PRODUCT MONOGRAPH

Pr Ebixa®

Memantine Hydrochloride Tablets 10 mg

Manufacturer's standard

N-methyl-D-aspartate (NMDA) receptor antagonist

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NAME OF DRUG

Pr Ebixa®

Memantine Hydrochloride Tablets 10 mg

THERAPEUTIC CLASSIFICATION

N-methyl-D-aspartate (NMDA) receptor antagonist

ACTION AND CLINICAL PHARMACOLOGY

Persistent activation of the central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease. Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open channel) NMDA receptor antagonist, which binds preferentially to the NMDA receptor-operated cation channels. It blocks the effects of pathologically elevated sustained levels of glutamate that may lead to neuronal dysfunction. There is no clinical evidence that memantine prevents or slows neurodegeneration or alters the course of the underlying dementing process in patients with Alzheimer's disease. Memantine exhibits low to negligible affinity for other receptors (GABA, benzodiazepine, dopamine, adrenergic, noradrenergic, histamine and glycine) or voltage-dependent Ca^{2+}, Na^{+} or K^{+} channels. In addition, it does not directly affect the acetylcholine receptor or cholinergic transmission, which have been implicated in the cholinomimetic side effects (e.g., increased gastric acid secretion, nausea and vomiting) seen with acetylcholinesterase inhibitors. Memantine showed antagonist effects at the $5HT_3$ receptor with a potency similar to that for the NMDA receptor.

In vitro studies have shown that memantine does not affect the reversible inhibition of acetylcholinesterase by donepezil or galantamine.

PHARMACOKINETICS

ABSORPTION

Orally administered memantine is completely absorbed. Oral bioavailability is almost 100%. Time to maximum plasma concentration (t_{max}) following single oral doses of 10 to 40 mg memantine ranged between 3 to 8 hours. It has a terminal elimination half-life of about 60-80 hours, with the majority of the dose excreted unchanged in urine. There is no indication that food influences the absorption of memantine.

Studies in volunteers have demonstrated linear pharmacokinetics in the dose range of 10 to 40 mg. Daily doses of 20 mg lead to steady-state plasma concentrations of memantine ranging from 70 to 150 ng/ml (0.5 - 1 μ*M*) with large inter-individual variations.

DISTRIBUTION

The apparent volume of distribution of memantine is approximately 9-11 L/kg and the plasma protein binding is approximately 45%. Memantine rapidly crosses the blood-brain barrier with a CSF/serum ratio of about 0.5.

METABOLISM AND ELIMINATION

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. Memantine undergoes little metabolism being in majority excreted unchanged in urine (75-90%). The remaining dose is converted primarily to three polar metabolites: the N-gludantan conjugate, 6-hydroxy memantine and 1-nitroso-deaminated memantine. These metabolites possess minimal NMDA receptor antagonist activity. The hepatic microsome CYP450 enzyme system does not play a significant role in the metabolism of memantine.

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 resulting in increased plasma levels of memantine (see WARNINGS, Genitourinary Conditions). 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.

SPECIAL POPULATIONS

ELDERLY PATIENTS

The pharmacokinetics of memantine in young and elderly subjects is similar. No adjustment of dosage on the basis of age is recommended.

REDUCED HEPATIC FUNCTION

Memantine is metabolized to a minor extent into metabolites with no NMDA-antagonistic activity, and is excreted primarily in an unchanged form by the kidneys. In a study comparing the pharmacokinetics of memantine in subjects with normal hepatic function and moderate hepatic impairment (Child-Pugh B), moderate hepatic impairment did not significantly alter the pharmacokinetics of memantine following administration of a single 20 mg oral dose of memantine (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

REDUCED RENAL FUNCTION

In elderly volunteers with normal and reduced renal function (creatinine clearance of 50 to ≤80 ml/min/1.73 m^2), a significant correlation was observed between creatinine clearance and total renal clearance of memantine. Following a single 20 mg oral dose of memantine, systemic exposure in geriatric subjects with mild and moderate renal impairment was 14% and 39% greater, respectively, compared to geriatric subjects with normal renal function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

The potential efficacy of Ebixa® (memantine hydrochloride) as a treatment for the symptomatic management of moderate to severe Alzheimer's disease was demonstrated by the results of 2 randomized, double-blind, placebo-controlled 6-month clinical studies. Both studies were conducted in patients with Alzheimer's disease. The mean age of patients participating in the Ebixa® trials was 76 with a range of 50 to 93 years. Approximately 66% of patients were women. Female patients participating in the clinical trials were required to be at least 50 years of age and at least 2 years postmenopausal or surgically sterile. The racial distribution was approximately 91% Caucasian. Patient demographics were similar in a third randomized, double-blind, placebo controlled, 6-month clinical trial in patients with moderate to severe Alzheimer's disease: mean age was 78 years, approximately 71% were female and approximately 81% were Caucasian. In all studies, for patients randomized to Ebixa®, treatment was initiated at 5 mg/day and increased weekly by 5 mg/day to a dose of 20 mg/day (10 mg twice a day).

Study Outcome Measures: In each study, the efficacy of Ebixa® was evaluated using validated assessments for patients with moderate to severe dementia in a dual outcome strategy that included assessment of activities of daily living (modified Alzheimer's Disease Cooperative Study – Activities of Daily Living inventory) (Study 1 and Study 2), and a clinician's global assessment of change (Clinician's Interview Based Impression of Change with caregiver input [Study 1]) or a measure of cognition (Severe Impairment Battery [Study 2 and Study 3]).

The Alzheimer's Disease Cooperative Study – Activities of Daily Living inventory (ADCS-ADL$_{sev}$) measures the functional capabilities of patients and is based on interview of a caregiver familiar with the behaviour of the patient. The modified ADCS-ADL$_{sev}$ includes 19 items that rate the patients' abilities to eat, dress, bathe, telephone, travel, shop, and perform other household chores from the highest level of independent performance to complete loss. Lower total modified ADCS-ADL$_{sev}$ scores indicate greater functional impairment.

The Severe Impairment Battery (SIB) assesses selected aspects of cognitive performance including elements of attention, orientation, language, memory, visuospatial ability, construction, praxis, and social interaction and is sensitive to longitudinal changes in cognitive

function in patients with moderate to severe dementia. Lower total SIB scores indicate greater cognitive impairment.

The ability of Ebixa® to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change, which evaluates four domains: general (overall clinical status), functional (including activities of daily living), cognitive, and behavioural. The CIBIC-Plus represents the assessment of a skilled clinician using validated scales based on his/her observation at an interview with the patient, in combination with information provided by a caregiver familiar with the behaviour of the patient over the interval rated. The CIBIC-Plus is scored as a seven point categorical rating, ranging from a score of 1, indicating "markedly improved" to a score of 4, indicating "unchanged" to a score of 7, indicating "markedly worse."

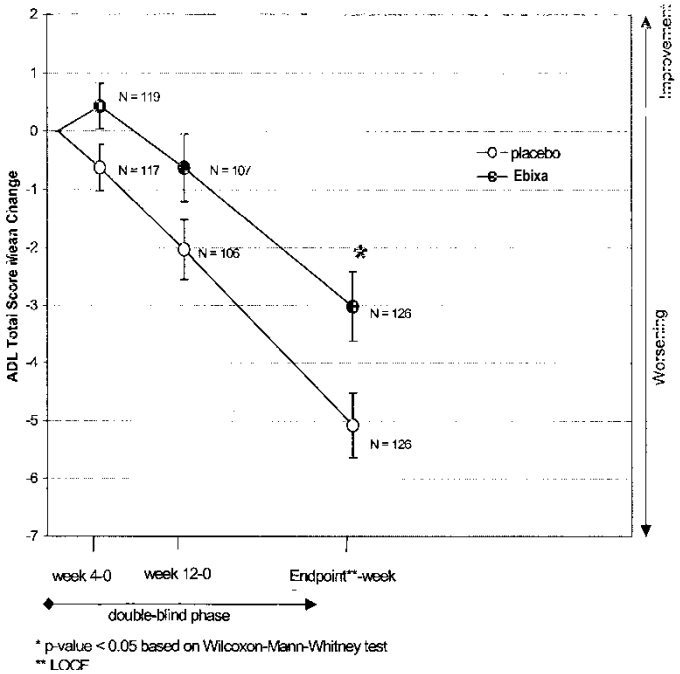
Clinical trial results are summarized for the last observation carried forward (LOCF) analysis of the Intent-to-Treat (ITT) population. The ITT population corresponds to all patients who were randomized to treatment regardless of treatment received and the LOCF analysis is based on carrying the last observation while on treatment forward to the study endpoint when patients were unable to complete the study.

