PROFESSIONAL INFORMATION for

EMORIX

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

EMORIX, 10 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of memantine hydrochloride equivalent to 8,31 mg memantine.

Each film-coated tablet contains 2,06 mg of sodium (as sodium croscarmellose).

Emorix is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oblong biconvex white film-coated tablets, bearing a break mark.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EMORIX 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 daily (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).

Elderly:

On the basis of the clinical studies the recommended dose for patients over the age of 65 years 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/litre) no dose reduction is needed. In patients with moderate renal impairment (creatinine clearance 40 - 60 ml/min/1,73 m²) daily dose should be reduced to 10 mg per day. No data are available for patients with severely reduced kidney
function (see sections 4.4 and section 5.2).

Hepatic impairment:

There are no data on the use of EMORIX in patients with hepatic impairment (see section 5.2). Emorix is not recommended in patients with hepatic impairment.

Paediatric population:

Safety and efficacy in children and adolescents under the age of 18 years have not been established (see section 4.3).

Method of administration:

Emorix is for oral administration.

Emorix can be taken with or without food.

4.3 Contraindications:

- Hypersensitivity to memantine hydrochloride or any of the excipients of EMORIX 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

Medicine interactions

EMORIX, used concomitantly with N-methyl-aspartate (NMDA)-antagonists such as amantadine, ketamine or dextromethorphan, should be avoided. As these compounds act at the same receptor system as memantine as in EMORIX, adverse reactions, mainly CNS related, may be more frequent or more pronounced.

Severe renal impairment:

The use of memantine as in EMORIX is not recommended in patients with severe renal impairment (creatinine clearance less than 9 ml/min/1,73 m^2) as no data are available for these patients.

Epilepsy

Caution should be exercised with patients suffering from epilepsy based on pharmacological

considerations and single case reports.

Some factors that may raise urine pH (see section 5.2) may necessitate careful monitoring of the patient. These factors include drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or a massive ingestion of alkalising gastric buffers. Also, urine pH may be elevated by states of renal tubulary acidosis (RTA) or severe infections of the urinary tract with *Proteus* bacteria.

Only limited data are available in patients with recent myocardial infarction, congestive heart failure (NYHA III-IV) and uncontrolled hypertension. Patients with these conditions should be closely monitored.

4.5 Interaction with other medicines and other forms of interaction

Due to the pharmacological effects and the mechanisms of action of memantine as in EMORIX the following interactions may occur:

Studies have shown that the effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with NMDA-antagonists such as memantine.

The effects of barbiturates and neuroleptics may be reduced. Concomitant administration of memantine with the antispasmodic medicines, dantrolene or baclofen, can modify their effects and a dose adjustment may be necessary.

Due to the risk of pharmacotoxic psychosis, the use of memantine as in EMORIX concomitantly with amantadine should be avoided as both compounds are chemically related NMDA-antagonists. This may apply to ketamine and dextromethorphan (see section 4.4).

Medicines such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine that use the same renal cationic transport system as amantadine, may also possibly interact with memantine as in EMORIX which may lead to a potential risk of increased plasma levels.

When EMORIX is administered concomitantly with hydrochlorothiazide or any combination medicine with hydrochlorothiazide, the diuretic affect may be reduced.

Memantine as in EMORIX did not inhibit CYP 1A2, 2A6, 2C9, 2D6, 2E1, 3A, flavin containing monoxygenase, epoxide hydrolase and sulphation *in vitro*.

Cases of 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Memantine as in EMORIX is not recommended in pregnant women as the safety and efficacy have not been established.

Breastfeeding

Breastfeeding is not recommended as no information is available regarding the use of memantine as in EMORIX.

Fertility

No effects of memantine as in EMORIX on male and female fertility were observed.

4.7 Effects on ability to drive and operate machinery

Compromising of the ability to use machinery and the impairment of driving performance is usually caused by moderately severe to severe Alzheimer's disease.

Patients should take special care when driving a vehicle or operating machinery as EMORIX may change reactivity**.**

Emorix may cause dizziness and somnolence (see section 4.8). Patients must be advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicine affects their ability to perform these activities.

4.8 Undesirable effects

Studies have shown that the overall incidence rates for adverse events did not differ in patients diagnosed with moderately severe to severe dementia and that was treated with memantine and treated with placebo respectively.

Infections and infestations:

Less frequent: Fungal infections, Cystitis.

***I**mmune system disorders*

Frequent: Medicine hypersensitivity.

Psychiatric disorders:

Frequent: Insomnia, Somnolence

Less frequent: Confusion, hallucinations[1].

Frequency unknown: Psychotic reactions[2].

Nervous system disorders:

Frequent: Agitation, balance disorder, dizziness, fall, headache.

Less frequent: Gait abnormal, seizures.

Cardiac disorders:

Less frequent: Cardiac failure.

Vascular disorders:

Frequent: Hypertension.

Less frequent: Venous thrombosis/thromboembolism.

