

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Axura 10 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of memantine hydrochloride (equivalent to 8.31 mg memantine).
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

The film-coated tablets are white to off-white, centrally tapered oblong, biconvex, with a single breakline on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. Therapy should only be started if a caregiver is available who will regularly monitor drug intake by the patient. Diagnosis should be made according to current guidelines.

Adults: The maximum daily dose is 20 mg per day. In order to reduce the risk of side effects the maintenance dose is achieved by upward titration 5 mg per week over the first 3 weeks as follows: Treatment should be started with 5 mg daily (half a tablet in the morning) during the 1st week. In the 2nd week 10 mg per day (half a tablet twice a day) and in the 3rd week 15 mg per day is recommended (one tablet in the morning and half a tablet in the afternoon). From the 4th week on, treatment can be continued with the recommended maintenance dose of 20 mg per day (one tablet twice a day).

The tablets can be taken with or without food.

Elderly: On the basis of the clinical studies the recommended dose for patients over the age of 65 years is 20 mg per day (10 mg twice a day) as described above.

Children and adolescents under the age of 18 years: The safety and efficacy of memantine in children and adolescents have not been established.

Renal impairment: In patients with normal to mildly impaired renal function (serum creatinine levels of up to 130 µmol/l) no dose reduction is needed. In patients with moderate renal impairment (creatinine clearance 40 - 60 ml/min/1.73 m²) daily dose should be reduced to 10 mg per day. No data are available for patients with severely reduced kidney function (see sections 4.4 and 5.2).

Hepatic impairment: There are no data on the use of memantine in patients with hepatic impairment (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and special precautions for use

As no data are available for patients with severe renal impairment (creatinine clearance less than 9 ml/min/1.73 m²) therapy is not recommended (see section 4.2).

Caution is recommended in patients with epilepsy, former history of convulsions or patients with predisposing factors for epilepsy.

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 (see also section 4.5).

Some factors that may raise urine pH (see section 5.2 “Elimination”) may necessitate careful monitoring of the patient. These factors include drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or a massive ingestion of alkalisating 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*.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

- The mode of action suggests that the effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with NMDA-antagonists such as memantine. The effects of barbiturates and neuroleptics may be reduced. Concomitant administration of memantine with the antispasmodic agents, dantrolene or baclofen, can modify their effects and a dosage adjustment may be necessary.
- Concomitant use of memantine and amantadine should be avoided, owing to the risk of pharmacotoxic psychosis. Both compounds are chemically related NMDA-antagonists. The same may be true for ketamine and dextromethorphan (see also section 4.4). There is one published case report on a possible risk also for the combination of memantine and phenytoin.
- Other drugs such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine that use the same renal cationic transport system as amantadine may also possibly interact with memantine leading to a potential risk of increased plasma levels.
- There may be a possibility of reduced serum level of hydrochlorothiazide (HCT) when memantine is co-administered with HCT or any combination with HCT.

Memantine did not inhibit CYP 1A2, 2A6, 2C9, 2D6, 2E1, 3A, flavin containing monooxygenase, epoxide hydrolase and sulphation *in vitro*.

4.6 Pregnancy and lactation

Pregnancy: For memantine, no clinical data on exposed pregnancies are available. Animal studies indicate a potential for reducing intrauterine growth at exposure levels which are identical or slightly higher than at human exposure (see section 5.3). The potential risk for humans is unknown. Memantine should not be used during pregnancy unless clearly necessary.

Lactation: It is not known whether memantine is excreted in humans breast milk but, taking into consideration the lipophilicity of the substance, this probably occurs. Women taking memantine should not breast-feed.

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

4.8 Undesirable effects

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

The following table gives an overview of the most frequent (> 4% for memantine) adverse events (irrespective of causal relationship) that were observed in the trial population of patients with moderately severe to severe dementia.

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

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

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

Based on spontaneous reports, seizures have been reported, mostly in patients with a history of convulsions.

4.9 Overdose

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

Treatment of overdosage should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-dementia drugs, ATC code: N06DX01.

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

Memantine is a voltage-dependent, moderate-affinity uncompetitive NMDA-receptor antagonist. It blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

Clinical studies: A clinical trial in a population of patients suffering from moderately severe to severe Alzheimer's disease (MMSE total scores at baseline of 3 - 14) showed beneficial effects of memantine treatment in comparison to placebo over a treatment period of 6 months.

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

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

5.2 Pharmacokinetic properties

Absorption: Memantine has an absolute bioavailability of approximately 100%. t_{\max} is between 3 and 8 hours. There is no indication that food influences the absorption of memantine.

Linearity: Studies in volunteers have demonstrated linear pharmacokinetics in the dose range of 10 to 40 mg.

Distribution: Daily doses of 20 mg lead to steady-state plasma concentrations of memantine ranging from 70 to 150 ng/ml (0.5 - 1 μmol) with large interindividual variations. When daily doses of 5 to 30 mg were administered, a mean CSF/serum ratio of 0.52 was calculated. The volume of distribution is around 10 l/kg. About 45% of memantine is bound to plasma-proteins.

Biotransformation: In man, about 80% of the circulating memantine-related material is present as the parent compound. Main human metabolites are N-3,5-dimethyl-gludantan, the isomeric mixture of 4- and 6-hydroxy-memantine, and 1-nitroso-3,5-dimethyl-adamantane. None of these metabolites exhibit NMDA-antagonistic activity. No cytochrome P 450 catalysed metabolism has been detected *in vitro*.

In a study using orally administered ^{14}C -memantine, a mean of 84% of the dose was recovered within 20 days, more than 99% being excreted renally.

