AUSTRALIAN PRODUCT INFORMATION – EBIXA (MEMANTINE HYDROCHLORIDE) FILM-COATED TABLETS

1 NAME OF THE MEDICINE

Memantine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Film-coated tablets containing 10 mg memantine hydrochloride.

Film-coated tablets containing 20 mg memantine hydrochloride.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Ebixa 10 mg tablets are pale yellow to yellow, oval shaped film-coated tablets with break line and engravings ‘M’ on both parts right and left of the break line and on the other side, ‘1’ left and ‘0’ right of the break line.

Ebixa 20 mg tablets are pink to grey-red oval biconvex film-coated tablets with ’20’ embossed on one side and ‘MEM’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of the symptoms of moderately severe to severe Alzheimer's disease (see Section 5 Pharmacological properties; Section 4.4 Special warnings and precautions for use).

4.2 Dose and method of administration

Ebixa should be administered once a day and should be taken at the same time every day. Tablets should be taken with a little liquid, with or without food.

The tolerance and dosing of memantine should be reassessed on a regular basis, preferably within three months after start of treatment. Thereafter, the clinical benefit of memantine and the patient’s tolerance of treatment should be reassessed on a regular basis according to current clinical guidelines. Maintenance treatment can be continued for as long as a therapeutic benefit is favourable and the patient tolerates treatment with memantine. 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 is 20 mg per day. This is achieved by upward titration of 5 mg per week. The 10 mg tablet is required for titration as follows: -

Dose titration

Week 1 (day 1 - 7)

The patient should take 5 mg (½ x 10 mg tablet) per day.

Week 2 (day 8 - 14)

The patient should take 10 mg (1x 10 mg tablet) per day.

Week 3 (day 15 - 21)

The patient should take 15 mg (1½ x 10 mg tablets) per day.

Maintenance dose from week 4

The recommended maintenance dose is 20 mg per day.

Children

The use of Ebixa in children is not recommended.

Hepatic impairment

In patients with mild or moderate hepatic impairment (Child-Pugh A and Child-Pugh B), no dosage adjustment is required. No data on the use of memantine in patients with severe hepatic impairment is available. 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 tolerated well after at least 7 days of treatment, the dose can be increased up to 20 mg/day according to the standard titration scheme.

In patients with severe renal impairment (creatinine clearance 5 - 29 mL/min), the daily dose should be 10 mg per day.

4.3 Contraindications

Ebixa is contraindicated in patients with:

- hypersensitivity to either the active ingredient or any of the excipients
- patients with a current seizure disorder or with any history of seizures

4.4 Special warnings and precautions for use

Risk of seizures - Memantine is contraindicated in patients with epilepsy. Caution is recommended in patients with a former history of convulsions or patients with predisposing factors for epilepsy.

Patient care - Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of dementia. Diagnosis should be made according to current guidelines. Therapy should usually be started only when a caregiver is available who will regularly monitor patient compliance. Treatment with memantine hydrochloride should only be continued where there is a therapeutic benefit to the patient. The clinical benefit should be reassessed on a regular basis.

Ocular toxicity - Animal studies have reported adverse effects of memantine on the visual system. Dietary administration of memantine to rats for one year was associated with abnormal lysosomal storage in ganglion cells and retinal pigment cells at systemic exposures (plasma AUC) 10-fold anticipated clinical exposure at the recommended dose, while administration for 8 weeks was associated with lens opacity, increased corneal and lens capsular densities, and histological changes in cornea and lens at exposures (plasma AUC) of 20fold clinical exposure. Oral administration of memantine to dogs with systemic exposures (plasma AUC) of 3 - 8-fold clinical exposure was associated with corneal clouding/opacity and baboons showed swollen lenticular fibres in the eyes following oral memantine for 3 months at less than clinical exposure.