Respiratory, thoracic and mediastinal disorders:

Frequent: Coughing, Dyspnoea.

Gastrointestinal disorders:

Frequent: Constipation, Diarrhoea.

Less frequent: Vomiting.

Frequency unknown: Pancreatitis[2].

Hepatobiliary disorders

Frequent: Elevated liver function test.

Frequency unknown: Hepatitis.

Renal and urinary disorders:

Frequent: Urinary incontinence.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Hypertonia.

Reproductive system and breast disorders:

Less frequent: Increased libido.

General disorders and administrative site conditions:

Frequent: Inflicted injury

Less frequent: Fatigue.

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

[2] Cases reported in post-marketing experience.

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 EMORIX.

Reporting of suspected adverse reactions

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

Adverse reactions also must be reported to Unicorn Pharmaceuticals (Pty) Ltd to vigilance@unicornpharma.co.za.

4.9 Overdose

Signs and symptoms

A patient who received 400 mg memantine orally survived and recovered. The patient experienced central nervous system symptoms such as restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor, and unconsciousness.

Management of overdose

Overdose must be treated symptomatic and supportive. No specific antidote for intoxication or overdose is available, Appropriate standard clinical procedures to remove active material should be used e.g. carbo-medicinalis (interruption of potential entero-hepatic recirculation), acidification of urine, forced diuresis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties:

Category and Class: 5.11 Medicines affecting autonomic function; others

Pharmacotherapeutic group: Psychoanaleptics, Other anti-dementia drugs, ATC code:

N06DX01.

There is increasing evidence 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.

Memantine is a voltage-dependent, moderate-affinity uncompetitive NMDA-receptor antagonist. It blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

5.2 Pharmacokinetic Properties

Absorption: Memantine has an absolute bioavailability of approximately 100%. T_{max} is between 3 and 8 hours. There is no indication that food influences the absorption of memantine.

Linearity: Studies in volunteers have demonstrated linear pharmacokinetics in the dose range of 10 to 40 mg.

Distribution: Daily doses of 20 mg lead to steady-state plasma concentrations of memantine ranging from 70 to 150 ng/ml (0,5-1 µmol) with large interindividual variations. When daily doses of 5 to 30 mg were administered, a mean CSF/serum ratio of 0,52 was calculated. The volume of distribution is around 10 litres/kg. About 45 % of memantine is bound to plasma-proteins.

Biotransformation: In man, about 80 % of the circulating memantine-related material is present as the parent compound. Main human metabolites are N-3, 5-dimethyl-gludantan, the isomeric mixture of 4- and 6-hydroxy-memantine, and 1-nitroso-3, 5-dimethyl-adamantane. None of these metabolites exhibit NMDA-antagonistic activity. No cytochrome P 450 catalysed metabolism has been detected *in vitro.*

In a study using orally administered ^{14}C-memantine, a mean of 84 % of the dose was recovered within 20 days, more than 99 % being excreted renally.

Elimination: Memantine is eliminated in a monoexponential manner with a terminal $t_{½}$ of 60 to 100 hours. In volunteers with normal kidney function, total clearance ($Cl_{tot)}$ amounts to 170 ml/min/1,73 m² and part of total renal clearance is achieved by tubular secretion.

Renal handling also involves tubular reabsorption, probably mediated by cation transport proteins. The renal elimination rate of memantine under alkaline urine conditions may be reduced by a factor of 7 to 9 (see section 4.4). Alkalisation of urine may result from drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or from the massive ingestion of alkalising gastric buffers.

Specific patient population: In elderly volunteers with normal and reduced renal function (creatinine clearance of 50-100 ml/min/1,73 m²), a significant correlation was observed between creatinine clearance and total renal clearance of memantine (see section 4.2).

The effect of liver disease on the pharmacokinetics of memantine has not been studied. As memantine is metabolised to a minor extent only, and into metabolites with no NMDA-antagonistic activity, clinically relevant changes in the pharmacokinetics are not expected in mild to moderate liver impairment.

Pharmacokinetic/pharmacodynamic relationship: At a dose of memantine of 20 mg per day the cerebrospinal fluid (CSF) levels match the k_i-value (k_i = inhibition constant) of memantine, which is 0,5 µmol in human frontal cortex.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Microcrystalline cellulose, povidone K-25, croscarmellose sodium and magnesium stearate

Film coating:

Opadry which contains: Hydroxipropylcellulose and talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C

Keep blisters in carton until required for use.

6.5 Nature and contents of container

EMORIX is packaged in transparent and colourless flexible blistering polymer (PVC/PCTFE/PVC), sealed against aluminum hard foil and sealing lacquer.

The blisters are packed in an outer cardboard carton.

Pack size: Emorix is supplied in pack sizes of 14, 28, 56, 98 and 112 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Cnr. Searle & Pontac Streets

Cape Town, 8001

South Africa

8 REGISTRATION NUMBER(S)

47/5.11/1102

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 08 February 2022

10 DATE OF REVISION OF THE TEXT

Not applicable