Study 1 (Twenty-Eight-Week Study)

Study 1 was a 28 week study in which 252 patients with moderate to severe Alzheimer's disease (diagnosed according to DSM-IV and NINCDS-ADRDA criteria, with Mini-Mental State Examination scores ≥3 and ≤14 and Global Deterioration Scale Stages 5-6) were randomized to Ebixa® or placebo. Sixty-seven percent and 77% of patients randomized to placebo and Ebixa, respectively, completed the study. The two primary efficacy endpoints were the mean change from baseline to endpoint (Week 28 LOCF) on the ADCS-ADL$_{sev}$ and CIBIC-Plus rating at endpoint (Week 28 LOCF).

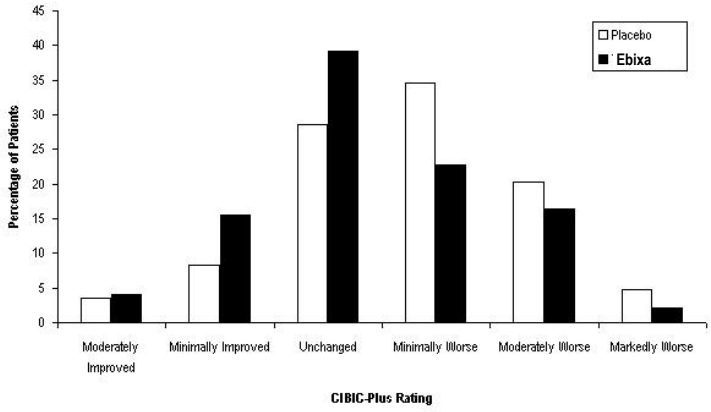
At endpoint (Week 28 LOCF), the mean change from baseline in the ADCS-ADL$_{sev}$ score was statistically significantly less for the Ebixa® -treated patients compared to the patients on placebo (treatment difference of 2.1 units ($p=0.022$) (Figure 1).

Figure 1: Time course of the change from baseline in ADCS-ADLsev score at week 28-LOCF (ITT population)



The percentage distribution of CIBIC-Plus scores for patients in each treatment group is shown in Figure 2. The mean CIBIC-Plus rating for the Ebixa® group was numerically superior, but not statistically significantly superior, to that of the placebo group (treatment difference of 0.25 units, p = 0.06).

Figure 2: Distribution of CIBIC-Plus ratings at week 28 -LOCF (ITT population)



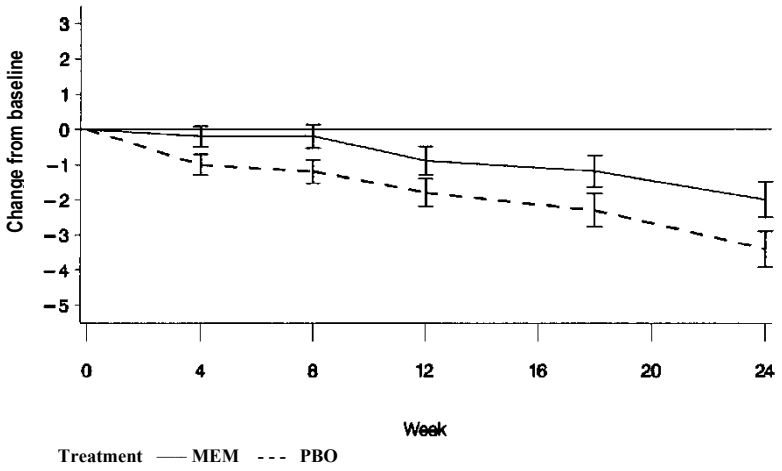
The Severe Impairment Battery was a secondary efficacy measure. At study endpoint (Week 28 LOCF), the mean difference in the SIB change scores from baseline for the Ebixa®-treated patients compared to the patients on placebo was 5.9 units, with the Ebixa group showing less decline than the placebo group.

Study 2 (Twenty-Four-Week Study)

Study 2 was a 24 week study that evaluated the efficacy of memantine as adjunctive therapy with donepezil in 404 patients with moderate to severe Alzheimer's disease (diagnosed by according to NINCDS-ADRDA criteria, with Mini-Mental State Examination scores ≥5 and ≤14). Prior to randomization to treatment with Ebixa® or placebo, patients had been treated with donepezil for at least 6 months and were on a stable dose of donepezil for 3 months. All patients continued to receive donepezil while being treated with placebo or memantine. Seventy-five percent and 85% of randomized patients on placebo/donepezil and Ebixa®/donepezil, respectively, completed the study. The two primary endpoints were the mean changes from baseline to endpoint (Week 24 LOCF) on the ADCS-ADLsev and SIB.

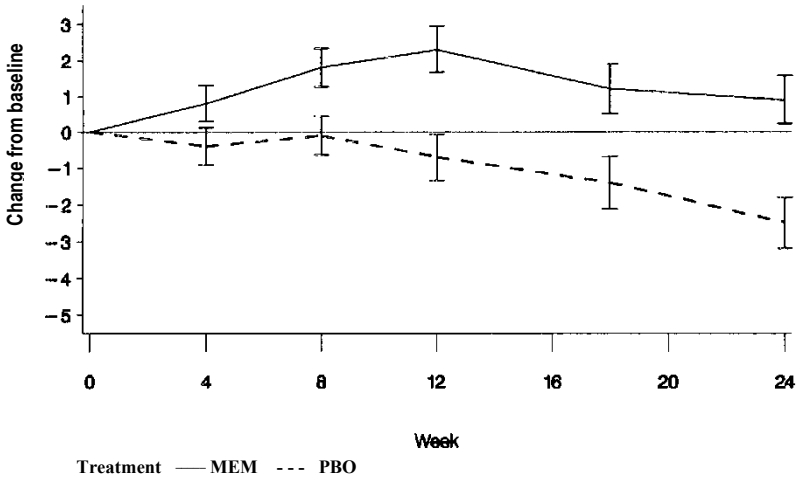
The mean change in the ADCS-ADLsev scores from baseline to Week 24 LOCF was statistically significantly less for the Ebixa®/donepezil treated patients compared to the patients on placebo/donepezil (treatment difference 1.4 units, p=0.028).

Figure 3: Time course of the change from baseline in ADCS-ADLsev score at 24 weeks-LOCF (ITT Population)



At study endpoint (Week 24 LOCF) the mean difference in the SIB change scores for the Ebixa®/donepezil treated patients compared to the patients on placebo/donepezil was 3.4 units ($p<0.001$). Ebixa®/donepezil treatment was statistically significantly superior to placebo/donepezil.

Figure 4: Time course of the change from baseline in SIB score at 24 weeks-LOCF (ITT Population)



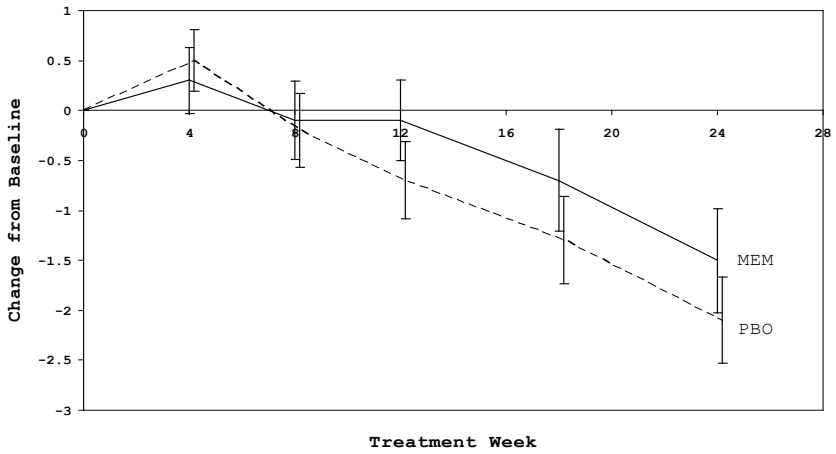
The CIBIC-Plus was a secondary efficacy measure. The mean CIBIC-Plus rating for the Ebixa/donepezil group was lower than that of placebo/donepezil group (treatment difference of 0.25 units).

Study 3 (Twenty-four-Week Study)

Study 3 was a 24 week study, in which 350 patients with moderate to severe Alzheimer's disease (diagnosed according to DSM-IV and NINCDS-ADRDA criteria, with Mini-Mental State Examination scores ≥5 and ≤14) were randomized to Ebixa® or placebo. Seventy-three percent and 75% of patients randomized to placebo and Ebixa, respectively, completed the study. The two primary efficacy endpoints were the mean change from baseline to endpoint (Week 24 LOCF) on the ADCS-ADL$_{sev}$ and SIB. Differences between treatment groups on the two primary endpoints were not statistically significant based on the primary analysis of efficacy.

