PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

REMINYL® CR 8 mg (Prolonged Release Capsules)

REMINYL® CR 16 mg (Prolonged Release Capsules)

REMINYL® CR 24 mg (Prolonged Release Capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:

8 mg capsule: sucrose 59 mg

16 mg capsule: sucrose 117 mg

24 mg capsule: sucrose 176 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REMINYL CR 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 section 4.4)

4.2 Posology and method of administration

Adults

Posology

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.

Treatment Withdrawal

- There is no rebound effect after abrupt discontinuation of treatment (e.g.in preparation for surgery).

Renal impairment

REMINYL CR plasma concentrations may be increased in patients with moderate to severe renal impairment.

For patients with a creatinine clearance ≥ 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 CR is contraindicated.

Hepatic impairment

Galantamine plasma concentrations may be increased in patients with moderate to severe hepatic impairment.

For prolonged release capsules, based on pharmacokinetic modelling, dosing should begin with 8 mg every other day for at least one week, preferably taken in the morning. Thereafter, patients should take 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- PUGH score >9), the use of REMINYL CR is contraindicated.

Concomitant treatment

In patients treated with potent CYP2D6 or CYP3A4 inhibitors, dose reductions can be considered. (See section 4.5).

Children:

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

Method of Administration

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

4.3 Contraindications

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

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

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

4.4 Special warnings and precautions for use

Types of dementia other than Alzheimer's dementia

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

Serious skin reactions

Serious skin reactions (Stevens-Johnson syndrome and acute generalised exanthematous pustulosis) have been reported in patients receiving REMINYL CR. It is recommended that patients be informed about the signs of serious skin reactions, and that the use of REMINYLCR be discontinued at the first appearance of skin rash.

Weight monitoring

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

Conditions requiring caution:

REMINYL CR should be given with caution in the following conditions:

Cardiovascular conditions

Bradycardia: The potential for bradycardia and all types of atrioventricular node block (See section 4.8) 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 CR has been associated with syncope and 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 CR is not recommended in patients with gastro-intestinal obstruction or recovering from gastro-intestinal surgery.

Neurological conditions

Convulsions have been reported with REMINYL CR (See section 4.8, Postmarketing data). Seizure activity may also be a manifestation of Alzheimer's disease.

Pulmonary conditions

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

Genitourinary

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

Safety in Subjects with Mild Cognitive Impairment (MCI)

REMINYL CR 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 CR 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 CR 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 CR treated subjects over time. More subjects from the placebo than the REMINYL CR group discontinued prior to death, which may account for the difference in mortality initially recorded

REMINYL CR capsules contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take REMINYL CR

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Because of its mechanism of action, REMINYL CR should not be given concomitantly with other cholinomimetics. REMINYL CR 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 section 4.4).

REMINYL CR 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 CR.

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

Other medicines affecting the metabolism of REMINYL CR

Drugs that are potent inhibitors for CYP2D6 or CYP3A4 may increase the AUC of REMINYL CR. Multiple dose pharmacokinetic studies demonstrated that the AUC of REMINYL CR increased 30 – 40 %, respectively, during co-administration of ketoconazole and paroxetine. As co-administered with erythromycin, another CYP3A4 inhibitor, the REMINYL CR AUC only increased approximately 10 %. Population PK analysis for patients with Alzheimer's disease showed that the clearance of REMINYL CR 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 CR 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 twice a day for 12 days had no effect on the pharmacokinetics of REMINYL CR 16 mg/day at steady state.

Effect of REMINYL CR on the metabolism of other medicines

Therapeutic doses of REMINYL CR (12 mg twice a day) had no effect on the kinetics of digoxin and warfarin. REMINYL CR did not affect the increased prothrombin time induced by warfarin.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Lactation

It is not known whether REMINYL CR is excreted in human breast milk and there are no studies in lactating women. REMINYL CR should not be used during breastfeeding.

4.7 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. REMINYL CR may cause adverse reactions (such as dizziness and somnolence), which could affect the ability to drive or use machines, especially during the first weeks after initiation of treatment.

4.8 Undesirable effects

Clinical Trial Data

Table 1. Adverse Drug Reactions Reported in Clinical Trials

System/Organ Class	Frequency category				
	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Body as a Whole – General Disorders		Fatigue; Syncope; Asthenia; Malaise; Fall; Injury; Back pain; Chest pain; Fever			
Central & Peripheral Nervous system Disorder		Dizziness; Headache; Tremor; Lethargy	Dysgeusia; Hypersomnia; Paresthaesia; Vertigo; Hypertonia; Convulsions; Involuntary muscle contractions; Ataxia; Hypokinesia; Hyperkinesia; Apraxia; Aphasia; Leg cramps; Tinnitus; Transient ischaemic attack; Cerebrovascular accident		

