

EBIXA® F

memantine HCl

N-methyl-D-aspartate (NMDA) Receptor Antagonist

Lundbeck

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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 μM) 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 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 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 alkalizing 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](#)).

Reduced Renal Function

In elderly volunteers with normal and reduced renal function (creatinine clearance of 50 to ≤80 mL/min/1.73 m²), 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](#)).

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."

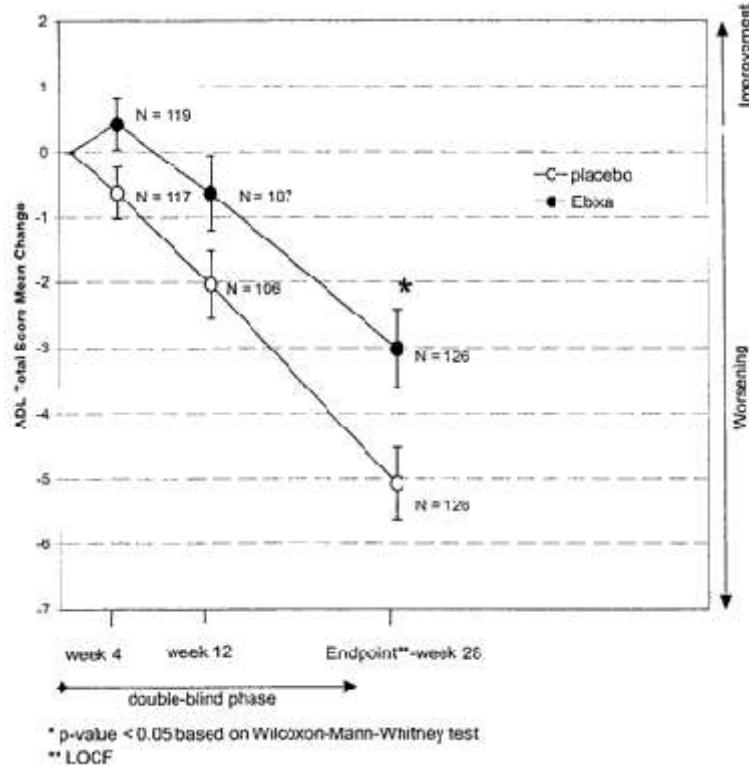
Clinical trial results are summarized for the last observation carried forward (LOCF) analysis of the Intent-to-Treat (ITT) population. The ITT population corresponds to all patients who were randomized to treatment regardless of treatment received and the LOCF analysis is based on carrying the last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

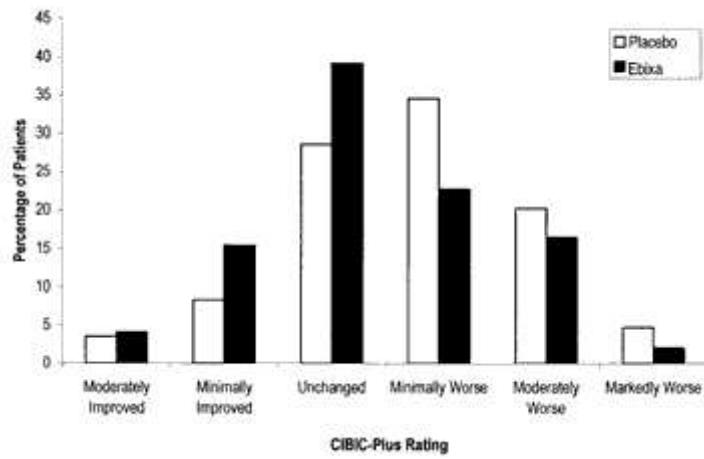
At endpoint (Week 28 LOCF), the mean change from baseline in the ADCS-ADL_{sev} score was statistically significantly less for the Ebixa-treated patients compared to the patients on placebo (treatment difference of 2.1 units ($p=0.022$) ([Figure 1](#)).