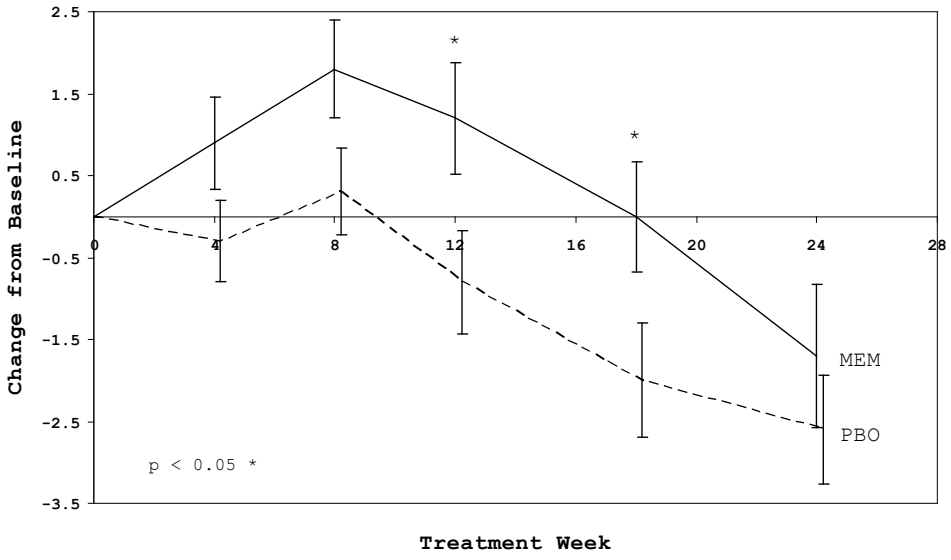
At endpoint (Week 24 LOCF), the mean change from baseline in the ADCS-ADL$_{sev}$ score was numerically less for the Ebixa® -treated patients compared to the patients on placebo (treatment difference of 0.7 units (Figure 5).

Figure 5: Time course of the change from baseline in ADCS-ADL$_{sev}$ score at 24 weeks-LOCF (ITT Population)



At study endpoint (Week 24 LOCF) the mean difference in the SIB change scores was numerically less for the Ebixa- treated patients compared to the patients on placebo (treatment difference of 0.6 units).

Figure 6: Time course of the change from baseline in SIB score at 24 weeks-LOCF (ITT Population)



A post-hoc nonparametric re-analysis of the primary efficacy endpoint data showed that at study endpoint (Week 24 LOCF) the mean difference in the SIB change scores was statistically significantly less for the Ebixa- treated patients compared to the patients on placebo ($p = 0.031$).

INDICATION AND CLINICAL USE

Ebixa® (memantine hydrochloride) may be useful as monotherapy or as adjunctive therapy with cholinesterase inhibitors[1] for the symptomatic treatment of patients with moderate to severe dementia of the Alzheimer's type.

Ebixa® tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease.

In a 28-week placebo controlled monotherapy trial, patients with moderate to severe Alzheimer's disease showed stabilization or less worsening of functional and cognitive symptoms and of global assessment when treated with Ebixa® compared to placebo.

In a 24 week "add-on" placebo controlled trial in which patients were treated with either Ebixa® or placebo as add-on to ongoing donepezil therapy, stabilization or less worsening of functional and cognitive symptoms and of global assessment was observed in patients with moderate to severe Alzheimer's disease when treated with Ebixa® compared to placebo.

Ebixa® has not been studied in controlled clinical trials for the symptomatic treatment of moderate to severe Alzheimer's disease for more than 6 months.

CONTRAINDICATIONS

Ebixa® (memantine hydrochloride) is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

[1] Cholinesterase inhibitors refers to only those which are approved in Canada for the symptomatic treatment of Alzheimer's disease.

WARNINGS

NEUROLOGICAL CONDITIONS

Seizures: Ebixa® (memantine hydrochloride) has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the premarketing testing of Ebixa®. In clinical trials, seizures occurred in 0.3% of patients treated with Ebixa® and 0.4% of patients treated with placebo. Seizure activity may be a manifestation of Alzheimer's disease. The risk/benefit of memantine treatment for patients with a history of seizure disorder or predisposing factors for epilepsy must, therefore, be carefully evaluated.

GENITOURINARY CONDITIONS

Conditions that raise urine pH may reduce the urinary elimination of memantine by a factor of 7 to 9, resulting in increased plasma levels of memantine (see ACTIONS AND CLINICAL PHARMACOLOGY). These conditions include drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or a massive ingestion of alkalising gastric buffers (see Drugs Which Makes Urine Alkaline, PRECAUTIONS). Also, urine pH may be elevated by states of renal tubulary acidosis (RTA) or severe infections of the urinary tract with *Proteus bacteria*.

CARDIOVASCULAR CONDITIONS

In most clinical trials, patients with recent myocardial infarction, uncompensated congestive heart failure (NYHA III-IV), and uncontrolled hypertension were excluded. However, patients such as those with controlled hypertension (DBP < 105 mm/Hg), right bundle branch blockage and pacemaker were included. Although cardiovascular adverse events occurred at low frequencies in the two placebo-controlled clinical trials involving patient with moderate to severe Alzheimer's disease, there were increased frequencies of hypertension, chest pain, bradycardia and cardiac failure adverse events in patients who were treated with Ebixa® compared to placebo in these trials. Consequently, caution should be observed when memantine is initiated in patients with cardiovascular conditions.

PRECAUTIONS

OPHTHALMIC CONDITIONS

In an open label study where Ebixa® was administered to 10 elderly patients at a dose of 20 mg per day for approximately 48 months, memantine concentrations in lacrimal fluid were about 3 fold higher than in plasma and did not show ophthalmologic effects. In another 6-month placebo-controlled trial, no major treatment differences were reported for ocular effects but worsening of the corneal condition was reported for slightly more patients treated with Ebixa® than placebo (5.4% memantine vs. 3.3% placebo). Repeat-dose toxicology studies demonstrated corneal and lens histopathological changes in rodents treated with Ebixa®. Therefore, periodic monitoring of the patient's ophthalmic condition is recommended.

HYPERSENSITIVITY

Skin Hypersensitivity Reactions - Serious skin reactions (Stevens Johnson syndrome and acute generalized exanthematous pustulosis), and other less serious skin reactions (e.g., erythema multiforme), have been reported in patients receiving EBIXA (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). Patients or caregivers should be instructed to inform their health care provider of any skin reactions that occur during treatment with EBIXA. It is recommended that treatment should be discontinued at the first appearance of skin rash.

CONCOMITANT USE WITH OTHER DRUGS

Use with compounds chemically related to N-methyl-D-aspartate (NMDA) antagonists: As these compounds act at the same receptor system as memantine, adverse drug reactions (mainly CNS-related) may be more frequent or pronounced. Pharmacotoxic psychosis has been reported in the literature in two Parkinson's disease patients who were treated concomitantly with memantine, amantadine, L-dopa and terguride (see PRECAUTIONS, Drug Interactions, Other agents). The combined use of Ebixa® with other compounds chemically related to NMDA antagonists such as amantadine, ketamine or dextromethorphan has not been systematically evaluated and is therefore not recommended.

CONDITIONS THAT MAKE URINE ALKALINE

The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions (see PHARMACOKINETICS and WARNINGS).

SPECIAL POPULATIONS

HEPATIC IMPAIRMENT

Ebixa® undergoes minimal hepatic metabolism and is excreted primarily in its unchanged form by the kidneys. The pharmacokinetics of memantine have been studied in subjects with moderate hepatic impairment (see PHARMACOKINETICS). In patients with mild or moderate hepatic impaired function (Child-Pugh A and Child-Pugh B) no dose adjustment is needed. There are no data available for use of memantine in patients with severe hepatic impairment. Therefore, administration of Ebixa® is not recommended in patients with severe hepatic impairment.

RENAL IMPAIRMENT

In patients with mildly impaired renal function (creatinine clearance 50 - 80 ml/min) no dosage adjustment is required. In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) the daily dose should be 10 mg per day. If well tolerated after at least 7 days of treatment, and based on clinical response, the dose may be increased up to 20 mg/day according to the standard titration scheme. In patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) the daily dosage should be 10 mg per day (see PHARMACOKINETICS and DOSAGE AND ADMINISTRATION).

USE IN PATIENTS ≥ 85 YEARS OLD

In placebo-controlled clinical studies, the number of patients aged 85 years or older who received memantine at the therapeutic dose of 20 mg/day was 40. There is limited safety information for Ebixa® in this patient population.

USE IN PATIENTS WITH SERIOUS CO-MORBID CONDITIONS.

There is limited information on the safety of memantine treatment in patients with moderate to severe Alzheimer's disease with serious co-morbidities, as these patients were excluded from clinical trials. The use of Ebixa® in Alzheimer's disease patients with chronic illnesses common among the geriatric population should be considered only after a proper risk/benefit assessment. Dose escalation in this patient population should proceed with caution.

PREGNANCY

Oral treatment of female rats with memantine once daily during organogenesis produced mild maternal toxicity at doses of 6-18 mg/kg/day (3-9 times the Maximum Recommended Human Dose [MRHD] on a mg/m^2 basis); however, memantine was not teratogenic at doses up to 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis), the highest dose tested. In a rat reproduction and fertility study, reduced growth and a developmental delay were observed at 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis).

