Proposed Professional Information for MEMINIST 10

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MEMINIST 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg memantine hydrochloride.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Off-white, capsule shaped, biconvex, film-coated tablets, debossed with “M” and 10 on either side of the break line on one side and break line on other side. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MEMINIST 10 is indicated for the treatment of patients with moderately severe to severe Alzheimer's disease.

Efficacy has not been established beyond 6 months.

4.2 Posology and method of administration

Posology

Treatment should be initiated and supervised by a medical practitioner experienced in the diagnosis and treatment of Alzheimer's dementia. Therapy should only be started if a caregiver is available who will regularly monitor medicine intake by the patient. Diagnosis should be made according to current guidelines.

Adults:

The maximum daily dose is 20 mg per day.

In order to reduce the risk of side effects, the maintenance dose is achieved by upward titration of 5 mg per week over the first 3 weeks as follows:

Treatment should be started with 5 mg per day (half a tablet in the morning) during the 1st week. In the 2nd week 10 mg per day (half a tablet twice a day), and in the 3rd week 15 mg per day is recommended (one tablet in the morning and half a tablet in the afternoon). From the 4th week on, treatment can be continued with the recommended maintenance dose of 20 mg per day (one tablet twice a day).

Special populations

Elderly: The recommended dose for patients > 65 years of age is 20 mg per day (10 mg twice a day) as described above.

Renal impairment: In patients with normal to mildly impaired renal function (serum creatinine levels of up to 130 µmol/L) no dose reduction is needed.

In patients with moderate renal impairment (creatinine clearance 40 – 60 mL/min/1,73 m^2) the dose should be reduced to 10 mg per day.

No data are available for patients with severely reduced kidney function (see section 4.4).

Hepatic impairment: There are no data on the use of MEMINIST 10 in patients with hepatic impairment.

Method of administration

MEMINIST 10 tablets should be taken orally once a day and should be taken at the same time every day.

The tablets can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to memantine hydrochloride or to any of the excipients listed in section 6.1.
- Children and adolescents under the age of 18 years, as safety and efficacy have not been established.

4.4 Special warnings and precautions for use

MEMINIST 10 therapy is not recommended for patients with severe renal impairment (creatinine clearance less than 9 mL/min/1,73 m^2) as no data are available (see section 4.2).

Under alkaline conditions the rate of elimination of MEMINIST 10 is reduced (see section 5.2). Factors that may raise urine pH therefore may necessitate careful monitoring of the patient. These factors include drastic changes in diet, e.g. from a diet rich in meat products to a vegetarian diet, or a massive ingestion of alkalising gastric buffers.

Urine pH may also be elevated by states of renal tubular acidosis (RTA) or severe infections of the urinary tract with *Proteus* bacteria.

Caution is recommended in patients at risk of convulsions, former history of convulsions or patients with predisposing factors for epilepsy.

Concomitant use of *N*-methyl-D-aspartate (NMDA)-antagonists, such as amantadine, ketamine or dextromethorphan, with MEMINIST 10 should be avoided. These compounds act at the same receptor system as MEMINIST 10, and therefore side effects (mainly central nervous system (CNS)-related) may be more frequent or more pronounced (see section 4.5).

Limited data are available on patients with recent myocardial infarction, uncompensated

congestive heart failure (NYHA III-IV) and uncontrolled hypertension. These patients should be closely supervised.

4.5 Interaction with other medicines and other forms of interaction

- The effects of L-dopa, dopaminergic agonists and anticholinergics may be enhanced by concomitant treatment with MEMINIST 10 .
- The effects of barbiturates and neuroleptics may be reduced during concomitant treatment with MEMINIST 10 .
- MEMINIST 10 may alter the effects of the antispasmodic medicines dantrolene and baclofen, and a dosage adjustment may be necessary.
- Use of other NMDA antagonists such as amantadine, ketamine or dextromethorphan with MEMINIST 10 should be avoided, as it may increase the incidence and severity of pharmacotoxic psychosis (see section 4.4).
- There is one published case report on a possible risk also for the combination of MEMINIST 10 and phenytoin.
- Medicines such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine, that use the same renal cationic transport system as amantadine, may interact with MEMINIST 10 leading to a potential risk of increased plasma levels.
- MEMINIST 10 decreases the area under the curve (AUC) and peak plasma concentration (C_{max}) of hydrochlorothiazide by 20 %.
- In post-marketing experience, isolated cases with international normalised ratio (INR) increases have been reported in patients concomitantly treated with warfarin. Although no causal relationship has been established, close monitoring of prothrombin time or INR is advisable for patients concomitantly treated with oral anticoagulants.
- In single-dose pharmacokinetic (PK) studies in young healthy patients, no relevant interaction of memantine with glyburide/metformin or donepezil was observed.
- In a clinical study in young healthy patients, no relevant effect of memantine on the

pharmacokinetics of galantamine was observed.