Figure 1: Time Course of the Change From Baseline in ADCS-ADL_{sev} 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.

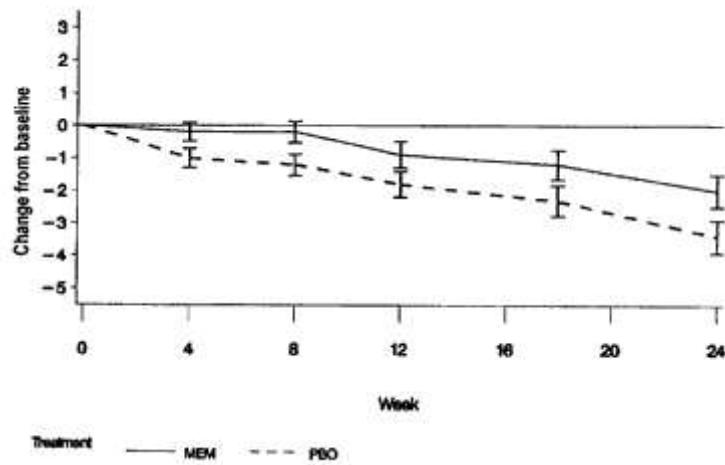
Study 2 (Twenty-Four-Week Study)

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-ADL_{sev} and SIB.

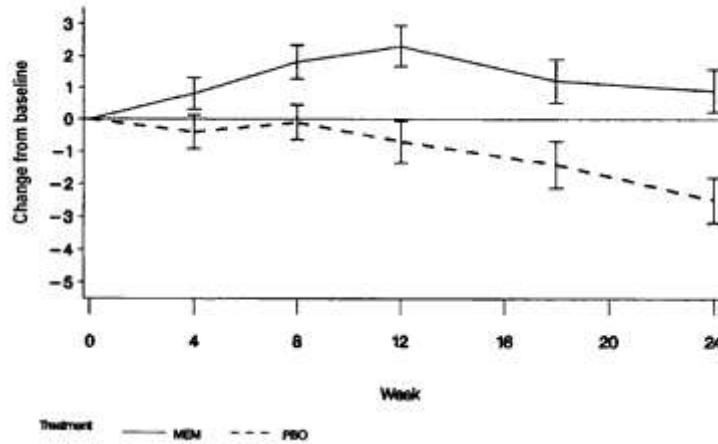
The mean change in the ADCS-ADL_{sev} scores from baseline to Week 24 LOCF was statistically significantly less for the Ebixa/donepezil treated patients compared to the patients on placebo/donepezil (treatment difference 1.4 units, p=0.028) (Figure 3).

Figure 3: 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 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).

Figure 4: Time Course of the Change From Baseline in SIB Score at 24 Weeks-LOCF (ITT Population)



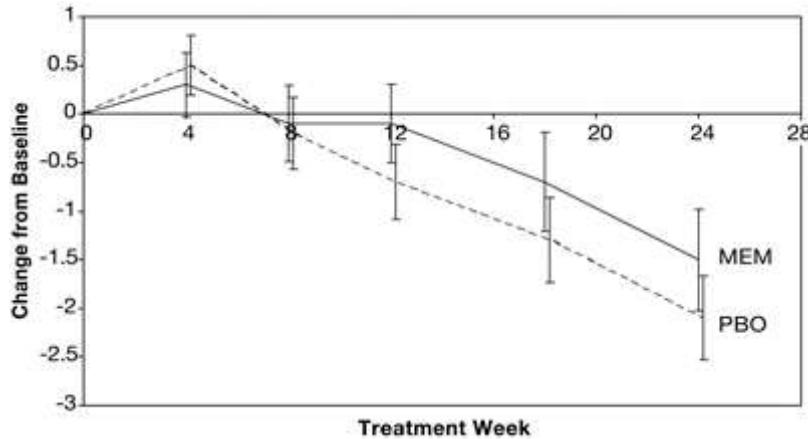
The CIBIC-Plus was a secondary efficacy measure. The mean CIBIC-Plus rating for the Ebixa/donepezil group was lower than that of placebo/donepezil group (treatment difference of 0.25 units).