Memantine doses of 0, 3, 10 and 30 mg/kg/day were orally administered to pregnant rabbits during the period of organogenesis. At 30 mg/kg/day (30 times the MRHD on a mg/m^2 basis) maternal toxicity and a slight increase in post-implantation loss were observed. No teratogenic effects were observed in rabbits administered memantine 30 mg/kg/day (30 times the MRHD on a mg/m^2 basis). The maternal and fetal no observed effect level (NOEL) was 10 mg/kg/day (10 times the MRHD on a mg/m^2 basis).

In a peri and postnatal study, memantine was orally administered to rats at up to 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis). At 18 mg/kg/day pups showed reduced mean body weights but there was no effect on their development or behaviour. Animal studies showed no indication of an adverse effect of memantine on labour and delivery.

There are no adequate and well-controlled studies of memantine in pregnant women to establish the safe use of Ebixa® for this population. Therefore, Ebixa® should not be used in women of childbearing potential, unless, in the opinion of the physician, the expected benefits to the patient markedly outweigh the possible hazards to the foetus.

NURSING MOTHERS

It is not known whether memantine is excreted in human breast milk. Therefore Ebixa® should not be used in nursing mothers.

PEDIATRIC USE

The safety and effectiveness of Ebixa® in any illness occurring in pediatric patients have not been established. Therefore, Ebixa® is not recommended for use in children.

DRUG INTERACTIONS

Compounds chemically related to N-methyl-D-aspartate (NMDA) antagonists: The combined use of Ebixa® with other compounds chemically related to NMDA antagonists such as amantadine, ketamine or dextromethorphan has not been systematically evaluated and is therefore not recommended (see PRECAUTIONS, Concomitant Use With Other Drugs).

Effects of Ebixa® on substrates of microsomal enzymes: In vitro studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) revealed minimal inhibition of these enzymes by memantine. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Effects of inhibitors and/or substrates of microsomal enzymes on Ebixa®: Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.

Acetylcholinesterase (AChE) inhibitors: In vitro studies have shown that memantine does not affect the reversible inhibition of acetylcholinesterase by donepezil or galantamine. In young healthy adult subjects (n=19, age range 18-35 years) under steady-state conditions of the AChE inhibitor donepezil HCl (10 mg/day), co-administration of a single 10 mg oral dose of memantine did not affect the pharmacokinetics of either drug and did not affect donepezil-mediated AChE inhibition. In a 24-week study of patients with moderate to severe Alzheimer's disease the adverse event profiles were similar for patients treated with a combination of memantine and donepezil or placebo and donepezil.

In a pharmacokinetic study in healthy adult subjects (n=15, age range 21-55 years), co-administration of memantine (10 mg b.i.d.) did not significantly affect the steady state pharmacokinetics of galantamine (16 mg/day). The effect of galantamine on memantine pharmacokinetics was not evaluated. The safety of co-administering memantine and galantamine in patients with Alzheimer's disease has not been evaluated in clinical trials.

Drugs eliminated via renal mechanisms: Co-administration of drugs that use the same renal cationic transport system as memantine, such as cimetidine, ranitidine, quinidine, hydrochlorothiazide (HCTZ), triamterene (TA), and nicotine could potentially alter the plasma levels of both agents. Co-administration of Ebixa® and hydrochlorothiazide/triamterene (HCTZ/TA) did not affect the bioavailability of either memantine or triamterene, and the bioavailability of HCTZ decreased by 20%. The pharmacokinetics of memantine is similar in smokers and non-smokers, suggesting that nicotine may not affect the disposition of memantine. The potential for compromised renal function in elderly patients should be considered when memantine will be used concomitantly with other drugs eliminated via renal mechanisms (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).

Drugs highly bound to plasma proteins: Because the plasma protein binding of memantine is low (45%), an interaction with drugs that are highly bound to plasma proteins, such as warfarin and digoxin, is unlikely.

Oral Anticoagulants: In post marketing experience isolated cases of international normalized ratio (INR) increases have been reported in patients treated concomitantly with memantine and warfarin. Although no causal relationship has been established, close monitoring of prothrombin time or INR is advised for patients treated concomitantly with memantine and oral anticoagulants.

Antihyperglycemic drugs: In young healthy adult subjects (n=21, age range 19-35 years), co-administration of a single 20 mg oral dose of memantine under steady state conditions of glyburide/metformin (1.25 mg glyburide/250 mg metformin) did not affect the pharmacokinetics of memantine, glyburide or metformin. The renal excretion of metformin and memantine, and potential for compromised renal function in elderly patients should be considered when memantine and metformin will be used concomitantly (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).

Other agents: Since the effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with Ebixa®, dosage adjustment of these other agents may be necessary.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY.

There was no evidence of carcinogenicity in a 113-week oral study in mice for either sex at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (19 and 10 times the MRHD on a mg/m^2 basis, respectively) through 128 weeks.

Memantine did not show any genotoxic potential in assays for gene mutation (bacterial and mammalian cells in vitro) or in clastogenicity assays (human lymphocytes in vitro and mouse bone marrow in vivo).

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

ADVERSE EVENTS

A total of 916 patients were treated with memantine in double-blind, placebo-controlled dementia studies. Of these patients, 726 (79%) completed the studies. Patients were treated with memantine for a mean of 148.5 days. Approximately 61% of patients received memantine for at least 24 weeks.

Adverse Events Leading to Discontinuation of Treatment: In placebo-controlled trials in which dementia patients received doses of Ebixa® up to 20 mg/day, 11.1 % (102/916) of the Ebixa®-treated patients discontinued treatment due to an adverse event. The discontinuation rate in the placebo-treated patients was 11.6% (109/893). The most frequent adverse event leading to discontinuation was agitation with an observed frequency among patients who discontinued treatment of 1.0% in patients receiving memantine vs. 1.8% in patients administered placebo. None of the other adverse events leading to discontinuation met the criteria for most common adverse events, defined as those occurring at a frequency of at least 2% and at twice the incidence seen in placebo patients.

Adverse Events Reported in Placebo-Controlled Dementia Trials: Table 1 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with Ebixa® than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative

contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Ebixa® and at a Higher Frequency than Placebo-treated Patients

Body System Adverse Event	Placebo (N = 893) %	Ebixa® (N = 916) %
Body as a Whole		
Pain	0.8	2.0
Cardiovascular System		
Hypertension	1.9	2.6
Central and Peripheral Nervous System		
Dizziness	3.7	5.5
Headache	2.9	4.5
Gastrointestinal System		
Constipation	2.8	4.8
Diarrhoea	2.8	3.4
Nausea	1.8	2.3
Vomiting	1.7	2.3
Musculoskeletal System		
Back pain	1.9	2.2
Psychiatric Disorders		
Anxiety	0.7	2.1
Confusion	4.3	4.6
Hallucinations	1.0	2.1
Somnolence	1.8	2.3
Respiratory System		
Coughing	3.2	3.4

Other adverse events occurring with an incidence of at least 2% in Ebixa®-treated patients but at an equal or lower rate than placebo were agitation, arthralgia, bronchitis, cataract, depression, fall, gait abnormal, inflicted injury, influenza-like symptoms, insomnia, urinary incontinence and urinary tract infection.

Vital Sign Changes: Ebixa® and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Ebixa® treatment.

Laboratory Changes: Ebixa® and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Ebixa® treatment.

ECG Changes: Ebixa® and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with Ebixa® treatment.

Adverse Events Observed In Placebo-Controlled Trial in Patients Previously Treated with Donepezil.

In an additional double-blind, placebo-controlled study, 202 patients who had been treated with donepezil for at least 6 months and who had been on stable doses of donepezil for 3 months prior to randomization were treated with memantine for a period of 24 weeks while still receiving donepezil. Of these patients, 172 (85%) completed the study. In this clinical trial, a total of 14.9% (30/202) of the memantine/donepezil patients discontinued the study compared to 25.4% (51/201) of the placebo/donepezil patients. The most frequent reason for discontinuation was adverse events and included 12% of placebo/donepezil patients and 7% of memantine/donepezil patients.

Overall, the safety profile of the memantine/donepezil treated patients was similar to the one observed for the placebo-controlled dementia trials. The adverse events leading to

discontinuation of the treatment, and for which the incidence was greater in the memantine/donepezil than in the placebo/donepezil group were: asthenia (memantine 1.0%; placebo 0%) dehydration (memantine 1.5%; placebo 0%) and confusion (memantine 2.0 %; placebo 1.5%).

Table 2 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with Ebixa®/donepezil than for those treated with placebo/donepezil.

