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), all in the tablet coating.

PHARMACOLOGICAL CLASSIFICATION
A 34 Other

PHARMACOLOGICAL ACTION

Pharmacodynamic properties
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.

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.

In this multicentre, double-blind, randomised, placebo-controlled study, a total of 252 outpatients (33% male, 67% female, mean age 76 years) were included. The dosing was 10 mg memantine twice a day. Primary outcome parameters included assessment of the global domain (using the Clinicians Interview-Based Impression of Change (CIBIC-Plus)) and the functional domain (using the Activities of Daily Living Inventory (ADCS-ADLsev)). Cognition was assessed as a secondary endpoint with the Severe Impairment Battery (SIB). The results in these domains favoured memantine over placebo (Observed Cases Analysis for CIBIC-Plus: p=0.025; ADCS-ADLsev: p=0.003; SIB: p=0.002).

After 6 months, the rate of individual responders (response prospectively defined as stabilisation or improvement in two independent domains) was 29% for the memantine group versus 10% for placebo (p=0.0004). With a triple criterion (response defined as stabilisation or improvement in all three domains: cognition, functional and global domain), there were 11% responders for memantine versus 6% for placebo (p=0.17).

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 "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").

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
Treatment of patients with moderately severe to severe Alzheimer's disease.

Efficacy has not been established beyond 6 months.

CONTRA-INDICATIONS
Hypersensitivity to the active substance or to any of the excipients.

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

WARNINGS
As no data are available for patients with severe renal impairment (creatinine clearance less than 9 ml/min/1.73 m²) therapy is not recommended (see "Dosage and Directions for Use").

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

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 NMDA-antagonists such as memantine. The effects of barbiturates and neuroleptics may be reduced. Concomitant administration of Ebixa with the antispasmodic agents, 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 compounds 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 drugs 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.

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 physician experienced in the diagnosis and treatment of Alzheimer's dementia. Therapy should only be started if a caregiver is available who will regularly monitor drug 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 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 "Warnings" and "Pharmacokinetic properties").

Hepatic impairment: There are no data on the use of Ebixa in patients with hepatic impairment (see "Pharmacokinetic properties").

SIDE-EFFECTS AND SPECIAL PRECAUTIONS
In clinical trials in moderately severe 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 table gives an overview of the most frequent (> 4% for Ebixa) adverse events (irrespective of causal relationship) that were observed in the trial population of patients with moderately severe to severe dementia.

Preferred term (WHO ART)	*Memantine n=299*	*Placebo n=288*
Agitation	*27 (9.0%)*	*50 (17.4%)*
Inflicted Injury	*20 (6.7%)*	*20 (6.9%)*
Urinary Incontinence	*17 (5.7%)*	*21 (7.3%)*
Diarrhoea	*16 (5.4%)*	*14 (4.9%)*
Insomnia	*16 (5.4%)*	*14 (4.9%)*
Dizziness	*15 (5.0%)*	*8 (2.8%)*
Headache	*15 (5.0%)*	*9 (3.1%)*
Hallucination	*15 (5.0%)*	*6 (2.1%)*
Fall	*14 (4.7%)*	*14 (4.9%)*
Constipation	*12 (4.0%)*	*13 (4.5%)*
Coughing	*12 (4.0%)*	*17 (5.9%)*

Common adverse reactions (1-10% and more frequent than with placebo) for memantine and placebo patients respectively were: hallucinations (2.0 vs. 0.7%), confusion (1.3 vs. 0.3%), dizziness (1.7 vs. 1.0%), headache (1.7 vs. 1.4%) and tiredness (1.0 vs. 0.3%).

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

Special precautions
Concomitant use of N-methyl-D-aspartate (NMDA)-antagonists such as amantadine, ketamine or dextromethorphan should be avoided. These compounds 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 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*.

In most clinical trials, 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
Treatment of overdosage should be symptomatic and supportive.

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 below 25 °C. Keep out of reach of children.

REGISTRATION NUMBER
38/34/0226

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