINYL is excreted in human breast milk and there are no studies in lactating women.

DOSAGE AND DIRECTIONS FOR USE

Adults

Prolonged Release Capsules

Administration:

REMINYL prolonged release capsules should be administered once daily in the morning, preferably with food.

Starting dose*:*

The recommended starting dose is 8 mg/day for 4 weeks.

Maintenance dose:

- The initial maintenance dose is 16 mg/day and patients should be maintained on 16 mg/day for at least 4 weeks.
- An increase to the maintenance dose of 24 mg/day should be considered after appropriate assessment including evaluation of clinical benefit and tolerability.
- In individual patients not showing an increased response or not tolerating 24 mg/day, a dose reduction to 16 mg/day should be considered.
- Maintenance treatment can be continued for as long as therapeutic benefit for the patient exists. Therefore, the clinical benefit of galantamine should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect is no longer present.

- 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 paediatric patients are available.

Hepatic and renal impairment:

REMINYL 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 should begin with 4 mg once daily with immediate release tablets, preferably taken in the morning for at least one week. For prolonged release capsules, based on pharmacokinetic modeling, dosing should begin with 8 mg every other day for at least one week, preferably taken in the morning. Thereafter, patients should proceed with 4 mg twice daily for immediate release tablets or 8 mg once daily for prolonged release capsules at least four weeks. In these patients total daily doses-should not exceed 16 mg.

In patients with severe hepatic impairment (CHILD- score greater than 9), the use of REMINYL is contraindicated.

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 contraindicated.

Concomitant treatment

In patients treated with potent CYP2D6 or CYP3A4 inhibitors, dose reductions can be considered. (See INTERACTIONS).

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects:

Clinical Trial Data

The specific adverse events data described in this section are based on studies of the immediate-release tablet formulation. In clinical trials, the safety profile of once-daily treatment with REMINYL CR (prolonged release capsules) was similar to that seen with tablets.

In the controlled trials, the majority of the adverse events occurred during the dose-escalation period. The most frequently reported adverse event was nausea and vomiting, which lasted 5 - 7 days. Administration of REMINYL with food, the use of anti-emetic medication, and ensuring adequate fluid intake may reduce the impact of these events.

All adverse events reported in clinical trials are listed below in Table 1, using the following reporting frequencies: common (≥1/100 to <1/10), uncommon (≥ 1/1000 to ≤ 1/100).

Table 1. Adverse Drug Reactions Reported in Clinical Trials

System/Organ Class	**Adverse Events reported by ≥ 1 % (≥ 1/100) of REMINYL-treated subjects**	**Adverse Events reported by < 1 % (< 1/100) of REMINYL-treated subjects**
Body as a Whole – General Disorders	Fatigue Syncope Asthenia Malaise Fall Injury Back pain Chest pain Fever	
Central & Peripheral Nervous system	Dizziness Headache	Dysgeusia Hypersomnia

Table 1. Adverse Drug Reactions Reported in Clinical Trials

System/Organ Class	**Adverse Events reported by ≥ 1 % (≥ 1/100) of REMINYL-treated subjects**	**Adverse Events reported by < 1 % (< 1/100) of REMINYL-treated subjects**
Disorder	Tremor Lethargy	Paresthesia Vertigo Hypertonia Convulsions Involuntary muscle contractions Ataxia Hypokinesia Hyperkinesia Apraxia Aphasia Leg cramps Tinnitus Transient ischaemic attack Cerebrovascular accident
Gastrointestinal System Disorders	Nausea Vomiting Diarrhoea Abdominal pain Abdominal pain upper Dyspepsia Stomach discomfort Abdominal discomfort Constipation Flatulence	Retching Gastritis Melaena Dysphagia Rectal haemorrhage Dry mouth Saliva increased Diverticulitis Gastroenteritis Hiccup Oesophageal perforation
Cardiac Disorders	Bradycardia	Atrioventricular block first degree

Table 1. Adverse Drug Reactions Reported in Clinical Trials

System/Organ Class	**Adverse Events reported by ≥ 1 % (≥ 1/100) of REMINYL-treated subjects**	**Adverse Events reported by < 1 % (< 1/100) of REMINYL-treated subjects**
		Palpitations Sinus bradycardia Supraventricular extrasystoles Cardiac failure Myocardial ischemia or infarction Atrial dysrhythmias Atrial fibrillation Supraventricular tachycardias, QT prolonged Bundle branch block T-wave inversion, Ventricular tachycardia Severe bradycardia
Metabolic and Nutritional Disorders	Decreased appetite Weight decreased	Dehydration Hyperglycaemia Alkaline phosphate increased
Musculoskeletal and Connective Tissue Disorders	Muscle spasms	Muscular weakness
Psychiatric Disorders	Anorexia Depression Insomnia Somnolence Hallucination Agitation Confusion	Apathy Paroniria Paranoid reaction Libido increased Delirium Suicidal ideation Suicide