Specific ophthalmological examinations including slit lamp examinations in a 6-month clinical study with memantine did not disclose any ocular changes in the double-blind placebo-controlled treatment period. In the following 6 months open label extension period 368 patients underwent eye examinations. At the end of open label treatment, the incidence of cataract (lens previously clear but unclear at end of open label treatment) was reported in 11 out of 197 patients (6%) treated with memantine for 12 months compared to 5 out of 171 patients (3%) who received placebo in the double-blind period and then memantine for 6 months (p=0.3059, Fisher’s Exact Test).

Urinary pH - Some factors that may raise urinary pH may necessitate careful monitoring of the patient. These factors include drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or a massive ingestion of alkalising gastric buffers. Also, urine pH may be elevated by states of renal tubular acidosis (RTA) or severe infections of the urinary tract with *Proteus bacteria.*

Use in renal impairment - In patients with mildly impaired renal function (creatinine clearance 50 - 80 mL/min), no dosage adjustment is required. A reduction in dosage is advised for patients with moderate to severe renal impairment (see Section 4.2 Dose and method of administration).

Use in hepatic impairment - In patients with mild or moderate hepatic impairment (Child-Pugh A and Child-Pugh B), no dosage adjustment is required. No data is available for patients with severe hepatic impairment (see Section 4.2 Dose and method of administration). Administration of Ebixa is not recommended in patients with severe hepatic impairment.

Cardiovascular disease - In most clinical trials, patients with recent myocardial infarction, uncompensated congestive heart failure (NYHA III-IV), and uncontrolled hypertension were excluded. As a consequence, only limited data are available and patients with these conditions should be closely supervised.

Use in the elderly
No dosage adjustment is required.

Paediatric use
No data available.

Effects on laboratory tests
No data available.

4.5 Interactions with other medicines and other forms of interactions

NMDA antagonists - Concomitant use of N-methyl-D-aspartate (NMDA) antagonists such as amantadine, ketamine or dextromethorphan should be avoided. These compounds act at the same receptor system as memantine, and therefore adverse drug reactions (mainly CNS-related) may be more frequent or more pronounced. There is a risk of pharmacotoxic psychosis when memantine and amantadine are used concomitantly. Both compounds are chemically related NMDA antagonists. The same may be true for ketamine and dextromethorphan.

Drugs affecting the central nervous system - The mode of action suggests that the effects of L-dopa, dopaminergic agonists (e.g. bromocriptine), anticholinergics and amantadine on the central nervous system may be potentiated.

If barbiturates, neuroleptics, anticonvulsants, dantrolene or baclofen are being given simultaneously, their effect can be modified, possibly necessitating a dose adjustment.

These recommendations are mainly based on theoretical considerations.

In *in vitro* studies, interactions with reversible acetylcholinesterase inhibitors (donepezil, tacrine) were not seen. In single dose PK studies in young healthy subjects, no relevant drug-drug interaction of memantine with donepezil was observed. Similarly, no relevant effect of memantine on the pharmacokinetics of galantamine was observed in a clinical study in young healthy subjects.

In clinical trials, clinically relevant interactions with aspirin, tocopherol, paracetamol and chloral hydrate were not observed.

Glyburide/metformin - In single dose PK studies in young healthy subjects, no relevant drug-drug interaction of memantine with glyburide/metformin was observed.

Hepatic enzymes **-** Because of its low extent of metabolism by CYP450 isoenzymes, metabolic drug interactions appear unlikely. *In vitro* interaction investigations using human liver microsomes did not reveal interaction with markers of CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A. The only reaction slightly affected by the addition of 10 µM memantine was methimazole oxidation (marker of Ziegler's enzyme, a flavin containing monoxygenase).

Highly protein bound drugs **-** As memantine is bound to plasma proteins at only 42% to 54%, interactions with highly protein bound drugs (e.g. warfarin) would not be expected.

Warfarin **-** In post marketing experience, isolated cases with international normalised ratio (INR) increases have been reported in patients concomitantly treated with warfarin. Although no causal relationship has been established, close monitoring of prothrombin time or INR is advisable for patients concomitantly treated with oral anticoagulants.