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.

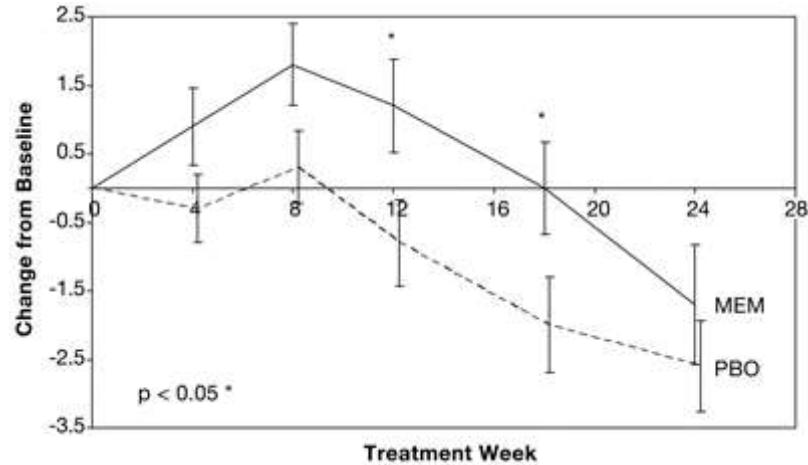
At endpoint (Week 24 LOCF), the mean change from baseline in the ADCS-ADL_{sev} score was numerically less for the Ebixa-treated patients compared to the patients on placebo (treatment difference of 0.7 units) (Figure 5).

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).

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 ($p=0.031$).

Indications

Ebixa (memantine hydrochloride) may be useful as monotherapy or as adjunctive therapy with cholinesterase inhibitors^[*] 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.

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 [Pharmacology](#)). These conditions include drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or a massive ingestion of alkalisng gastric buffers (see [Precautions](#), [Conditions That Make Urine Alkaline](#)). Also, urine pH may be elevated by states of renal tubular 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 Effects, [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 Pharmacology, [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 Pharmacology, [Pharmacokinetics](#) and [Dosage](#)).

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.

Lactation

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

Children

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](#) and [Dosage](#)).

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](#) and [Dosage](#)).

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/m² 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/m² 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/m² basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

Adverse Effects

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

Body System Adverse Event	Placebo (N=893) %	Ebixa (N=916) %
Central and Peripheral Nervous Systems		
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

Body System Adverse Event	Placebo/Donepezil (N=201) %	Ebixa/Donepezil (N=202) %
Central and Peripheral Nervous Systems		
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
Musculoskeletal 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

Body System Adverse Event	Placebo/Donepezil (N=201) %	Ebixa/Donepezil (N=202) %
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 [Table 1](#) and [Table 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, edema peripheral, pallor, rigors, sudden death.

Cardiovascular

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 Systems

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, erythema 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.

Overdose

For management of a suspected drug overdose, contact your regional Poison Control Centre. See the eCPS Directory section for a list of [Poison Control Centres](#).

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

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

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 Pharmacology, [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 Pharmacology, [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 Pharmacology, [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.

Supplied

Each white to off-white, centrally tapered oblong, biconvex, film-coated tablet with a single break line on both sides, contains: memantine hydrochloride 10 mg. Nonmedicinal ingredients: colloidal anhydrous silica, lactose monohydrate, magnesium stearate, methacrylic acid-ethyl acrylate copolymer, microcrystalline cellulose, polysorbate 80, simethicone emulsion, sodium lauryl sulfate, talc and triacetin. Blister packages of 30, 50 and 100. Store in a dry place at room temperature between 15 and 30°C.

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

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