- Memantine did not inhibit CYP 1A2, 2A6, 2C9, 2D6, 2E1, 3A, flavin containing monooxygenase, epoxide hydrolase or sulphation *in vitro*.

4.6 Fertility, pregnancy and lactation

The safety and efficacy of MEMINIST 10 have not been established in pregnant and lactating women.

Pregnancy

There are no or limited amount of data from the use of memantine, as in MEMINIST 10 in pregnant women. Animal studies indicate a potential for reducing intrauterine growth at exposure levels, which are identical or slightly higher than at human exposure. The potential risk for humans is unknown.

Breastfeeding

It is not known whether memantine, as in MEMINIST 10 is excreted in human breast milk but, taking into consideration the lipophilicity of the substance, this probably occurs. Women taking MEMINIST 10 should not breastfeed.

4.7 Effects on ability to drive and use machines

MEMINIST 10 may change reactivity and outpatients should be warned to take special care when driving a vehicle or operating machinery. Moderate to severe Alzheimer's disease also usually causes impairment of driving performance and compromises the ability to use machinery.

4.8 Undesirable effects

Infections and infestations

Less frequent: Fungal infections.

Immune system disorders

Frequent: Hypersensitivity.

Blood and lymphatic system disorders

Frequency unknown: Thrombocytopenia.

Endocrine disorders

Frequency unknown: Acute pancreatitis[1], hypoglycaemia.

Metabolism and nutrition disorders

Less frequent: Anorexia.

Frequency unknown: Hyperlipidaemia.

Psychiatric disorders

Frequent: Agitation, hallucinations[2], insomnia, somnolence.

Less frequent: Depression.

Frequency unknown: Psychotic reactions[1].

Nervous system disorders

Frequent: Confusion, dizziness, headache, balance disorders.

Less frequent: Anxiety, abnormal gait, seizures.

Frequency unknown: Dyskinesia, neuroleptic malignant syndrome, tardive dyskinesia, carpal tunnel syndrome, restlessness.

Cardiac disorders

Less frequent: Cardiac failure.

Frequency unknown: Atrioventricular block, prolonged QT interval, supraventricular tachycardia, tachycardia.

Vascular disorders

Frequent: Hypertension.

Less frequent: Venous thrombosis/ thromboembolism.

Frequency unknown: Cerebral infarction, intracranial haemorrhage, claudication.

Respiratory, thoracic and mediastinal disorders

Frequent: Coughing, dyspnoea.

Less frequent: Bronchitis, upper respiratory tract infection.

Frequency unknown: Aspiration pneumonia.

Gastrointestinal disorders

Frequent: Constipation.

Less frequent: Vomiting, diarrhoea, nausea.

Frequency unknown: Ileus, colitis, dysphagia, gastritis, gastro-oesophageal reflux.

Hepatobiliary disorders

Frequent: Elevated liver function tests.

Frequency unknown: Hepatic failure, hepatitis.

Skin and subcutaneous tissue disorders

Frequency unknown: Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders

Less frequent: Hypertonia (increased muscle tone), arthralgia, back pain.

Frequency unknown: Bone fracture.

Renal and urinary disorders

Frequent: Urinary incontinence.

Less frequent: Cystitis, urinary tract infection.

Frequency unknown: Acute renal failure.

Reproductive system and breast disorders

Less frequent: Increased libido.

Frequency unknown: Impotence.

General disorders and administrative site conditions

Frequent: Inflicted injury.

Less frequent: Peripheral oedema, tiredness, fatigue, influenza-like syndrome, pain.

Frequency unknown: Chest pain, malaise.

[1] Isolated cases reported in post-marketing experience.

[2] Hallucinations have mainly been observed in patients with severe Alzheimer's disease.

Alzheimer's disease has been associated with depression, suicidal ideation and suicide. In post-marketing experience these reactions have been reported in patients treated with MEMINIST 10.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of MEMINIST 10 is important. It allows continued monitoring of the benefit/risk balance of MEMINIST 10 . Health care providers are asked to report any suspected adverse reactions via the **"6.04 Adverse Drug Reaction**

Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

See section 4.8.