Table 1. Adverse Drug Reactions Reported in Clinical Trials		
System/Organ Class	**Adverse Events reported by ≥ 1 % (≥ 1/100) of REMINYL-treated subjects**	**Adverse Events reported by < 1 % (< 1/100) of REMINYL-treated subjects**
	Anxiety	
Respiratory System Disorder	Rhinitis Upper respiratory tract infection Bronchitis Coughing	
Skin and Sub-cutaneous Tissue Disorders	Hyperhydrosis	
Urinary system Disorders	Urinary tract infection Haematuria Urinary incontinence	Micturition frequency Cystitis Urinary retention Nocturia Renal calculi
Vascular and Blood cell Disorders	Anaemia Peripheral oedema Hypertension	Flushing Hypotension Postural hypotension Dependent oedema Purpura Epistaxis Thrombocytopenia

Post-marketing Experience

Table 2 includes adverse events from post-approval controlled and uncontrolled clinical trials and post-marketing experience observed in patients treated with REMINYL. These adverse events may or may not be causally related to the medicine.

Table 2. Adverse Reactions Identified During Postmarketing Experience with REMINYL

Immune System Disorders

Hypersensitivity

Body as a Whole – General Disorders

Dehydration (including rare, severe cases leading to renal insufficiency and renal failure).

Psychiatric Disorders

Aggression, hallucination, hallucination visual, hallucination auditory.

Gastrointestinal System Disorders

Upper and lower GI bleeding, stomach discomfort, abdominal discomfort.

Hepatobiliary Disorders

Elevated liver enzymes**,** hepatitis.

Metabolic & Nutritional Disorders

Hypokalemia.

Nervous System Disorders

Lethargy, dysgeusia, hypersomnia.

Ear and Labyrinth Disorders

Tinnitus.

Eye disorders

Vision blurred.

Vascular Disorders

Hypertension.

Special precautions:

Alzheimer's disease may cause gradual impairment of driving performance or compromise the ability to use machinery. Furthermore, like other cholinomimetics, 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms:

Signs and symptoms of significant overdosing of REMINYL are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous system, and the neuromuscular junction. In addition to muscle weakness or fasciculations, some or all of the signs of a cholinergic crisis may develop: severe nausea, vomiting, gastro-intestinal cramping, salivation, lacrimation, urination, defecation, sweating, bradycardia, hypotension, collapse and convulsions. Increasing muscle weakness together with tracheal hypersecretions and bronchospasm, may lead to vital airway compromise.

There have been post-marketing reports of Torsade de Pointes, QT prolongation; bradycardia, ventricular tachycardia and loss of consciousness in association with inadvertent overdoses of galantamine.

In one case where the dose was known, eight 4 mg tablets (32 mg total) were ingested on a single day.

Two additional cases of accidental ingestion of 32 mg (nausea, vomiting, and dry mouth; nausea, vomiting, and substernal chest pain) and one of 40 mg (vomiting) resulted in brief hospitalisations for observation with full recovery. One patient, who was prescribed 24 mg/day and had a history of hallucinations over the previous two years, mistakenly received 24 mg twice daily for 34 days and developed hallucinations requiring hospitalisation. Another patient, who was prescribed 16 mg/day of oral solution, inadvertently ingested 160 mg (40 ml) and experienced sweating, vomiting, bradycardia, and near-syncope one hour later, which necessitated hospital treatment. His symptoms resolved within 24 hours.

Treatment:

As in any case of overdose, general supportive measures should be used. In severe cases, anticholinergics such as atropine can be used as a general antidote for cholinomimetics. An initial dose of 0,5 to 1,0 mg i.v. is recommended, with subsequent doses based on the clinical response.

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

IDENTIFICATION

Prolonged release capsules for oral use

REMINYL® CR 8 mg:	White opaque, size 4 hard gelatin capsules with the inscription “G8”, containing white to off-white pellets.
REMINYL® CR 16 mg:	Pink opaque, size 2 hard gelatin capsules with the inscription “G16”, containing white to off-white pellets.
REMINYL® CR 24 mg:	Caramel opaque, size 1 hard gelatin capsules with the inscription “G24”, containing white to off-white pellets.

PRESENTATION

The prolonged release capsules are packed in white HDPE bottles containing 30 or 300 capsules or in blister packs of 7 capsules. One or more blisters are packed in a cardboard box.

Pack sizes (blisters) include:

8 mg: 7 or 28 capsules

16 mg: 28, 56 or 84 capsules

24 mg: 28, 56 or 84 capsules

STORAGE INSTRUCTIONS

Store below 25 ºC.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

Prolonged Release Capsules

CR 8 mg - 38/5.3/0311

CR 16 mg – 38/5.3/0312

CR 24 mg - 38/5.3/0313

Namibia Reg. No.:

CR 8 mg – 10/5.3/0601

CR 16 mg – 10/5.3/0602

CR 24 mg – 10/5.3/0603

NS 2

Botswana Reg. No.:

CR 8 mg – BOT1202079A-F

CR 16 mg – BOT1202078A-F

CR 24 mg – BOT1202080A-F

S2

NAME AND BUSINESS ADDRESS OF THE HOLDER OF CERTIFICATE OF REGISTRATION

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