Drugs using the same renal cationic transport system **-** *In vitro* studies to examine potential interactions at renal tubular secretion sites revealed a potential competition with drugs which are secreted via the same basic cation transporter. In rat proximal and distal tubules (*in vitro*), memantine inhibited renal tubular uptake of amantadine.

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

Diuretics **-** The potential interaction with hydrochlorothiazide/triamterene in humans was also studied. Elderly volunteers received hydrochlorothiazide/triamterene and/or memantine, and the pharmacokinetics of memantine was analysed under steady state-conditions. AUC, C_{max} and T_{max} values were within the 80 - 125% bioequivalence limits compared to values obtained for memantine alone. Similarly, memantine had no significant effect on the kinetics of triamterene or its hydroxymetabolite. However, the rate and extent of hydrochlorothiazide bioavailability was reduced by memantine by about 20%. No clinically relevant impact on the pharmacokinetics of memantine or hydrochlorothiazide/triamterene was observed.

Atropine - Serious interactions between atropine and memantine have been noted in a toxicity study in rats. The interaction with atropine occurred at very high doses of memantine under conditions not relevant to humans treated at therapeutic doses of memantine.

4.6 Fertility, pregnancy and lactation

Effects on fertility
Fertility was not affected by oral administration of memantine to male and female rats prior to and during mating at doses associated with respective systemic exposures (plasma AUC) of twice and 4-fold anticipated clinical exposure at the recommended dose.

Use in pregnancy
Category B2

There was no evidence of teratogenicity in rats following oral administration of memantine during the period of organogenesis at estimated exposures (plasma AUC) of up to 4-fold anticipated clinical exposure at the recommended dose. There was also no teratogenicity in rats following oral administration to males prior to and during mating and to females from prior to mating to late gestation or to weaning, with respective estimated systemic exposures (plasma AUC) of twice and 4-fold anticipated clinical exposure. There was no teratogenicity in rabbits following oral administration of memantine during the period of organogenesis at doses up to 25-fold the clinical dose, based on body surface area.

Use in lactation
Oral administration of memantine to rats during late gestation and lactation was associated with increased post-implantation loss and transiently reduced neonatal bodyweight at estimated systemic exposures (plasma AUC) of 4-fold anticipated clinical exposure at the recommended dose. It is not known whether memantine is excreted in animal or human milk. Because of the potential for causing toxicity, memantine should be contraindicated in nursing women.

4.7 Effects on ability to drive and use machines

Moderately severe to severe Alzheimer's disease usually causes impairment of driving performance and compromises the ability to use machinery. Furthermore, Ebixa may change reactivity and therefore outpatients should be warned to take special care when driving a vehicle or operating heavy machinery.

4.8 Adverse effects (Undesirable effects)

The following table gives an overview of the most frequent (≥ 2% for memantine) adverse events (irrespective of causal relationship) that were observed in the trial population with moderately severe to severe dementia.

System Organ Class & Preferred Term	**Placebo n=288 (%)**	**Memantine n=299 (%)**
BODY AS A WHOLE – GENERAL DISORDERS		
Fatigue	3 (1.0)	7 (2.3)
CARDIOVASCULAR DISORDERS - GENERAL		

