SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

REMCEPT XL 8 mg (Prolonged release hard capsules)

REMCEPT XL 16 mg (Prolonged release hard capsules)

REMCEPT XL 24 mg (Prolonged release hard capsules)

Sugar free.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

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

For the full list of excipients, **see section 6.1**.

3. PHARMACEUTICAL FORM:

REMCEPT XL 8 mg: Opaque white-white size 2 hard gelatine capsules containing one round biconvex tablet of 8 mg.

REMCEPT XL 16 mg: Opaque, flesh-flesh size 2 hard gelatine capsules containing two round biconvex tablets of 8mg.

REMCEPT XL 24 mg: Opaque orange-orange size 2 hard gelatine capsules containing three round biconvex tablets of 8mg.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications:

REMCEPT XL 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.

4.2. Posology and method of administration:

Posology:

Adults:

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 **REMCEPT XL** 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 **REMCEPT XL** in children is not recommended. No data on the use of **REMCEPT XL** in paediatric patients are available.

Hepatic and renal impairment:

REMCEPT XL 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 modelling, dosing should begin with 8 mg every other day for at least one week, preferably taken in the morning. Thereafter, patients should proceed with 8 mg once daily for at least four weeks. In these patients total daily doses should not exceed 16 mg.

In patients with severe hepatic impairment (Child Pugh score greater than 9), the use of **REMCEPT XL** 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 **REMCEPT XL** is contraindicated.

Concomitant treatment:

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

Patients currently being treated with **REMCEPT XL** immediate release tablets can convert to **REMCEPT XL** prolonged release capsules by taking their last dose of **REMCEPT XL** immediate release tablets in the evening and starting **REMCEPT XL** prolonged release capsules once daily treatment the next morning. When converting from **REMCEPT XL** twice daily immediate release tablets to **REMCEPT XL** once daily prolonged release capsules, the same total daily dose should be administered.

Method of administration:

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

4.3. Contraindications:

- **REMCEPT XL** should not be administered to patients with a known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulations.
- Severe impaired hepatic function (Child Pugh score > 9)
- Severe renal function (Cl_{CR} = 9 – 51 ml/min)
- The use of **REMCEPT XL** 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:

REMCEPT XL is indicated for a patient with mild to moderately severe dementia of the Alzheimer type. The benefit of **REMCEPT XL** in patients with other types of dementia or other types of memory impairment has not been demonstrated. A diagnosis of Alzheimer's dementia should be made according to current guidelines by an experienced medical practitioner. Therapy with **REMCEPT XL** should occur under the supervision of a medical practitioner and should only be initiated if a caregiver is available who will regularly monitor medicine intake by the patient.

Mild Cognitive Impairment (MCI):

REMCEPT XL 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.

Serious skin reactions:

Serious skin reactions (Stevens Johnson syndrome and acute generalised exanthematous pustulosis) have been reported in patients receiving **REMCEPT XL** (see **section 4.8**). It is

recommended that patients be informed about the signs of serious skin reactions, and that use of **REMCEPT XL** be discontinued at the first appearance of skin rash.

Weight monitoring:

Treatment with cholinesterase inhibitors, including **REMCEPT XL**, has been associated with weight loss in these patients. During therapy, patient's weight should be monitored.

Conditions requiring caution:

REMCEPT XL should be given with caution in the following conditions:

Cardiac disorders:

Cholinomimetics 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 in those who use medicines that significantly reduce heart rate concomitantly, such as digoxin and beta-blockers or for patients with an uncorrected electrolyte disturbance (e.g. hyperkalaemia, hypokalaemia).

Caution should therefore be exercised when administering **REMCEPT XL** to patients with cardiovascular diseases, e.g. immediate post-myocardial infarction period, new-onset atrial fibrillation, second degree heart block or greater, unstable angina pectoris or congestive heart failure, especially NYHA group III – IV.

There have been reports of QTc prolongation in patients using therapeutic doses of galantamine and of Torsade de pointes in association with overdoses (see **section 4.9**).

Galantamine should therefore be used with caution in patients with prolongation of the QTc interval, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease or electrolyte disturbances.

Gastrointestinal disorders:

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 non-steroidal anti-inflammatory drugs (NSAIDS), should be monitored for symptoms. The use of **REMCEPT XL** is not recommended in patients with gastro-intestinal obstruction or recovering from gastro-intestinal surgery.

Nervous system disorders

Seizures have been reported with **REMCEPT XL** (see **section 4.8**). Seizure activity may also be a manifestation of Alzheimer's disease. In some cases an increase in cholinergic tone may worsen Parkinsonian symptoms.