Elimination: Memantine is eliminated in a monoexponential manner with a terminal $t_{1/2}$ of 60 to 100 hours. 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 (see section 4.4). Alkalisiation of urine may result from drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or from the massive ingestion of alkalisating gastric buffers.

Specific patient population: In elderly volunteers with normal and reduced renal function (creatinine clearance of 50 - 100 ml/min/1.73 m^2), a significant correlation was observed between creatinine clearance and total renal clearance of memantine (see section 4.2).

The effect of liver disease on the pharmacokinetics of memantine has not been studied. As memantine is metabolised to a minor extent only, and into metabolites with no NMDA-antagonistic activity, clinically relevant changes in the pharmacokinetics are not expected in mild to moderate liver impairment.

Pharmacokinetic/pharmacodynamic relationship: At a dose of memantine of 20 mg per day the cerebrospinal fluid (CSF) levels match the k_i -value (k_i = inhibition constant) of memantine, which is 0.5 μmol in human frontal cortex.

5.3 Preclinical safety data

In short term studies in rats memantine like other NMDA-antagonists have induced neuronal vacuolisation and necrosis (Olney lesions) only after doses leading to very high peak serum

concentrations. Ataxia and other preclinical signs have preceded the vacuolisation and necrosis. As the effects have neither been observed in long term studies in rodents nor in non-rodents, the clinical relevance of these findings is unknown.

Ocular changes were inconsistently observed in repeat dose toxicity studies in rodents and dogs, but not in monkeys. Specific ophthalmoscopic examinations in clinical studies with memantine did not disclose any ocular changes.

Phospholipidosis in pulmonary macrophages due to accumulation of memantine in lysosomes was observed in rodents. This effect is known from other drugs with cationic amphiphilic properties. There is a possible relationship between this accumulation and the vacuolisation observed in lungs. This effect was only observed at high doses in rodents. The clinical relevance of these findings is unknown.

No genotoxicity has been observed following testing of memantine in standard assays. There was no evidence of any carcinogenicity in life long studies in mice and rats. Memantine was not teratogenic in rats and rabbits, even at maternally toxic doses, and no adverse effects of memantine were noted on fertility. In rats, foetal growth reduction was noted at exposure levels which are identical or slightly higher than at human exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Microcrystalline cellulose
Colloidal anhydrous silica
Talc
Magnesium stearate

Tablet coat:

Methacrylic acid - ethyl acrylate copolymer (1:1)
Sodium lauryl sulphate
Polysorbate 80
Talc
Triacetin
Simethicone emulsion

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Blister packs containing either 7, 10, 14 or 20 tablets per blister strip (Alu/PP). Pack sizes of 28, 30, 50, 56, 100, 112 or 1000 (20 x 50) tablets are presented.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Merz Pharmaceuticals GmbH
Eckenheimer Landstr. 100
D-60318 Frankfurt/Main
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/001
EU/1/02/218/002
EU/1/02/218/003
EU/1/02/218/007
EU/1/02/218/008
EU/1/02/218/009
EU/1/02/218/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/05/2002

10. DATE OF REVISION OF THE TEXT

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Axura 10 mg/g oral drops, solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of solution contains 10 mg of memantine hydrochloride (equivalent to 8.31 mg memantine).
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral drops, solution.

The solution is clear and colourless to light yellowish.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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Adults: The maximum daily dose is 20 mg per day. In order to reduce the risk of side effects the maintenance dose is achieved by upward titration 5 mg per week over the first 3 weeks as follows: Treatment should be started with 5 mg daily (10 drops in the morning) during the 1st week. In the 2nd week 10 mg per day (10 drops twice a day) and in the 3rd week 15 mg per day is recommended (20 drops in the morning and 10 drops in the afternoon). From the 4th week on, treatment can be continued with the recommended maintenance dose of 20 mg per day (20 drops twice a day).

The drops can be taken with or without food.

Elderly: On the basis of the clinical studies the recommended dose for patients over the age of 65 years is 20 mg per day (10 mg twice a day) as described above.

Children and adolescents under the age of 18 years: The safety and efficacy of memantine in children and adolescents have not been established.

Renal impairment: In patients with normal to mildly impaired renal function (serum creatinine levels of up to 130 $\mu\text{mol/l}$) no dose reduction is needed. In patients with moderate renal impairment (creatinine clearance 40 - 60 ml/min/1.73 m²) daily dose should be reduced to 10 mg per day. No data are available for patients with severely reduced kidney function (see sections 4.4 and 5.2).

Hepatic impairment: There are no data on the use of memantine in patients with hepatic impairment (see section 5.2).

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Treatment of overdosage should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-dementia drugs, ATC code: N06DX01.

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Pharmacokinetic/pharmacodynamic relationship: At a dose of memantine of 20 mg per day the cerebrospinal fluid (CSF) levels match the k_i -value (k_i = inhibition constant) of memantine, which is 0.5 μmol in human frontal cortex.

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No genotoxicity has been observed following testing of memantine in standard assays. There was no evidence of any carcinogenicity in life long studies in mice and rats. Memantine was not teratogenic in rats and rabbits, even at maternally toxic doses, and no adverse effects of memantine were noted on fertility. In rats, foetal growth reduction was noted at exposure levels which are identical or slightly higher than at human exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potassium sorbate
Sorbitol
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

Once opened, the contents of the bottle should be used within 3 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Brown glass bottles (Hydrolytic Class III) with dropper containing either 20, 50, 100 g or 10 x 50 g solution.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Merz Pharmaceuticals GmbH
Eckenheimer Landstr. 100
D-60318 Frankfurt/Main
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/004
EU/1/02/218/005
EU/1/02/218/006
EU/1/02/218/011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/05/2002

10. DATE OF REVISION OF THE TEXT