Table 2. Adverse Drug Reactions Reported in Clinical Trials

System/Organ Class	Frequency category				
	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
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; Increased salivation; Diverticulitis; Gastroenteritis; Hiccup; Oesophageal perforation		
Cardiac Disorders		Bradycardia	First degree atrioventricular block; Palpitations; Sinus bradycardia; Supraventricular extrasystoles; Cardiac failure; Myocardial ischaemia or infarction; Atrial dysrhythmias; Atrial fibrillation; Supraventricular tachycardias, Prolonged QT interval; Bundle branch block;		

Table 3. Adverse Drug Reactions Reported in Clinical Trials

System/Organ Class	Frequency category				
	Very common	Common	Uncommon	Rare	Not known
			T-wave inversion; Ventricular tachycardia; Severe bradycardia		
Metabolic and Nutritional Disorders		Decreased appetite; Weight decreased	Dehydration; Hyperglycaemia; alkaline phosphate		
Musculoskeletal and Connective Tissue Disorders		Muscle spasms	Muscular weakness		
Psychiatric Disorders		Anorexia; Depression Insomnia; Somnolence; Hallucination; Agitation; Confusion; Anxiety	Apathy; Paroniria; Paranoid reaction; Increased libido; Delirium; Suicidal ideation; Suicide		
Respiratory System Disorder		Rhinitis; Upper respiratory tract infection; Bronchitis; Coughing			
Skin and Sub-cutaneous Tissue Disorders		Hyperhydrosis			

Table 4. Adverse Drug Reactions Reported in Clinical Trials					
System/Organ Class	**Frequency category**				
	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
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 data

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

Table 2. Adverse Reactions Identified During Postmarketing Experience with REMINYL CR

System/Organ Class	Frequency category				
	Very common	Common	Uncommon	Rare	Not known
Immune System Disorders			Hypersensitivity		
Body as a Whole – General Disorders			Dehydration (including, severe cases leading to renal insufficiency and renal failure).		
Psychiatric Disorders		Hallucination	Hallucination visual; hallucination auditory		Aggression

Table 2. Adverse Reactions Identified During Postmarketing Experience with REMINYL CR					
System/Organ Class	**Frequency category**				
	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Gastrointestinal System Disorders		Abdominal discomfort			Upper and lower GI bleeding; stomach discomfort
Hepatobiliary Disorders			Elevated liver enzymes	Hepatitis	
Metabolic & Nutritional Disorders					Hypokalaemia
Nervous System Disorders		Lethargy	Dysgeusia; hypersomnia; convulsions		
Ear and Labyrinth Disorders			Tinnitus		
Cardiac Disorders				Atrioventricular block complete	
Eye disorders			Blurred vision		
Vascular Disorders		Hypertension			
Skin and subcutaneous tissue disorders					Stevens-Johnson Syndrome; acute generalized exanthematous pustulosis; erythema multiforme

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of REMINYL CR is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the 6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

Signs and symptoms of significant overdosing of REMINYLCR 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.

Treatment

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 intravenously 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification : A. 5.3 - Cholinomimetics

Mechanism of action

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.

5.2 Pharmacokinetic properties

Absorption

The absolute oral bioavailability of galantamine is 88.5 %.

The C_{max} value of the 24mg once-daily prolonged release capsule is reached after 4.4 hours, was about 24 % lower than that of the 12 mg twice-daily immediate-release tablet.

After repeated administration of 8 mg prolonged release capsule once daily the mean AUC (0-24h) was 390 ng*h/mL and C_{max} was reached after 5 hours.

The terminal elimination half life after multiple oral doses was 9.9 hours.

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.

Biotransformation

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

The pharmacokinetics of galantamine prolonged release capsules is dose proportional within the studied dose range of 8 mg to 24 mg once daily in old and young age groups.

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.

Hepatic Impairment

The pharmacokinetics of galantamine in subjects with mild hepatic impairment (CHILD - PUGH score of 5 – 6) was comparable to that in healthy subjects. In patients with moderate hepatic impairment (CHILD - PUGH score of 7 – 9), the AUC and half-life of galantamine were increased by about 30 % % (See section 4.2)

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:

The capsules contain as inactive ingredients diethyl phthalate, ethyl cellulose, gelatin, hypromellose, maize starch, macrogol, sucrose, and titanium dioxide (E171).

The 16 mg capsules also contain red ferric oxide (E172).

The 24 mg capsules also contain red ferric oxide (E172) and yellow ferric oxide (E172).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 Years

6.4 Special precautions for storage

Store at or below 25 ºC.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

This medicine does not require any special storage conditions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (PTY) LTD

(Reg. No. 1980/011122/07)

2 Medical Road, Halfway House,

Midrand 1685, South Africa

MedInfo@its.jnj.com

8. REGISTRATION NUMBER(S)

Prolonged Release Capsules

8-mg; 16-mg; 24-mg capsules – 38/5.3/0311; 0312; 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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

- The date on the registration certificate of the medicine: REMINYL CR 8 mg, 16 mg, 24 mg Prolonged release capsules – 04 December 2009

10. DATE OF REVISION OF THE TEXT

TBA