Respiratory, thoracic and mediastinal disorders:

Cholinomimetics should be prescribed with care for patients with a history of severe asthma or obstructive pulmonary disease or active pulmonary infections (e.g. pneumonia).

Renal and urinary disorders:

The use of **REMCEPT XL** is not recommended in patients with urinary outflow obstruction or recovering from bladder surgery (see **section 4.3**).

Surgical and medical procedures:

REMCEPT XL, as a cholinomimetic, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia, especially in cases of pseudocholinesterase deficiency.

4.5. Interaction with other medicines and other forms of interaction:

Pharmacodynamic interactions:

Because of its mechanism of action, **REMCEPT XL** should not be given concomitantly with other cholinomimetics (such as ambenonium, donepezil, neostigmine, pyridostigmine,

rivastigmine or systemically administered pilocarpine). **REMCEPT XL** has the potential to antagonise the effect of anticholinergic medicine. Should anticholinergic medicine such as atropine be abruptly stopped there is a potential risk that **REMCEPT XL** effects could be exacerbated. As expected with cholinomimetics, a pharmacodynamic interaction is possible with medicines that significantly reduce the heart rate such as digoxin, beta-blockers, certain calcium-channel blocking medicines and amiodarone (see **section 4.4**).

Caution should be taken with medicines that have potential to cause *torsade's de pointes*. In such cases an ECG should be considered.

REMCEPT XL, as a cholinomimetic, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia, especially in cases of pseudocholinesterase deficiency.

Pharmacokinetic interactions:

Multiple metabolic pathways and renal excretion are involved in the elimination of **REMCEPT XL**. The occurrence of significant interactions may be clinically relevant in individual cases.

Concomitant administration with food slows the absorption rate of **REMCEPT XL** but does not affect the extent of absorption. It is recommended that **REMCEPT XL** be taken with food in order to minimise cholinergic side effects.

Other medicines affecting the metabolism of galantamine:

Formal interaction studies showed an increase in **REMCEPT XL** bioavailability of about 40 % during co-administration of paroxetine (a potent CYP2D6 inhibitor) and of 30 % and 12 % during co-treatment with ketoconazole and erythromycin (both CYP3A4 inhibitors). Therefore, during initiation of treatment with potent inhibitors of CYP2D6 (e.g. quinidine, paroxetine or fluoxetine) or CYP3A4 (e.g. ketoconazole or ritonavir) patients may experience an increased incidence of cholinergic adverse reactions, predominantly nausea and vomiting. Under these circumstances, based on tolerability, a reduction of the **REMCEPT XL** maintenance dose can be considered (see **section 4.2**).

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

Effect of REMCEPT XL on the metabolism of other medicines:

Therapeutic doses of galantamine as in **REMCEPT XL** 24 mg/day had no effect on the kinetics of digoxin, although pharmacodynamic interactions may occur.

Therapeutic doses of galantamine as in **REMCEPT XL** 24 mg/day had no effect on the kinetics and prothrombin time (INR) of warfarin.

4.6. Fertility, pregnancy and lactation:

Pregnancy:

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

Animal studies have shown reproductive toxicity.

Breastfeeding:

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

Women on **REMCEPT XL** should not breastfeed their infants.

Fertility:

The effect of galantamine on human fertility has not been evaluated.

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. **REMCEPT XL** may cause 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:

System Organ Class	Frequency	Undesirable effects
Blood and the lymphatic system disorders	*Frequent* *Less Frequent*	Anaemia Thrombocytopenia
Immune system disorders	*Less Frequent*	Hypersensitivity
Metabolism and nutrition disorders	*Frequent* *Less Frequent*	Decreased appetite, weight decrease Dehydration, hyperglycaemia, increased alkaline phosphate
Psychiatric disorders	*Frequent* *Less Frequent*	Hallucination, depression, insomnia, anorexia, somnolence, agitation, confusion, anxiety Hallucination visual, hallucination auditory, paranoid reaction, increased libido, delirium, suicidal ideation, suicide

Nervous system disorder	*Frequent* *Less Frequent*	Headache, somnolence, lethargy, tremor, dizziness, syncope Paraesthesia, dysgeusia, hypersomnia, seizures, vertigo, hypertonia, convulsions, involuntary muscle contractions, ataxia, hyperkinesia, apraxia, aphasia, leg cramps
Eye disorders	*Less Frequent*	Blurred vision
Ear and labyrinth disorders	*Less Frequent*	Tinnitus
Cardiac disorders	*Frequent* *Less Frequent*	Bradycardia Supraventricular extrasystoles, first degree atrioventricular block, sinus bradycardia, palpitations, cardiac failure, myocardial ischaemia or infarction, atrial dysrhythmias, atrial fibrillation, supraventricular tachycardia's, QT prolonged, bundle branch block, T-wave inversion, ventricular tachycardia
Vascular disorders	*Frequent*	Hypertension, peripheral oedema