Symptoms

Relatively large overdoses (200 mg and 105 mg/day for 3 days, respectively) have been associated with either only symptoms of tiredness, weakness and/or diarrhoea or no symptoms. In the overdose cases below 140 mg or unknown dose, the patients revealed symptoms from central nervous system (confusion, drowsiness, somnolence, vertigo, agitation, aggression, hallucination and gait disturbance) and/or of gastrointestinal origin (vomiting and diarrhoea).

In the most extreme case of overdose, the patient survived the oral intake of a total of 2 000 mg memantine with effects on the central nervous system (coma for 10 days, and later diplopia and agitation). The patient received symptomatic treatment and plasmapheresis. The patient recovered without permanent sequelae.

In another case of a large overdose, the patient also survived and recovered. The patient had received 400 mg memantine orally. The patient experienced central nervous system symptoms such as restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor and unconsciousness.

Treatment

Treatment of overdosage should be symptomatic and supportive. No specific antidote for intoxication or overdose is available. Standard clinical procedures to remove active substance material, e.g. activated charcoal (interruption of potential entero-hepatic recirculation), acidification of urine or forced diuresis should be used as appropriate.

In case of signs and symptoms of general central nervous system (CNS) overstimulation, careful symptomatic clinical treatment should be considered.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 5.11 Medicines affecting autonomic function. Others.

Pharmacotherapeutic group: Psychoanaleptics. Other Anti-dementia drugs, ATC code: N06DX01.

5.1 Pharmacodynamic properties

Memantine is a voltage dependent, moderate-affinity non-competitive antagonist of the NMDA-type glutamate receptor. It blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction. Memantine interacts with the Mg^{2+} binding site of the channel to prevent excessive activation, while sparing normal function.

Increasing evidence suggests that malfunctioning of glutamatergic neurotransmission, in particular at *N*-methyl-D-aspartate (NMDA)-receptors, contributes to both expression of symptoms and disease progression in neurodegenerative dementia.

5.2 Pharmacokinetic properties

Absorption:

Memantine has an absolute bioavailability of approximately 100 %. Peak plasma concentrations are achieved between 3 – 8 hours. There is no indication that food influences the absorption of memantine.

Linearity:

The pharmacokinetics of memantine are linear in the dose range between 10 – 40 mg.

Distribution:

The volume of distribution is approximately 10 L/kg. About 45 % of memantine is bound to plasma protein.

Biotransformation:

Approximately 80 % of the circulating memantine-related material is present as the parent compound. The main metabolites are *N*-3,5-dimethyl-gludantan, the isomeric mixture of 4- and 6-hydroxy-memantine, and 1-nitroso-3,4-dimethyl-adamantane. None of these metabolites exhibits NMDA-antagonistic activity, and *in vitro* no P450 catalysed metabolism has been detected.

Elimination:

Memantine is eliminated in a monoexponential manner, with a terminal half-life of 60 – 100 hours. The total clearance of memantine amounts to 170 mL/min/1,73 m^2, and part of total renal clearance is achieved by tubular secretion. Renal handling involves tubular reabsorption and is probably mediated by cation transport proteins. Alkaline urine conditions may reduce renal elimination of memantine (see section 4.4).

Special populations:

Renal impairment:

A significant correlation between creatinine clearance and total renal clearance of memantine has been observed in elderly patients with normal and reduced renal function (creatinine clearance of 50 – 100 mL/min/1,73 m^2) (see section 4.2).

Hepatic impairment:

The effects of liver impairment on the pharmacokinetics of memantine have not been evaluated. As memantine is metabolised only to a minor extent, and into metabolites with no NMDA-

antagonistic activity, the pharmacokinetics of memantine are not expected to produce clinically significant changes in patients with mild to moderate hepatic impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal anhydrous silica

Crospovidone

Magnesium stearate

Microcrystalline cellulose

Povidone

Purified talc.

Tablet coating:

Hypromellose

Polyethylene glycol

Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blister strips in outer carton until required for use.

6.5 Nature and contents of container

Clear transparent triplex (PVC/PE/PVDC) film blister strips with aluminium foil containing 10 tablets. Six blister strips are packed in an outer carton.

Pack size: 60 tablets.

6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unichem SA (Pty) Ltd

San Domenico, Ground Floor, Unit 4

10 Church Street, Durbanville

Cape Town

7551

8. REGISTRATION NUMBER

46/5.11/0427

9. DATE OF FIRST AUTHORISATION

18 February 2016

10. DATE OF REVISION OF THE TEXT

24 January 2022