PROPOSED PACKAGE INSERT

SCHEDULING STATUS
S4
PROPRIETARY NAME (and dosage form)
Ebixa® 10 mg film-coated tablets
COMPOSITION
Each tablet contains 10 mg of memantine hydrochloride (equivalent to 8.31 mg memantine).
The other ingredients are croscarmellose sodium, microcrystalline cellulose, colloidal anhydrous silica, and magnesium stearate all in the tablet core and hypromellose, macrogol 400, titanium dioxide (E171) and iron oxide yellow (E172) and all in the tablet coating.
PHARMACOLOGICAL CLASSIFICATION
A 34 Other
PHARMACOLOGICAL ACTION
Pharmacodynamic properties
There is 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.
Clinical studies: A clinical trial in a population of patients suffering from moderately severe to severe Alzheimer's disease (MMSE total scores at baseline of 3-14) showed beneficial effects of memantine treatment in comparison to placebo over a treatment period of 6 months.
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 liters/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 “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 m²), a significant correlation was observed between creatinine clearance and total renal clearance of memantine (see “Dosage and directions for use”).
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

Treatment of patients with moderately severe to severe Alzheimer's disease. Efficacy has not been established beyond 6 months.

CONTRA INDICATIONS

Hypersensitivity to memantine hydrochloride or to any of the excipients of Ebixa.

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

WARNINGS AND SPECIAL PRECAUTIONS

Based on pharmacological considerations and single case reports, caution is recommended with patients suffering from epilepsy.

Concomitant use of N-methyl-D-aspartate (NMDA)-antagonists such as amantadine, ketamine or dextromethorphan should be avoided. These medicines act at the same receptor system as Ebixa, and therefore adverse drug reactions (mainly CNS-related) may be more frequent or more pronounced (see "Interactions").

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 an omnivorous 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*.

Cardiovascular disease

In most clinical trials with Ebixa, patients with recent myocardial infarction, congestive heart failure (NYHA III-IV), and uncontrolled hypertension were excluded. As a

consequence only limited data are available and patients with these conditions should be closely supervised.

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. Furthermore, Ebixa may change reactivity such that outpatients should be warned to take special care when driving a vehicle or operating machinery.

INTERACTIONS

Due to the pharmacological effects and the mechanism of action of Ebixa the following interactions may occur:

- The mode of action suggests that the effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with memantine. The effects of barbiturates and neuroleptics may be reduced. Concomitant administration of Ebixa with the antispasmodic medicines, dantrolene or baclofen, can modify their effects and a dosage adjustment may be necessary.

- Concomitant use of Ebixa and amantadine should be avoided, owing to the risk of pharmacotoxic psychosis. Both medicines are chemically related NMDA-antagonists. The same may be true for ketamine and dextromethorphan (see "Special Precautions"). There is one published case report on a possible risk also for the combination of Ebixa and phenytoin.

- Other active substances such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine that use the same renal cationic transport system as amantadine, may also possibly interact with Ebixa leading to a potential risk of increased plasma levels.

• There may be a possibility of reduced diuretic effect of hydrochlorothiazide (HCT) when Ebixa is co-administered with HCT or any combination with HCT.
• In post-marketing experience, cases with international normalized ratio (INR) increases have been reported in patients concomitantly treated with warfarin or other vitamin K antagonists. Although no causal relationship has been established, close monitoring of prothrombin time or INR is advisable for patients concomitantly treated with oral anticoagulants that affect INR.
In single-dose pharmacokinetic studies in young healthy subjects, no relevant interactions of Ebixa with glyburide/metformin or donepezil was observed.
In a clinical study in young healthy subjects, no relevant effect of Ebixa on the pharmacokinetics of galantamine was observed.
Ebixa did not inhibit CYP 1A2, 2A6, 2C9, 2D6, 2E1, 3A, flavin containing monoxygenase, epoxide hydrolase and sulphation *in vitro*.
PREGNANCY AND LACTATION
The safety and efficacy of Ebixa 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 intake of Ebixa by the patient.
The tolerance and dosing of memantine should be reassessed on a regular basis, preferably within three months after start of treatment. Thereafter, the clinical benefit of