System Organ Class & Preferred Term	Placebo n=288 (%)	Memantine n=299 (%)
Oedema peripheral	2 (0.7)	6 (2.0)
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS		
Dizziness	8 (2.8)	15 (5.0)
Headache	9 (3.1)	15 (5.0)
Confusion	7 (2.4)	9 (3.0)
Gait abnormal	10 (3.5)	8 (2.7)
GASTROINTESTINAL SYSTEM DISORDERS		
Diarrhoea	14 (4.9)	16 (5.4)
Vomiting	6 (2.1)	11 (3.7)
Constipation	13 (4.5)	10 (3.3)
Anorexia	6 (2.1)	9 (3.0)
Faecal incontinence	8 (2.8)	8 (2.7)
Nausea	6 (2.1)	7 (2.3)
LIVER & BILIARY SYSTEM DISORDERS		
Phosphatase alkaline increased	4 (1.4)	6 (2.0)
METABOLIC & NUTRITIONAL DISORDERS		
Hyperglycaemia	5 (1.7)	6 (2.0)
ESR increased	5 (1.7)	8 (2.7)
MUSCULOSKELETAL SYSTEM DISORDERS		
Arthralgia	6 (2.1)	6 (2.0)
Back pain	6 (2.1)	6 (2.0)
PSYCHIATRIC DISORDERS		
Agitation	48 (16.7)	26 (8.7)
Insomnia	14 (4.9)	15 (5.0)
Hallucination	6 (2.1)	14 (4.7)
Somnolence	9 (3.1)	10 (3.3)
Anorexia	6 (2.1)	9 (3.0)
Depression	9 (3.1)	8 (2.7)
Anxiety	3 (1.0)	7 (2.3)
Delusion	4 (1.4)	6 (2.0)
Sleep disorder	3 (1.0)	6 (2.0)
RESPIRATORY SYSTEM DISORDERS		
Coughing	16 (5.6)	12 (4.0)
Bronchitis	13 (4.5)	11 (3.7)
Pneumonia	5 (1.7)	7 (2.3)
Upper respiratory tract infection	7 (2.4)	6 (2.0)

SECONDARY TERMS		
Inflicted injury	20 (6.9)	18 (6.0)
Fall	14 (4.9)	14 (4.7)
URINARY SYSTEM DISORDERS		
Urinary incontinence	19 (6.6)	17 (5.7)
Urinary tract infection	22 (7.6)	9 (3.0)
VISION DISORDERS		
Conjunctivitis	1 (0.3)	6 (2.0)

The following adverse events were reported with memantine at a frequency between 1% and < 2% at an incidence greater than placebo in patients with moderately severe to severe AD: pain, abnormal crying, influenza-like symptoms, leg pain, syncope, dependent oedema, hypertonia (increased muscle tone), gastroenteritis, bradycardia, hyperuricaemia, hypertension, dehydration, dyspnoea, hypokalaemia, arthrosis, angina pectoris, purpura, rash, basal cell carcinoma, cerebrovascular disorder, phlebitis, deep thrombophlebitis, tooth ache and tooth caries. As in the above table, causality to memantine has not been established.

Adverse events reported with memantine at a frequency between 1% and 2% that occurred at a similar rate to or less than placebo were: weight decrease, oedema, coma, abdominal pain, cardiac arrest, increased ALT, AST and GGT, diabetes mellitus, aggressive reaction, apnoea, rhinitis, abrasion, micturition frequency and leucocytosis.

Treatment - Emergent Adverse Drug Reactions

Although no causal relationship to Ebixa treatment has been found, the following adverse events were reported in at least one patient, either from clinical trials or spontaneous reports. All of these events, which are not listed above, either occurred rarely (< 1%) or at an unknown incidence from data originating from spontaneous reports.

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 memantine.

Body as a Whole – General Disorders

Fever, increased appetite, increased libido, asthenia, somnolence, tiredness.

Cardiovascular Disorders

Chest pain, hypotension, postural hypotension, rhythm and rate disturbance e.g. atrial fibrillation, QTc prolongation, ischaemic event and sudden death e.g. myocardial infarction. Cardiac failure - in placebo-controlled clinical trials of memantine an increase in the incidence rate has been observed in non-serious cases; no difference was seen in fatal or serious cases. Causal relationship to memantine has not been ascertained.

Gastro-intestinal System Disorders

Diverticulitis, dyspepsia, haemorrhoids, gastric ulcer, ileus, pancreatitis.

Hepatobiliary disorders

Hepatitis, elevated liver function test.

Infections and infestations

Fungal infections.

Metabolic and Nutritional Disorders

Bilirubinaemia, aggravated diabetes mellitus, hypernatraemia, hyponatraemia.

Musculoskeletal Disorders

Muscle weakness, myalgia, skeletal pain.