Table 2: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Ebixa®/donepezil and at a Higher Frequency than Placebo/donepezil-treated Patients

Body System Adverse Event	Placebo/ donepezil (N = 201) %	Ebixa®/ donepezil (N = 202) %
Body as a Whole		
Chest pain	0.0	2.5
Fall	7.0	7.4
Fever	0.5	2.0
Oedema peripheral	4.0	5.0
Pain	0.5	3.0
Cardiovascular System		
Hypertension	1.5	4.5
Central and Peripheral Nervous System		
Gait abnormal	1.0	3.0
Headache	2.5	6.4
Gastrointestinal System		
Constipation	1.5	3.0
Vomiting	3.0	3.5
Metabolic and nutritional disorders		
Weight increase	0.0	2.5
Musculo-skeletal System		
Arthralgia	1.5	2.5
Psychiatric Disorders		
Confusion	2.0	7.9
Depression	3.0	4.0

Red blood cell disorder		
Anemia	0.5	2.0
Reproductive disorders, male		
Prostatic disorder	0.0	4.1
Respiratory System		
Coughing	1.0	3.0
Influenza-like symptoms	6.5	7.4
Skin and appendages disorders		
Rash	1.5	2.5
Urinary system disorders		
Urinary tract infection	5.0	5.9
Urinary incontinence	3.0	5.4
Micturition frequency	0.5	2.0

Treatment emergent signs and symptoms that were reported in at least 2% of Ebixa®/donepezil treated patients (but less than 9%) and at an equal or lower rate than placebo/donepezil treated patients were abdominal pain, agitation, anorexy, anxiety, asthenia, back pain, bronchitis, dehydration, diarrhea, dizziness, fatigue, fecal incontinence, hallucinations, inflicted injury, insomnia, personality disorder, somnolence, syncope, tremor, upper respiratory tract infection.

Other Adverse Events Observed During Clinical Trials

Ebixa® has been administered to approximately 1333 patients with dementia, of whom more than 1200 received the maximum recommended dose of 20 mg/day. Approximately 830 patients received Ebixa® for at least 6 months of treatment and 387 patients were treated for approximately a year or more.

All adverse events occurring in at least two patients are included, except for those already listed in Tables 1 and 2, WHO terms too general to be informative, or events unlikely to be caused by the drug. Also included are the adverse events observed in the placebo-controlled trial in patients who had been previously treated with donepezil prior to Ebixa® treatment. Events are classified by body system and listed using the following definitions: *frequent* – those occurring on one or more occasions in at least 1/100 patients; *infrequent*– those occurring in less than 1/100 patients but at least in 1/1000 patients. These adverse events are not necessarily related to Ebixa®

treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Autonomic Nervous System: *Infrequent:* sweating increased, mouth dry.

Body as a Whole: *Frequent:* asthenia, fatigue, oedema, leg pain, malaise, sepsis, syncope, *Infrequent:* abscess, allergic reaction, allergy, chest pain precordial, choking, condition aggravated, ESR increased, flushing, hernia NOS, hot flushes, hypothermia, infection, infection fungal, infection viral, moniliasis, oedema peripheral, pallor, rigors, sudden death.

Cardiovascular System: *Frequent:* angina pectoris, bradycardia, cardiac failure, cardiac failure left, heart murmur, oedema dependent. *Infrequent*: aneurysm, arrhythmia, cardiac arrest, embolism pulmonary, fibrillation atrial, heart block, heart disorder, hypertension aggravated, hypotension, hypotension postural, myocardial infarction, palpitation, phlebitis, pulmonary oedema, tachycardia, thrombophlebitis, thrombophlebitis deep, vascular disorder.

Central and Peripheral Nervous System: *Frequent:* aphasia, ataxia, cerebrovascular disorder, hypokinesia, transient ischemic attack, vertigo. *Infrequent:* absences, cerebral hemorrhage, coma, convulsions, coordination abnormal, extrapyramidal disorder, hemiparesis, hemiplegia, hyperkinesia, hypertonia, hypoesthesia, muscle contractions involuntary, neuralgia, neuropathy, paralysis, paresthesia, ptosis, speech disorder, stupor, tremor.

Gastrointestinal System: *Frequent:* abdominal pain, dyspepsia, fecal incontinence, hemorrhoids, tooth disorder. *Infrequent:* diverticulitis, dysphagia, esophageal ulceration, esophagitis, flatulence, gastroenteritis, gastroesophageal reflux, gastrointestinal disorder NOS, GI hemorrhage, gingivitis, hemorrhage rectum, melena, mucositis NOS, oesophagitis, saliva altered, saliva increased, stomatitis ulcerative, tooth ache, tooth caries.

Hemic and Lymphatic Disorders: *Frequent:* purpura. *Infrequent:* epistaxis, hematoma, leukocytosis, leukopenia, polycythemia.

Metabolic and Nutritional Disorders: *Frequent:* hyperglycemia, hypernatremia, hypokalemia, phosphatase alkaline increased, weight decrease. *Infrequent*: bilirubinemia, BUN increased, dehydration, diabetes mellitus, diabetes mellitus aggravated, gamma-GT increased, gout, hepatic enzymes increased, hepatic function abnormal, hypercholesterolemia, hyperkalemia, hyperuricemia, hyponatremia, NPN increased, polydipsia, AST increased, ALT increased, thirst.

Musculoskeletal System: *Frequent:* arthritis, arthrosis, muscle weakness, myalgia. *Infrequent:* arthritis aggravated, arthritis rheumatoid, bursitis, skeletal pain.

Neoplasms: *Infrequent:* basal cell carcinoma, breast neoplasm benign (female), breast neoplasm malignant (female), carcinoma, neoplasm NOS, skin neoplasm malignant

Psychiatric Disorders: *Frequent:* aggressive reaction, anorexia, apathy, cognitive disorder, delusion, nervousness. *Infrequent:* amnesia, appetite increased, concentration impaired, crying abnormal, delirium, depersonalization, emotional lability, libido increased, neurosis, paranoid reaction, paroniria, personality disorder, psychosis, sleep disorder, suicide attempt, thinking abnormal.

Reproductive Disorders, Female: *Infrequent:* vaginal hemorrhage, moniliasis; **Male:** *Frequent:* moniliasis.

Respiratory System: *Frequent:* dyspnea, pharyngitis, pneumonia, upper respiratory tract infection, rhinitis. *Infrequent:* apnea, asthma, bronchospasm, hemoptysis, respiratory disorder, sinusitis.

Skin and Appendages: *Frequent:* bullous eruption, herpes zoster, skin disorder, skin ulceration. *Infrequent:* alopecia, blister, cellulitis, dermatitis, eczema, pruritus, rash erythematous, seborrhea, skin dry, skin erosion, skin reaction localized, toxic skin eruption, urticaria.

Special Senses: *Frequent:* cataract, eye abnormality, macula lutea degeneration, vision abnormal. *Infrequent:* blepharitis, blurred vision, conjunctival hemorrhage, conjunctivitis,

corneal opacity, decreased visual acuity, diplopia, ear ache, ear disorder NOS, eye infection, eye pain, glaucoma, hearing decreased, lacrimation abnormal, myopia, xerophthalmia, retinal detachment, retinal disorder, retinal hemorrhage, tinnitus.

Urinary System: *Frequent:* cystitis, dysuria. *Infrequent:* hematuria, micturition disorder, polyuria, pyuria, renal function abnormal, urinary retention.

Vascular Disorders: *Infrequent:* venous thrombosis/ thromboembolism.

POST-MARKET ADVERSE DRUG REACTIONS

The following adverse events of possible importance, for which there are inadequate data to determine the causal relationship to memantine treatment have been reported to be temporally associated with memantine treatment and are not described elsewhere in labeling:

acne, atrioventricular block, bone fracture, cerebral infarction, cholelithiasis, claudication, colitis, depressed level of consciousness (including loss of consciousness and coma), dyskinesia, encephalopathy, gastritis, grand mal convulsions, hepatic failure, hepatitis (including increased ALT and AST), hyperlipidemia, hypoglycemia, ileus, increased INR, intracranial hemorrhage, myoclonus, neuroleptic malignant syndrome, acute pancreatitis, aspiration pneumonia, acute renal failure, prolonged QT interval, psychotic reactions, restlessness, sepsis, supraventricular tachycardia, tardive dyskinesia, thrombocytopenia.

A search of postmarket data found cases of the following skin hypersensitivity reactions: Drug Eruption, Pemphigoid, Toxic Skin Eruption, Stevens-Johnson Syndrome, Skin Exfoliation, Blister, Erythma Multiforme, Dermatitis Bulous, Pemphigus, Acute Generalized Exanthematous Pustulosis.

Alzheimer's disease has been associated with depression, suicidal ideation and suicide. In post-marketing experience these events have been reported in patients treated with Ebixa.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

SYMPTOMS

Cases of accidental and intentional overdose have been reported with memantine. The highest ingested dose that has been reported in an overdose is 2000 mg. Reported signs and symptoms in this case were agitation, diplopia and coma followed by full recovery. Fatal overdoses have only been reported when memantine was taken with several other drugs by patients on polytherapy that included memantine. No fatal cases of overdose have been reported in which memantine was taken alone.