	Less Frequent	Hypotension, flushing, postural hypotension, dependent oedema, purpura, epistaxis
Gastrointestinal disorders	*Frequent* *Less Frequent*	Nausea, vomiting, constipation, flatulence, abdominal pain, upper abdominal pain, diarrhoea, dyspepsia, abdominal discomfort Retching ,gastritis, melaena, dysphagia, rectal haemorrhage, dry mouth, increased saliva, diverticulitis, gastroenteritis, hiccup, oesophageal perforation
Hepatobiliary disorders	*Less Frequent*	Hepatitis
Skin and subcutaneous tissue disorders	*Frequent* *Less Frequent*	Hyperhidrosis Stevens Johnson syndrome, acute generalised exanthematous pustulosis, erythema multiforme
Musculoskeletal, Connective tissue and bone disorders	*Frequent* *Less Frequent*	Muscle spasms Muscle weakness

Renal and urinary disorders	*Frequent* *Less Frequent*	Urinary tract infection, haematuria, urinary incontinence Micturition frequency, cystitis, urinary retention, nocturia, renal calculi
Respiratory, thoracic and mediastinal disorders	*Frequent*	Rhinitis, upper respiratory tract infection, bronchitis, coughing
General disorders and administrative site conditions	*Frequent*	Fatigue, syncope, asthenia, malaise, injury, back pain, chest pain, fever
Investigations	*Less Frequent*	Hepatic enzyme increase
Injury, poisoning and procedural complications	*Frequent*	Fall

Reporting of suspected adverse reactions:

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

4.9. Overdose:

Symptoms:

Signs and symptoms of significant overdosing of **REMCEPT XL** 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 fasciculation's, 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 bronchospasms, 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 **REMCEPT XL**.

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 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.

5. PHARMACOLOGICAL PROPERTIES:

5.1. Pharmacodynamic properties:

A 5.3 Cholinomimetics

ATC code: N06DA04

PHARMACOLOGICAL 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. As a consequence, an increased activity in the cholinergic system associated with improved

cognitive function can be achieved in patients with dementia of the Alzheimer type.

5.2. Pharmacokinetic properties:

Absorption:

After oral intake of a single dose 8 mg galantamine (as tablets), 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 twice daily 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 epimerisation. *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 to 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 to 97 % of the radioactivity was recovered in the urine and 2,2 – 6,3 % in the faeces. After I.V. and oral administration, 18 to 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 to 25 % of the total plasma clearance.

Dose-linearity:

After repeated oral dosing of 12 mg galantamine b.i.d. (as tablets), mean trough and peak plasma concentrations fluctuated between 30 and 90 ng/ml. The pharmacokinetics of galantamine is linear in the dose range 4 to16 mg b.i.d.

Special populations:

Elderly:

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 primarily due to the advanced age and reduced kidney function.

Hepatic impairment:

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

Renal Impairment:

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 to 104 ml/min) and by 67 % in severe impairment (Cl_{CR} = 9 to 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:

The other ingredients in **REMCEPT XL** are:

Ethyl cellulose, erythrocin FD&C Red 3, gelatine, hypromellose, Indigo carmine FD&C Blue 2, magnesium stearate, microcrystalline cellulose, red iron oxide (E172), titanium dioxide, (E172), yellow iron oxide (E172).

6.2. Incompatibilities:

Not applicable

6.3. Shelf life:

24 months

6.4. Special precautions for storage:

Store at or below 25 °C. Store in the original packaging. Keep blisters in the carton and capsules in the bottle until required for use. Keep the HDPE container tightly closed.

KEEP OUT OF THE REACH OF CHILDREN.

6.5. Nature and contents of container:

Packs of 28's or 30's prolonged release hard capsules packed in glossy, transparent , PVC/PE/PVDC film and aluminium foil, shiny on the inside and dull (matte) on the outside blisters in a cardboard carton.

White opaque, round HDPE bottles with a white plastic child-resistant tamper-evident screw cap and an aperture for desiccant in packs of 100's prolonged release hard capsules in a cardboard carton.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product:

No special requirements

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West, Waterfall City

Midrand, Gauteng,

South Africa

8. REGISTRATION NUMBER:

REMCEPT XL 8 mg: 46/5.3/0998

REMCEPT XL 16 mg: 46/5.3/0999

REMCEPT XL 32 mg: 46/5.3/1000

9. DATE OF FIRST AUTHORISATION:

29 September 2017

10. DATE OF REVISION OF TEXT:

30 April 2021