Neurological Disorders

Aphasia, speech disorder, hyperkinesia, dyskinesia, dementia, partial epileptic seizure, convulsions, tremor, extrapyramidal disorder, transient ischaemic attack, vertigo, numbness, paraesthesia, mental status changes, balance disorders.

Platelet, Bleeding & Clotting Disorders

Embolism.

Psychiatric Disorders

Delusion, nervousness, stupor, excitation/mania, suicide attempt, psychotic reactions.

Renal and Urinary Disorders

Acute renal failure, abnormal renal function, renal calculus.

Reproductive Disorders

Menstrual disorder.

Respiratory System Disorders

Atelectasis.

Red Blood Cell Disorders

Anaemia.

Skin and Appendages Disorders

Dermatitis, skin disorder, skin ulceration, bullous eruption, pruritus, increased sweating.

Urinary System Disorders

Cystitis, pyuria, haematuria, urinary retention.

Vascular (Extracardiac) Disorders

Cerebrovascular disorder, intracranial haemorrhage, venous thrombosis/thromboembolism (uncommon).

Vision Disorders

Cataract, abnormal vision, glaucoma.

Others

Tooth disorder, inguinal hernia, sepsis.

The following Immune System Disorder Adverse Reaction has been found in clinical studies with Ebixa and since its introduction in the market, at an incidence classified as common (≥1/100 to < 1/10): - Drug hypersensitivity.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

In general, the main therapy for all overdoses is supportive and symptomatic care.

Symptoms

In the event of accidental overdose, no life-threatening clinical signs and symptoms are expected. The toxic effects observed in early single-dose toxicity studies **in animals** were consistent with acute, high-dose NMDA receptor-blockage and included ataxia, tremor, prone position, bradypnoea, and amnesia.

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

Treatment

In the event of overdose, treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

There is increasing evidence that malfunctioning of glutamatergic neurotransmission, in particular at N-methyl-D-aspartate (NMDA) receptors, contributes to both expression of symptoms and disease progression in neurodegenerative dementia.

Memantine is a rapid, strongly voltage-dependent, uncompetitive NMDA receptor antagonist. Prolonged increased levels of glutamate in the brain of demented patients are sufficient to counter the voltage-dependent block of NMDA receptors by Mg^{2+} ions and allow continuous influx of Ca^{2+} ions into cells and ultimately neuronal degeneration. Studies suggest that memantine binds more effectively than Mg^{2+} ions at the NMDA receptor, and thereby effectively blocks this prolonged influx of Ca^{2+} ions through the NMDA channel whilst preserving the transient physiological activation of the channels by higher concentrations of synaptically released glutamate. Thus memantine protects against chronically elevated concentrations of glutamate.

In animal models of disturbances in glutamatergic transmission memantine has been shown both to improve learning and to inhibit neurodegeneration at doses achieving plasma levels similar to those seen in clinical use. This in turn may explain the effect of memantine on dementia of the Alzheimer type.

At later stages of dementia, a functional deficit in glutamatergic transmission occurs due to loss of neurones bearing NMDA receptors.

In humans, memantine has not been shown to slow or reverse the neurodegenerative processes of Alzheimer's disease.

Clinical trials

Two clinical trials in a population of patients suffering from moderately severe to severe dementia showed a beneficial effect of memantine treatment in comparison to placebo over a treatment period of three and six months, respectively. This benefit was measured by the patients' cognitive function, functional capacities (activities of daily living) and by clinical global status. There were no consistent differences between sexes observed in these trials.

6 month study

A pivotal 6-month multicentre, double-blind, randomised, placebo-controlled study conducted in a population of patients with moderately severe to severe Alzheimer's disease (MMSE 3 - 14) included a total of 252 outpatients of Asian American, African American and Caucasian background (33% male, 67% female, mean age 76 years). The dosing was 10 mg memantine b.i.d.