TREATMENT OF OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a regional Poison Control Center for the latest recommendations for the management of a suspected overdose of any drug.

Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric lavage and use of activated charcoal should be considered. Cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive measures. There are no specific antidotes for Ebixa®. Elimination of memantine can be enhanced by acidification of urine.

DOSAGE AND ADMINISTRATION

Ebixa® (memantine hydrochloride) should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease. 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. 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. Discontinuation of memantine should be considered when evidence of a therapeutic effect is no longer present or if the patient does not tolerate treatment.

Adults: The recommended maintenance dose for memantine is 20 mg/day. In order to reduce the risk of side effects the maintenance dose is achieved by upward titration as follows: the usual starting dose is 5 mg/day. The dose should then be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (10 mg and 5 mg as separate doses), and 20 mg/day (10 mg twice a day), depending on the patient's response and tolerability. The minimum recommended interval between dose increases is one week. The recommended dose titration is summarized in the following table.

10 mg Tablets		
	AM	PM
week 1	½ tablet	none
week 2	½ tablet	½ tablet
week 3	1 tablet	½ tablet
week 4 and beyond	1 tablet	1 tablet

The tablets can be taken with or without food. They should be swallowed whole with some water. If a dose is missed, the patient should be instructed to take the next dose as scheduled. There is no need to make up the missed dose.

SPECIAL POPULATIONS

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 (see PHARMACOKINETICS).

Renal impairment: In patients with mildly impaired renal function (creatinine clearance 50 - 80 ml/min) no dosage adjustment is required. In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) the daily dose should be 10 mg per day. If well tolerated after at least 7 days of treatment, and based on clinical response, the dose may be increased up to 20 mg/day according to the standard titration scheme. In patients with severe renal impairment (creatinine

clearance 15 - 29 ml/min) the daily dosage should be 10 mg per day. (see PHARMACOKINETICS and PRECAUTIONS).

Hepatic impairment: In patients with mild or moderate hepatic impaired function (Child-Pugh A and Child-Pugh B) no dose adjustment is needed (see PHARMACOKINETICS). There are no data available for use of memantine in patients with severe hepatic impairment. Therefore, administration of Ebixa® is not recommended in patients with severe hepatic impairment.

PHARMACEUTICAL INFORMATION

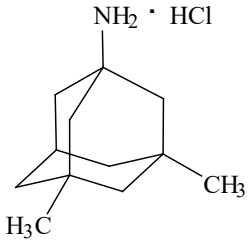
DRUG SUBSTANCE

Common Name: Memantine hydrochloride

Code Name: MEM3; D145; MRZ 2/145

Chemical Name: 1-amino-3,5-dimethyladamantane hydrochloride

Structural Formula:



Molecular Formula: $C_{12}H_{22}Cl\,N$

Molecular Weight: 215.77 (hydrochloride)
179.31 (base)

Description: White, crystalline, practically odourless powder

pH: 5.5 – 6.0

pKa: 10.27

Solubility: water, hydrochloridic acid, methanol, n-hexane (soluble), methylene chloride, chloroform (freely soluble), ethylacetate (practically insoluble)

Partition Coefficient: Log P (n-octanol/water): 3.28

DRUG PRODUCT

Composition

Ebixa® tablets contain 10 mg of memantine hydrochloride and the following non-medicinal ingredients:

For the lactose-containing tablets: lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, talc, magnesium stearate, methacrylic acid-ethyl acrylate copolymer, sodium lauryl sulphate, polysorbate 80, triacetin, simethicone emulsion.

For the lactose-free tablets: Colloidal anhydrous silica, croscarmellose sodium, hypromellose, iron oxide yellow E172, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, titanium dioxide E171.

Stability and Storage

Recommendations:

Ebixa® tablets should be stored in a dry place at room temperature between 15° and 30°C.

AVAILABILITY OF DOSAGE FORMS

Ebixa® (memantine hydrochloride) is available as 10 mg tablets.

For lactose containing tablets: White to off-white, centrally tapered oblong, biconvex, film-coated tablet with a single break line on both sides.

For lactose-free tablets: pale yellow to yellow, oval shaped film-coated tablet with breaking line and engravings "1 0" on one side and "M M" on the other side.

Blister packages of 30, 50 and 100 tablets.

PHARMACOLOGY

Persistent activation of the central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to be involved in the pathogenesis of Alzheimer's disease. Memantine, a low to moderate affinity uncompetitive (open channel) NMDA receptor antagonist, binds preferentially to the NMDA receptor-operated cation channels. It blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

In vitro electrophysiological studies suggest that memantine inhibits NMDA receptor-mediated currents in a use-dependent [i.e., it blocks the receptor channel in the presence of an agonist, e.g., glutamate] and voltage-dependent manner, with rapid receptor-unblocking kinetics. Because of these attributes, memantine can selectively antagonize pathological activation of NMDA receptors without affecting the physiological functioning of the receptor. Physiological activation of NMDA receptors is known to play a critical role in synaptic plasticity processes such as cognition.

(+) MK-801 (dizocilpine) is the prototypical NMDA uncompetitive receptor antagonist. Memantine binds to the MK-801 recognition site in the NMDA channel with a Ki of 0.5 μM and antagonises NMDA receptor-mediated inward currents in vitro with an IC50 of 1-3 μM. The Ki-value of memantine at the phencyclidine (PCP) binding site of the NMDA receptor is 0.5 μM in human frontal cortex (0.1 ppm).

In several *in vitro* and *in vivo* studies, memantine has been shown to protect neurons from cell death due to excitotoxicity. For example, memantine protects rat cortical and hippocampal cells from the neurotoxic effects of glutamate. In addition, memantine attenuates β-amyloid (Aβ)-induced hippocampal cell death (apoptosis) in rats *in vivo*, and protects cholinergic neurons of the rat nucleus basalis magnocellularis from NMDA-induced neurotoxicity.

Memantine also improves learning and memory in animal studies. For example, memantine prevents (Aβ)-induced impairment in learning in rats, and reverses neurodegeneration and

memory impairment in rats produced by the NMDA receptor agonist quinolinic acid. Memantine does not affect learning in normal (control) rats.

Memantine exhibits low to negligible affinity for other receptors (GABA, benzodiazepine, dopamine, adrenergic, noradrenergic, histamine and glycine) or voltage-dependent Ca^{2+}, Na^{+} or K^{+} channels. In addition, it does not directly affect the acetylcholine receptor or cholinergic transmission, which have been implicated in the cholinomimetic side effects (e.g., increased gastric acid secretion, nausea and vomiting) seen with acetylcholinesterase inhibitors. Memantine showed antagonist effects at the $5HT_3$ receptor with a potency similar to that for the NMDA receptor.

Standard safety pharmacology studies were conducted to evaluate memantine's effects on CNS, cardiovascular, gastrointestinal and renal functions. At doses higher than the pharmacologically relevant dose (≥30 mg/kg), memantine produced considerable CNS side effects. Decreased awareness, motor activity and reflexes were observed at high doses (100 mg/kg). High doses of memantine (≥30 mg/kg, intraduodenal) decreased cardiac minute output, stroke volume and systolic left ventricular pressure. Memantine inhibited intestinal motility in rats with an ED50 of 20 mg/kg, and produced diuresis and saluresis in rats at high doses (40 mg/kg; p.o.).

PHARMACOKINETICS

Absorption

Memantine is relatively rapidly and completely absorbed after oral administration.

Approximate peak plasma memantine concentrations after single and repeated oral doses (gavage or capsule) in rat and baboon are given in the table below**:**

Table 3. Peak plasma memantine concentrations

Species	Treatment duration	Dose (mg/kg)	Peak plasma concentration (ppm)	
			males	females
Rat	Single dose	25	1.0	1.6
		50	2.4	2.4
		100	4.4	4.9
	5-week	10	0.4	0.8
		20	1.2	1.3
		40	1.5	3.0
	26-week	10	0.8	1.0
		20	1.5	2.1
		40	2.4	2.4
	52-week (diet)	20/15 (m/f)	0.2	0.3
		40/30	0.7	0.8
		70/50	3.2	2.1
Baboon	2-week	8	0.4	0.3
	13-week	2	0.0	0.0
		4	0.02	0.01
		8	0.10	0.05
	52 week	2	0.01	0.01
		4	0.02	0.02
		8	0.06	0.07

There was no systematic sex difference, female levels were 0.5 to 2 times male levels in various samples, with no discernible pattern (and t_{max} did not differ between the sexes).

DISTRIBUTION

Mean plasma binding of memantine in the rat is 41%, comparable to the 45% binding found in man.