memantine and the patient's tolerance of treatment should be reassessed on a regular basis according to current clinical guidelines. Maintenance treatment [~~can~~] may be continued for as long as a therapeutic benefit is favourable and the patient tolerates treatment with memantine. Ebixa should be discontinued when evidence of a therapeutic effect is no longer present or if the patient does not tolerate treatment.
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 mildly impaired renal function (creatinine clearance 50 - 80 ml/min) no dose adjustment is required. In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) daily dose should be 10 mg per day. If tolerated well after at least 7 days of treatment, the dose could be increased up to 20mg/day according to standard titration scheme. In patients with severe renal impairment (creatinine clearance 5 – 29 ml/min) daily

dosage should be 10mg per day.

Hepatic impairment:

In patients with mild or moderate hepatic impaired function (Child-Pugh A and Child-Pugh B), no dose adjustment is needed.

No data on the use of Ebixa in patients with severe hepatic impairment are available.

Administration of Ebixa is not recommended in patients with severe hepatic impairment.

SIDE EFFECTS

In clinical trials in mild to severe dementia, overall incidence rates for adverse events did not differ from placebo treatment and adverse events were usually mild to moderate in severity.

The following Adverse Reactions listed below have been accumulated in clinical studies with Ebixa and post marketing.

Adverse reactions are ranked according to system organ class, using the following convention: very common (≥1/10), common (≥1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Fungal infections
Immune system disorders	Common	Hypersensitivity reactions
Psychiatric disorders	Common	Somnolence
	Uncommon	Confusion; Hallucinations[1]
	Not known	Psychotic reactions[2]
Nervous system disorders	Common	Dizziness Balance disorders
	Uncommon	Gait abnormal
	Very rare	Seizures
Cardiac disorders	Uncommon	Cardiac failure
Vascular disorders	Common	Hypertension
	Uncommon	Venous thrombosis/ thromboembolism
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
Gastrointestinal disorders	Common	Constipation
	Uncommon	Vomiting
	Not known	Pancreatitis[2]
Hepatobiliary disorders	Common	Elevated liver function test
	Not known	Hepatitis
General disorders and administration site conditions	Common	Headache
	Uncommon	Fatigue

[1] Hallucinations have mainly been observed in patients with severe Alzheimer´s disease.
[2] Isolated cases reported in post-marketing experience.

The most frequently occurring adverse reactions with a higher incidence in the Ebixa group than in the placebo group were dizziness (6,3 % vs 5,6 %), headache (5,2 % vs 3,9 %), constipation (4,6 % vs 2,6 %), somnolence (3,4 % vs 2,2 %) and hypertension (4,1% vs 2,8 %),

Uncommon adverse reactions (0.1-1% and more frequent than with placebo) were anxiety, hypertonia (increased muscle tone), vomiting, cystitis and increased libido.

In post- marketing experience depression, suicidal ideation and suicide have been reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Treatment of overdosage should be symptomatic and supportive see Side Effects.

In one case of suicidal overdosage the patient survived the oral intake of up to 400 mg memantine with effects on the central nervous system (e. g. restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor and unconsciousness) which resolved without permanent sequelae.

IDENTIFICATION

Pale yellow to yellow, oval shaped film-coated tablets with break line and engravings ‘M’ on both parts right and left of the break line and on the other side the imprint ‘1’ left and ‘0’ right of the break line.

PRESENTATION

Colourless, transparent blister packs containing 14 tablets per blister strip. The following printing appears on the blister pack: Ebixa® 10 mg film-coated tablets; Memantine hydrochloride; Lot: Exp: and H. Lundbeck A/S. Pack sizes of 56 tablets.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Keep out of reach of children.

REGISTRATION NUMBER
38/34/0226
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