Outcomes included assessment of the cognitive domain (using the Severe Impairment Battery (SIB)), the global domain (using the Clinicians Interview-Based Impression of Change (CIBIC-Plus)) and the functional domain (using the modified Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL)).

The efficacy results described are from the ITT dataset (all randomised patients) with the LOCF method (last observation carried forward) as well as the OC (observed cases). Based on the OC analyses, the results of this study met the requirement of the European Union Guideline CPMP/EWP/553/95 for statistically significant improvements in the functional and global endpoints as primary evidence of clinically relevant symptomatic improvement in more advanced forms of Alzheimer's disease. An overview of the results in the most important domains of efficacy is displayed in Table 1.

Table 1: Efficacy results of a 6-month study in patients suffering from Alzheimer's disease

Domain	ITT-LOCF Analysis				ITT-OC Analysis			
	Placebo (n=126)	**Memantine (n=126)**	**Mean difference**	**p value**	**Placebo (n=84)**	**Memantine (n=97)**	**Mean difference**	**p value**
Cognition: SIB (score range 0-100)	-9.84 (SD 13.43)	-3.93 (SD 11.26)	5.91	<0.001	-10.16 (SD 12.66)	-4.46 (SD 11.48)	5.7	0.002
Function: ADCS-ADL sev. (score range 0-54)	-5.08 (SD 6.30)	-3.02 (SD 6.75)	2.06	0.022	-5.86 (SD 6.78)	-2.49 (SD 6.27)	3.37	0.003
Global: CIBIC-plus (score range 1-7)	4.73 (SD 1.07)	4.48 (SD 1.09)	0.25	0.064	4.74 (SD 1.13)	4.38 (SD 1.12)	0.36	0.025

Memantine was very well tolerated with similar frequency and type of adverse events observed with memantine compared with placebo.

3-month study

A pivotal 3-month multicentre, double-blind, randomised, placebo-controlled study was conducted in Caucasian patients with moderately severe to severe Alzheimer's disease or vascular dementia (MMSE < 10). In this study a total of 79 nursing home residents (33% male, 67% female, mean age 74 years) had Alzheimer's disease. The dosing used was 10 mg memantine daily.

Outcomes included assessment of the cognitive domain (using the cognitive subscore of the rating scale for geriatric patients (BGP)), the global domain (using the Clinical Global

Impression of Change (CGI-C)) and the functional domain (using the subscore care dependency of the BGP).

Despite the small sample size, the results in all of these three domains were statistically significant in favour of memantine (see Table 2). The efficacy results described are from the ITT dataset (all randomised patients) with the LOCF method (last observation carried forward) as well as OC (observed cases).

Table 2: Efficacy results for a 3-month study in patients suffering from Alzheimer's disease

Domain	ITT-LOCF Analysis				ITT-OC Analysis			
	Placebo (n=38)	Memantine (n=41)	Mean difference	p value	Placebo (n=37)	Memantine (n=39)	Mean difference	p value
BGP cognitive (score range 0-10)	-1.03	-2.00	0.97	0.007	-1.05	-2.10	1.05	0.004
BGP functional (score range 0-46)	-2.79	-5.76	2.97	0.003	-2.89	-6.05	3.16	0.002
CGI-C (score range 1-7)	3.47	3.15	0.32	0.002	3.46	3.08	0.38	0.005

Memantine was well tolerated, with physicians rating tolerability as 'very good' in 71% of memantine and 69% of placebo treated patients. In the remaining patients, tolerability was assessed as 'good', with the exception of one memantine treated patient where it was assessed as 'moderate'.

5.2 Pharmacokinetic properties

Absorption

In humans, complete absorption of memantine with no first pass effect was demonstrated. The absolute bioavailability is approximately 100%. Peak plasma concentration is achieved between 5 and 8 hours. Food tended to slow the rate of memantine absorption but not the extent of absorption. The tablet and drop formulations are bioequivalent.

Distribution

Daily doses of 20 mg in humans lead to steady-state plasma concentrations ranging from 70 to 150 ng/mL (0.5 – 1 µM) with large interindividual variations. In healthy volunteers, the pharmacokinetics of memantine were linear over the dose range of 10 to 40 mg.