Distribution studies with memantine have been carried out in rats and baboons. Oral bioavailability of memantine is virtually complete, and distribution to target, the brain, is rapid. Once in the body, memantine distributes preferentially to the organs of metabolism and excretion, liver and kidney, but also to the lung. Exceptionally high concentrations of memantine were found in bile and Harderian glands, and at lower concentrations in the central nervous system, consistent with its lipophilicity. High concentrations are also found in the uveal tract of pigmented animals. The localization of ^{14}C-memantine and/or its labelled metabolites in the uveal tract (which includes choroid, ciliary body and iris) of the eyes of pigmented animals (239 ppm vs. 13 ppm in albinos) suggests that the test substance has an affinity with melanin, which has also been demonstrated in vitro.

More pharmacologically oriented studies have focused on determining the concentration in extracellular fluid. Based on the assumption that concentrations measured in the cerebrospinal fluid (CSF) or microdialysate allow conclusions to be drawn about the concentration at the site of action, the following results are of interest. After i.p. administration of 20 mg memantine per kg to rats, about 0.3 ppm memantine was found in the microdialysate, taking the recovery into account. Under the same conditions 0.8 ppm total memantine (free and bound memantine) was found in the plasma. Similar results have been reported for humans, with a CSF/serum ratio for total memantine of about 0.4-0.6. Monitoring of the plasma concentration therefore provides information about the presumed concentration at the site of action across different species.

Following 7 days infusion of memantine (20 mg/kg/day) whole brain concentrations were 44-fold higher than free concentrations in serum. The free brain ECF concentration of memantine (0.83±0.05 μM) corrected for in vivo recovery (39 %) was comparable to free serum and CSF concentrations.

METABOLISM AND ELIMINATION

Memantine metabolites are mainly derivatives hydroxylated on the methyl groups (-CH_2OH or –COOH) or on the cage structure, with an intact or oxidised amino function (hydroxylamino, nitro derivatives). In addition, conjugated compounds were found as phase II metabolites but they seem to be of minor importance.

The following table shows the proportion (%) of these metabolites in urine after memantine administration:

Table 4. Metabolites in urine after memantine administration

Metabolites	Mouse	Rat	Baboon	Man
Unmetabolised	68	28	9	68
Hydroxy derivatives*	46	65	41	17
N-oxidised**	4	1	43	10
Carboxy derivatives***	0	6	1	0
N-glucuronide****	5	<1	<1	6

* Hydroxylated metabolites were MRZ 2/371, 2/373, 2/374, 2/525, 2/564, 2/677
** N-oxidised (nitro, nitroso) metabolites were MRZ 2/523, 2/524, 2/529
*** MRZ 2/375
**** MRZ 2/325.
Other metabolites found were <1% in all species.

Memantine and its metabolites are excreted primarily via the kidney. After a single oral dose of ^{14}C-memantine, a minimum of 80-90% of the excreted radioactivity was excreted in the urine in rats, mice, rabbits, miniature pigs, dogs, baboons and humans.

In the baboon, a substantial portion of memantine radioactivity is associated with bile. Since excretion is predominantly renal, this indicates substantial enterohepatic circulation.

As for amantadine, memantine is partly excreted by tubular secretion.

Elimination half-life was approximately 4 hours in all species except man; there was no accumulation with repeat dosing. In baboon's 13 and 52 week oral toxicity studies, followed by a 4 week recovery period, no detectable memantine was present at the end of the recovery period in any tissue except the eye; concentrations in the eyes fell from 8 to 0.4 ppm during recovery in the 13 week study, and from 15 to 1 ppm in the 52 week study.

TOXICOLOGY

ACUTE TOXICITY

Acute oral and intravenous toxicity studies in rat and mouse demonstrated that memantine is moderately toxic. The lowest lethal oral dose is ≥300 mg/kg in both species. The results of standard LD_{50} studies are as follows:

Route of administration	Species	LD_{50} (mg/kg) male	female
Intravenous	Mouse	30	32
	Rat	38	38
Intraperitoneal	Rat	79	
Subcutaneous	Mouse	206	138
	Rat	436	386
Oral	Mouse	498	437
	Rat	370	328

Toxic symptoms were similar by all administration routes: ataxia, tremor, prone position and bradypnea. These motor effects at high doses are consistent with central nervous system blockade of glutamatergic transmission in neocortex and cortical projection fields. Recovery was relatively rapid in all cases, i.e. within hours after intravenous administration and within 1-2 days after intraperitoneal, subcutaneous or oral administration. No persistent clinical signs were seen in survivors 14 days after acute high dose memantine treatment.

REPEAT-DOSE AND LONG-TERM TOXICITY

In subchronic and chronic studies the most prominent clinical signs in all species were related to the central nervous system and included ataxia, tremor, and/or unsteadiness and aggressiveness or hyperexcitability in rodents, incoordination, tremors and apathy or quietness in dogs and baboons, and convulsions in dogs. Reduced body weight, which was sometimes accompanied by a change in food consumption, was noted in all studies.

Pathological changes, such as accumulation of foamy macrophages in several tissues, renal papillary mineralization, tubulo-interstitial nephritis, vacuolization of defined cortical neurons,

and corneal opacities were observed in repeat-dose toxicity studies in rodents. The neuronal vacuolation and corneal opacities occurred at dose levels that resulted in overt toxicity.

In rats, following repeat-dose administration of memantine for various durations, the accumulation of foamy macrophages was observed in several tissues including lungs, kidneys, liver Kupffer cells, cornea, lymphoid organs, testes, epididymides and tongue muscle. Accumulation of foamy macrophages is a form of phospholipidosis. In most tissues, except for lungs, the accumulation of foamy macrophages occurred when blood concentrations were several-fold greater than the potential concentrations in humans at therapeutic doses. In lungs accumulations of foamy macrophages were observed when systemic exposure was less than 2-times the potential systemic exposure at human therapeutic dose levels.

Renal papillary mineralization or calcification of the collecting tubuli of the renal medulla was observed in male rats at doses of 20 mg/kg (or higher) and in female rats 15 mg/kg (or higher) following repeat-dose administration of memantine for 52-weeks or 2 years. The kidney lesions were observed at memantine blood concentrations that were less than 2-fold the potential systemic exposure in humans following repeated administration of 20 mg/day.

Cerebrocortical neurons in adult rodent brain are prone to injury (or lesions) by systemic administration of high affinity uncompetitive (or open channel) NMDA receptor antagonists, such as, (+) MK-801, PCP, and ketamine. To determine the potential of memantine to induce Olney–type lesions, studies were conducted in rats that indicated that single intraperitoneal doses of memantine of 20 mg/kg (or higher) or oral doses of 100 mg/kg (or higher) produced a dose related increase in the frequency and severity of Olney-type lesions. These experiments also indicated that vacuolization was reversible and that only a small portion of cells became necrotic. Repeated daily oral doses of 40 mg/kg/day memantine administered in a dose-escalation manner did not demonstrate evidence of neurotoxicity when examined after appropriate tissue fixation procedures. Although body weight was reduced in the mid and high dose groups, no ataxia, neuronal vacuolisation or necrosis was observed at any dose level.

Experiments in rats comparing the effect of duration of dosing (acute vs. subchronic) and route of administration (dietary vs. gavage) of memantine on the development of Olney-type lesions demonstrated that regardless of duration or route of administration, ataxia occurred at doses 2 to 4 times lower than vacuolization or necrosis.

Numerous repeated dose toxicology studies with memantine were performed without any significant observations regarding neuropathology. Re-examination with appropriate preparation techniques of the existing brain tissue slides from 13-week and 52-weeks dietary study in mice and rat, respectively, and examination of the newly prepared slides from the 52-week rat study revealed no neurodegenerative changes. Histopathological examination of brains from the 13-week mouse study also revealed vacuolization in brainstem and cerebellum of males, but not cingulate and retrosplenial cortex, at 320 mg/kg/day, a dose that produced profound systemic toxicity including death.

The ability of memantine to produce Olney-type lesions in baboons was also examined. The highest dose (8 mg/kg/day) from the 52-week study was administered to baboons for 2 weeks. While ptosis was observed in all treated animals, perfusion fixation prepared brain revealed no evidence of vacuolization or necrosis. These results are consistent with the actions of other NMDA antagonists in primates, which have demonstrated that primates are resistant to the development of Olney-type lesions. Similarly in humans subjected to high doses of a low affinity uncompetitive NMDA receptor antagonist or amantadine, no necrosis in posterior cingulate/retrosplenial cortex or elsewhere in the brain was found at autopsy.

