PACKAGE INSERT FOR MEMANTINE UNICHEM 10

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

MEMANTINE UNICHEM 10 film coated tablets

COMPOSITION

Active ingredient:

Each film coated tablet contains 10 mg memantine hydrochloride

Inactive ingredients:

Colloidal anhydrous silica, crospovidone, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, purified talc and titanium dioxide.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION

A 5.11 Medicines affecting autonomic function. Others.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Memantine is a voltage dependant, 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.

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 **WARNINGS AND SPECIAL PRECAUTIONS**).

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 (creatine clearance of 50 - 100 ml/min/1,73 m^2) (see **DOSAGE AND DIRECTIONS FOR USE**).

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.

INDICATIONS

MEMANTINE UNICHEM 10 is indicated for the treatment of patients with moderately severe to severe Alzheimer's disease. Efficacy has not been established beyond 6 months.

CONTRAINDICATIONS

- Hypersensitivity to memantine or to any of the excipients in **MEMANTINE UNICHEM 10** (see **COMPOSITION**).
- Children and adolescents under the age of 18 years, as safety and efficacy have not been established.

WARNINGS AND SPECIAL PRECAUTIONS

MEMANTINE UNICHEM 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 **DOSAGE AND DIRECTIONS FOR USE**).

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Under alkaline conditions the rate of elimination of **MEMANTINE UNICHEM 10** is reduced (see **Pharmacokinetic properties**). 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.

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

Limited data are available on patients with recent myocardial infarction, congestive heart failure (NYHA III-IV) and uncontrolled hypertension. These patients should be closely supervised.

Effects on ability to drive and use machines

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

INTERACTIONS

- The effects of L-dopa, dopaminergic agonists and anticholinergics may be enhanced by concomitant treatment with **MEMANTINE UNICHEM 10**.
- The effects of barbiturates and neuroleptics may be reduced during concomitant treatment

with **MEMANTINE UNICHEM 10**.

- **MEMANTINE UNICHEM 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 **MEMANTINE UNICHEM 10** should be avoided, as it may increase the incidence and severity of pharmatoxic psychosis.
- Medicines such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine, that use the same renal cationic transport system as amantadine, may interact with **MEMANTINE UNICHEM 10** leading to a potential risk of increased plasma levels.
- **MEMANTINE UNICHEM 10** decreases the area under the curve (AUC) and peak plasma concentration (C_{max}) of hydrochlorothiazide by 20 %.

PREGNANCY AND LACTATION

The safety and efficacy of **MEMANTINE UNICHEM 10** have not been established in pregnant and lactating women.

DOSAGE AND DIRECTIONS FOR USE

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).

The tablets can be taken with or without food.

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 **WARNINGS AND SPECIAL PRECAUTIONS**).

Hepatic impairment:

There are no data on the use of **MEMANTINE UNICHEM 10** in patients with hepatic impairment.

SIDE EFFECTS

Blood and the lymphatic system disorders

Frequency unknown: Thrombocytopenia

Endocrine disorders

Frequency unknown: Acute pancreatitis, hypoglycaemia

Metabolism and nutrition disorders

Less frequent: Anorexia

Frequency unknown: Hyperlipidaemia

Psychiatric disorders

Frequent: Agitation, hallucinations, insomnia

Less frequent: Depression, somnolence

Nervous system disorders

Frequent: Confusion, dizziness, headache

Less frequent: Anxiety, abnormal gait

Frequency unknown: Dyskinesia, grand mal convulsions, neuroleptic malignant syndrome, tardive dyskinesia, carpal tunnel syndrome, restlessness

Cardiac disorders

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

Vascular disorders

Less frequent: Hypertension

Frequency unknown: Cerebral infarction, intracranial haemorrhage, claudication

Respiratory, thoracic and mediastinal disorders

Frequent: Coughing

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Less frequent: Bronchitis, dyspnoea, upper respiratory tract infection

Frequency unknown: Aspiration pneumonia

Gastrointestinal disorders

Less frequent: Vomiting, constipation, diarrhoea, nausea

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

Hepatobiliary disorders

Frequency unknown: Hepatic failure

Skin and subcutaneous tissue disorders

Frequency unknown: Stevens-Johnson syndrome

Musculoskeletal, connective tissue and bone 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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See **SIDE EFFECTS**.

Treatment of overdosage should be symptomatic and supportive.

IDENTIFICATION

Off-white, capsule shaped, biconvex, uncoated tablets, debossed with “M” and 10 on either side of the break line on one side and break line on other side.

PRESENTATION

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

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Keep blister strips in outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

46/5.11/0416

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Unichem S.A. (Pty) Ltd.

Signed: _____

1st Floor, Pinewood Park

Lonsdale Road, Pinelands

Cape Town 7405

DATE OF PUBLICATION OF THE PACKAGE INSERT

18 February 2016

Signed: _____