SCHEDULING STATUS

S4

PROPRIETARY NAME (and dosage form)

COGNIMET 10 (film-coated tablets 10 mg)

COMPOSITION

Each film-coated tablet contains 10 mg memantine hydrochloride.

Contains sugar (lactose monohydrate).

The other ingredients are colloidal silicon dioxide, corn starch, magnesium stearate, povidone and talc. The film coating contains Opadry grey (hypromellose, iron oxide black, macrogol 400 and titanium dioxide).

PHARMACOLOGICAL CLASSIFICATION

A 34 Other

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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.

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 inter-individual 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 mono-exponential 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 m^2 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 "Special Precautions"). 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 m^2), a significant correlation was observed between creatinine clearance and total renal clearance of memantine (see "Dosage and Directions for Use").

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.

INDICATIONS

COGNIMET 10 is indicated for moderately severe to severe Alzheimer's disease.

Efficacy has not been established beyond 6 months.

CONTRA-INDICATIONS

Hypersensitivity to memantine hydrochloride or any of the excipients used in the formulation.

Children under the age of 18 years, as safety and efficacy have not been established.

WARNINGS AND SPECIAL PRECAUTIONS

Not recommended for patients with severe renal impairment (creatinine clearance less than 30 ml/min/1,73 m^2) as no data are available (see “Dosage and Directions for Use”).

Caution is recommended with patients suffering from epilepsy based on pharmacological considerations and single case reports.

Concomitant use of amantadine, ketamine or dextromethorphan due to an increased risk of pharmacotoxic psychosis.

Special Precautions

Alzheimer’s disease is associated with depression, suicidal ideation and suicide. These events have been reported in patients who received memantine hydrochloride as contained in COGNIMET 10.

Some factors that may raise urine pH (see "Pharmacokinetics - Elimination") 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 for patients with recent myocardial infarction, congestive heart failure (NYHA III-IV), and uncontrolled hypertension and therefore these conditions should be closely supervised.

COGNIMET 10 contains lactose. Patients with rare hereditary problems of galactose intolerance, the lapp-lactose deficiency, or glucose-galactose malabsorption should not take **COGNIMET 10**.

INTERACTIONS

The following interactions may occur due to the pharmacological effects and the mechanism of action of **COGNIMET 10**:

The mode of action suggests 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 **COGNIMET 10** with the antispasmodic agents, dantrolene or baclofen, can modify their effects and a dosage adjustment may be necessary.

Concomitant use of **COGNIMET 10** and N-methyl-D-aspartate (NMDA)-antagonists such as amantadine, ketamine or dextromethorphan should be avoided, owing to the risk of pharmaco-toxic psychosis. These compounds are chemically related NMDA-antagonists and act at the same receptor system as **COGNIMET 10**, and therefore adverse drug reactions (mainly CNS-related) may be more frequent or more pronounced. There is one published case report on a possible risk also for the combination of memantine hydrochloride tablets 10 mg and phenytoin.

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 **COGNIMET 10** leading to a potential risk of increased plasma levels.

There may be a possibility of reduced diuretic effect of hydrochlorothiazide (HCTZ) when **COGNIMET 10** is co-administered with HCTZ or any combination with HCTZ.

Increase in the international normalised ratio (INR) was reported with concomitant administration of **COGNIMET 10** and warfarin.

PREGNANCY AND LACTATION

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

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 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).

The tablets can be taken with or without food.

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 30 - 50 ml/min/1,73 m^2) daily dose should be reduced to 10 mg per day. No data is available for patients with severely reduced kidney function (see "Warnings" and "Pharmacokinetic properties").

Hepatic impairment: There is no data on the use of **COGNIMET 10** in patients with hepatic impairment (see "Pharmacokinetic properties").

SIDE-EFFECTS

Infections and infestations

Less frequent: Fungal infections

Immune system disorders

Frequent: Hypersensitivity reactions

Gastrointestinal Disorders

Frequent: Diarrhoea, constipation

Less frequent: Vomiting

Frequency unknown: Pancreatitis

Injury and Poisoning

Frequent: Inflicted injury

Musculoskeletal and Connective Tissue Disorders

Less frequent: Hypertonia (increased muscle tone)

Nervous System Disorders

Frequent: Dizziness, headache, tiredness, balance disorders

Less frequent: Abnormal gait

Frequency unknown: Seizures

Cardiac Disorders

Less frequent: Cardiac failure

Vascular Disorders

Frequent: Hypertension

Less frequent: Venous thrombosis/thromboembolism

Psychiatric Disorders

Frequent: Insomnia, agitation, hallucination, confusion, somnolence

Less frequent: Anxiety, confusion

Frequency unknown: Psychotic reactions

Renal and Urinary Disorders

Frequent: Urinary incontinence

Less frequent: Cystitis

Reproductive System and Breast Disorders

Less frequent: Increased libido

Respiratory, Thoracic and Mediastinal Disorders

Frequent: Coughing, dyspnoea

Hepato-biliary Disorders/Investigations

Frequent: Abnormal liver function test results

Frequency unknown: Hepatitis

General Disorders and Site Administrative conditions:

Frequency unknown: Fatigue

Effects on ability to drive and use machines

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Restlessness, psychosis, visual hallucinations, pro-convulsiveness, somnolence, stupor and loss of consciousness were experienced in a documented case of an overdosage with up to 400 mg memantine. All resolved without permanent sequelae.

Treatment should be symptomatic and supportive.

IDENTIFICATION

Grey-coloured, dumbbell shaped, biconvex, film coated tablet with a break line on both sides.

PRESENTATION

HDPE containers: The tablets are packed in white HDPE containers with white child resistant or white ribbed caps with 30, 60, 90 or 500 tablets per container. Each container is packed in an outer printed cardboard carton.

Blister packs: The tablets are packed in silver coloured PVC-PVdC/Alu or PVC/Alu blister strips, 10 tablets per strip: 3 or 6 strips (30 or 60 tablets) are packed in an outer cardboard carton.

STORAGE INSTRUCTIONS

Store at or below 25 °C in a dry place.

Keep tablets in the original container and keep tightly closed.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

44/34/0438

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