REPRODUCTION STUDIES

Reproductive performance of rats was examined after treatment in all segments of the reproductive cycle in a series of three studies**,** all using the same doses: 2, 6 and 18 mg/kg/day. The doses were chosen on the basis of a range-finding gavage study with low doses of up to 12.5 mg/kg, and on previous repeat dose oral studies in rats showing dose-related weight loss at 15-30 mg/kg. Treatment of female rats with memantine orally once daily during organogenesis produced mild maternal toxicity at doses of 6-18 mg/kg/day (3-9 times the Maximum Recommended Human Dose [MRHD] on a mg/m^2 basis); however, memantine was not

teratogenic at doses up to 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis), the highest dose tested. In a rat reproduction and fertility study, reduced growth and a developmental delay were observed in offspring of mothers administered 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis).

At 30 mg/kg/day (30 times the MRHD on mg/m^2 basis) maternal toxicity and slight increase in post-implantation loss were observed in rabbits administered memantine once daily during organogenesis. No teratogenic effects were observed at that dose level. The maternal and fetal no observed effect level (NOEL) was 10 mg/kg/day (10 times the MRHD on a mg/m^2 basis).

In a peri and postnatal study, memantine was orally administered in rats at up to 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis). At 18 mg/kg/day pups showed reduced mean body weights but there was no effect on their development or behaviour. Animal studies showed no indication of an adverse effect of memantine on labor and delivery.

Considering memantine's molecular weight and its lipophilicity, it is likely that it will be present in the treated mother's milk during lactation (at unknown levels). In a peri and postnatal study there were dose-related increases in memantine levels in milk in lactating rats when memantine was administered from mating through postnatal day 4, although no toxic effects were seen in suckling offspring.

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PART III: CONSUMER INFORMATION

Ebixa®
Memantine hydrochloride tablets

Information in this leaflet is intended for patients and/or caregivers. "You" refers to the patient or someone in your care.

This leaflet is part III of a three-part "Product Monograph" published when Ebixa was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Ebixa. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information before you start to take your medication, even if you have taken this drug before. Keep this leaflet with your medication in case you need to refer to it again.

ABOUT THIS MEDICATION

What the medication is used for:
Ebixa has been prescribed to you, by a doctor to relieve symptoms of Alzheimer's disease.

What it does:
The brain contains N-methyl-D-aspartate (NMDA) receptors that are involved in transmitting nerve signals and may be important for learning and memory. Abnormal transmission of nerve signals through NMDA-receptors in the brain may affect memory and other mental functions and contribute to symptoms of Alzheimer's disease. Ebixa belongs to a group of medicines called NMDA-receptor antagonists. The action of Ebixa on NMDA-receptors may help normalize the transmission of nerve signals, which may help slow the decline in some of the symptoms of Alzheimer disease.

When it should not be used:
- You should not be taking Ebixa if you are pregnant, unless in the opinion of the doctor, the expected benefit to the patient markedly outweighs the possible hazards to the foetus.
- You should not be taking Ebixa if you are breast-feeding.
- Do not take Ebixa if you are allergic to it, or to any of the other ingredients listed in this leaflet (see **'What the non-medicinal ingredients are'**).
- Stop taking Ebixa if you experience an allergic reaction or any severe side effect.

What the medicinal ingredient is:
Memantine hydrochloride

What the nonmedicinal ingredients are:
For the lactose-containing (white to off-white) tablets: Colloidal anhydrous silica, lactose monohydrate, magnesium stearate, methacrylic acid - ethyl acrylate copolymer (1:1), microcrystalline cellulose, polysorbate 80, sodium lauryl sulphate, simethicone emulsion, talc and triacetin.

For the lactose-free (pale yellow to yellow) tablets: Colloidal anhydrous silica, croscarmellose sodium, hypromellose, iron oxide yellow E172, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, titanium dioxide E171.

What dosage forms it comes in:
White to off-white or pale yellow to yellow, 10 mg tablets in blister packs.

WARNINGS AND PRECAUTIONS

BEFORE you use Ebixa talk to your doctor or pharmacist if:

- You have/had a medical condition, including heart problems, uncontrolled hypertension (high blood pressure), history of seizures or kidney disease
- You are taking any medications (prescription or non-prescription) or have taken any within the last 14 days.
- You ever had an allergic reaction to any medication
- You are pregnant or thinking of becoming pregnant, or if you are breast-feeding.
- There are conditions which can change the speed at which the body would normally eliminate the drug over time and you should tell your doctor, as Ebixa dosage may have to be adjusted if:
    - You have recently changed or intend to change your diet substantially (e.g. from normal diet to strict vegetarian diet)
    - You are suffering from renal tubulary acidosis (RTA, an excess of acid-forming substances in the blood due to renal dysfunction [kidney problems])
    - You have a urinary tract infection

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Ebixa include:
- NMDA-receptor antagonists (e.g. amantadine)
- Cimetidine
- Ranitidine
- Procainamide
- Quinidine
- Quinine
- Hydrochlorothiazide (or any combination with hydrochlorothiazide)
- Anticholinergics (generally used to treat movement disorders or intestinal cramps)
- L-dopa and dopaminergic agonists (drugs such as bromocriptine, ropinirole, pramipexole)
- Ketamine
- Dextromethorphan (found in cough syrup labelled DM)
- Anticoagulant (blood thinner) medications taken by mouth

PROPER USE OF THIS MEDICATION

Usual dose:

- It is important that you take Ebixa exactly as your doctor has instructed.
- Usually your doctor will prescribe 20 mg per day, which you will take as two separate doses of 10 mg. In order to reduce the risk of side effects this dose will be achieved gradually by the following daily treatment scheme, starting at a dose of 5 mg per day:

10 mg Tablets		
	AM	PM
Week 1	½ tablet	None
Week 2	½ tablet	½ tablet
Week 3	1 tablet	½ tablet
Week 4 and beyond	1 tablet	1 tablet

- Never change the dose of Ebixa unless your doctor tells you to.
- Swallow the tablets whole with some water. Do not chew tablets. Ebixa can be taken with or without food.
- Continue to take Ebixa as long as directed by your doctor and you do not experience any unacceptable side effects. Your doctor should assess your treatment on a regular basis.

Overdose:

If you think you, or a person you are caring for, have taken too much EBIXA, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

- If you miss a dose, do not worry. Do not take the missed tablet(s) – just take the next dose when it is due.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Ebixa can cause side effects, although not everybody gets them. In general, these are mild to moderate. If any of the side effects become severe or if they are troublesome or persistent, talk to your doctor.

Common side effects (affects 1 to 10 users in 100) may include:

- headache
- sleepiness
- constipation
- tiredness
- confusion
- hallucinations (strange visions or sounds)
- vomiting
- loss of appetite
- dizziness
- sleep disturbance
- anxiety
- high blood pressure
- change in frequency of urination

Uncommon side effects (affects 1 to 10 users in 1000) may include:

- fungal infections
- changes in vision
- skin allergies

Your doctor will tell you whether your illness allows you to drive or operate machinery. Also, as this product may cause sleepiness or dizziness, do not drive or operate machinery under these conditions.

Alzheimer's disease has been associated with depression, thoughts of suicide and suicide. These events have been reported in patients treated with Ebixa.

If you have previously experienced epileptic seizures, there is a possibility that Ebixa may increase the chances of one occurring.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency treatment
		Only if severe	In all cases	
Uncommon	Fungal infection	√		
	Abnormal gait [Abnormal way of walking]		√	
	Heart failure [persistent chest pain, rapid heart rate, severe shortness of breath, swelling of legs or ankles, increased tiredness, lack of appetite, confusion]			√
	Venous blood clotting [pain, swelling, changes in skin color, increased warmth in one leg]			√
Very rare	Seizures [loss of consciousness with uncontrollable shaking]			√
	Hepatitis/hepatic failure [yellow skin and eyes, nausea, loss of appetite, dark-coloured urine]			√
	Inflammation of the pancreas [severe upper stomach pain, often with nausea and vomiting]			√
	psychotic reactions			√
	Serious skin reactions [rash, red skin, blistering of the lips, eyes or mouth, skin peeling]			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency treatment
		Only if severe	In all cases	
Very rare (continued)	For example: Stevens-Johnson Syndrome: Severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals Acute Generalized Exanthematous Pustulosis: Red rash covered with small pus-filled bumps that can spread over the body, sometimes with a fever Erythema Multiforme: Rash that may blister, with spots that look like small targets			√

This is not a complete list of side effects. For any unexpected effects while taking Ebixa, contact your doctor or pharmacist.

If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

HOW TO STORE IT

- As with all medicines, keep Ebixa out of the reach and sight of children.
- Store your tablets at room temperature (15°C-30°C) and in a dry place. Protect from moisture.
- If your doctor tells you to stop taking your medicine you should return any leftover tablets to the pharmacist, unless the doctor tells you to keep them at home.

REMEMBER: This medicine is for YOU or for someone in your care. Only a doctor can prescribe it, so never offer it to

any other person, even if their symptoms seem to be the same as yours or as for the person in your care.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For questions or concerns and to find the full product monograph prepared for healthcare professionals, go to http://www.lundbeck.ca or contact the sponsor, Lundbeck Canada Inc. at 1-800-586-2325.

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