When daily doses of 5 to 30 mg were administered, a mean cerebrospinal fluid (CSF)/serum ratio of 0.52 was obtained. The inhibition constant (k_i) of memantine at its site of action in human frontal cortex has been determined to be 0.5 µM. In subjects receiving a daily dose of

2 x 10 mg steady-state plasma levels were reached around day 11 and varied between 0.5 and 1.0 µM, which leads to CSF levels close to the k_i of memantine.

The volume of distribution is approximately 10 L/kg. Protein binding in humans varied from 42% to 54% and no relationship was observed between plasma memantine concentration and protein binding.

Metabolism

In humans, memantine is excreted mainly (60 - 80%) in its unchanged form in urine. Human metabolites are 1-amino-3-hydroxymethyl-5-methyl-adamantane, 3-amino-1-hydroxy-5, 7-dimethyl-adamantane and various secondary hydroxylated not yet definitively identified memantine-derivatives; phase II metabolism amounts for up to 10%. The known metabolites do not have any NMDA-antagonistic activity. In view of the minor degree of metabolism, variation with respect to polymorphic metabolism is not anticipated.

In vitro experiments have indicated that memantine is not metabolised by CYP isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A4.

Excretion

Memantine is eliminated predominantly by the kidneys in a monoexponential manner with a terminal half-life of 60 to 100 h. In volunteers with normal kidney function, systemic clearance amounts to 170 mL/min.

In a study on the absorption, metabolism and excretion of orally administered ^{14}C-memantine, a mean of 84% of the dose was recovered within 20 days, the majority being excreted unchanged renally.

Renal clearance has been shown to depend on the pH of the urine. Under alkaline conditions the renal clearance of unchanged memantine is markedly reduced compared to neutral or acidic urine conditions. This is presumably due to tubular reabsorption of memantine under alkaline conditions.

5.3 Preclinical safety data

Genotoxicity

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*).

Carcinogenicity

Long term dietary administration of memantine to mice (2 years) and rats (2.5 years), with respective estimated systemic exposures of 9-fold (plasma levels) and 4 – 8-fold (plasma AUC) the anticipated clinical exposure at the recommended dose, did not reveal any carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ebixa 10 mg tablets contain the following excipients: microcrystalline cellulose, croscarmellose sodium, hypromellose, iron oxide yellow, macrogol 400, magnesium stearate, colloidal anhydrous silica and titanium dioxide.

Ebixa 20 mg tablets contain the following excipients: microcrystalline cellulose croscarmellose sodium, hypromellose, iron oxide red CI77491, iron oxide yellow CI77492, macrogol 400, magnesium stearate, colloidal anhydrous silica and titanium dioxide.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Ebixa 10 mg tablets: Blister packs of 14 and 56 tablets.

Ebixa 20 mg tablets: Blister packs of 28 tablets.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical name:

1-amino-3, 5-dimethyl-adamantane hydrochloride

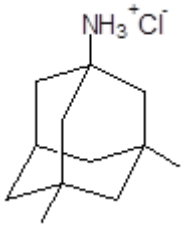
Molecular formula:

$C_{12}H_{21}N.HCl$

Molecular weight:

215.77

Chemical structure



Memantine hydrochloride is a colourless crystalline substance with a bitter taste. The solubility of memantine hydrochloride in water at room temperature is about 3.5%. No polymorphic forms have been detected.

CAS number

19982-08-2 (free base)

4110-52-1 (hydrochloride salt)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only medicine

8 SPONSOR

Lundbeck Australia Pty Ltd
1 Innovation Road
North Ryde NSW 2113
Ph: 02 8669 1000

9 DATE OF FIRST APPROVAL

17 April 2003

10 DATE OF REVISION

13 February 2020

Summary table of changes

Section Changed	Summary of new information
All	Reformatted in line with the revised Australian form for providing product information format.