

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Axura 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of memantine hydrochloride equivalent to 8.31 mg memantine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Pale yellow to yellow, oval shaped film-coated tablet with breaking line and engravings "1-0" on one side and "M M" on the other side

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

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 the intake of the medicinal product 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. 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:

Dose titration

The maximum daily dose is 20 mg per day. In order to reduce the risk of undesirable effects the maintenance dose is achieved by upward titration of 5 mg per week over the first 3 weeks as follows:

Week 1 (day 1-7):

The patient should take half a 10 mg film-coated tablet (5 mg) per day for 7 days.

Week 2 (day 8-14):

The patient should take one 10 mg film-coated tablet (10 mg) per day for 7 days.

Week 3 (day 15-21):

The patient should take one and a half 10 mg film-coated tablet (15 mg) per day for 7 days.

From Week 4 on:

The patient should take two 10 mg film-coated tablets (20 mg) per day.

Maintenance dose

The recommended maintenance dose is 20 mg per day.

Older people: On the basis of the clinical studies, the recommended dose for patients over the age of 65 years is 20 mg per day (two 10 mg tablets once a day) as described above.

Renal impairment: In patients with mildly impaired renal function (creatinine clearance 50 - 80 ml/min) no dose adjustment is required. In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) daily dose should be 10 mg per day. If tolerated well after at least 7 days of treatment, the dose could be increased up to 20 mg/day according to standard titration scheme. In patients with severe renal impairment (creatinine clearance 5 – 29 ml/min) daily dose should be 10 mg per day.

Hepatic impairment: In patients with mild or moderate hepatic impaired function (Child-Pugh A and Child-Pugh B) no dose adjustment is needed. No data on the use of memantine in patients with severe hepatic impairment are available. Administration of Axura is not recommended in patients with severe hepatic impairment.

Children and adolescents : Axura is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Method of administration

Axura should be administered once a day and should be taken at the same time every day. The film-coated tablets can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 reactions (mainly central nervous system (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 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*.

In most clinical trials, patients with recent myocardial infarction, uncompensated congestive heart failure (NYHA III-IV), or 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 dose 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 active substances 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.
- In post-marketing experience isolated cases with international normalized 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.

In single-dose pharmacokinetic (PK) studies in young healthy subjects no relevant active substance-active substance interaction of memantine with glyburide/metformin or donepezil was observed.

In a clinical study in young healthy subjects no relevant effect of memantine on the pharmacokinetics of galantamine was observed.

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

4.6 Fertility, 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.

Breast-feeding

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

Fertility

No adverse effects of memantine were noted on non-clinical male and female fertility studies.

4.7 Effects on ability to drive and use machines

Moderate to severe Alzheimer's disease usually causes impairment of driving performance and compromises the ability to use machinery. Furthermore, Axura has minor to moderate influence on the ability to drive and use machines such that outpatients should be warned to take special care.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials in mild to severe dementia, involving 1,784 patients treated with Axura and 1,595 patients treated with placebo, the overall incidence rate of adverse reactions with Axura did not differ from those with placebo; the adverse reactions were usually mild to moderate in severity. The most frequently occurring adverse reactions with a higher incidence in the Axura group than in the placebo

group were dizziness (6.3% vs 5.6%, respectively), headache (5.2% vs 3.9%), constipation (4.6% vs 2.6%), somnolence (3.4% vs 2.2%) and hypertension (4.1% vs 2.8%).

The following Adverse Reactions listed in the Table below have been accumulated in clinical studies with Axura and since its introduction in the market. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

Adverse reactions are ranked according to system organ class, using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Infections and infestations	Uncommon	Fungal infections
Immune system disorders	Common	Drug hypersensitivity
Psychiatric disorders	Common	Somnolence
	Uncommon	Confusion
	Uncommon	Hallucinations ¹
	Not known	Psychotic reactions ²
Nervous system disorders	Common	Dizziness
	common	Balance disorder
	Uncommon	Gait abnormal
	Very rare	Seizures
Cardiac disorders	Uncommon	Cardiac failure
Vascular disorders	Common	Hypertension
	Uncommon	Venous thrombosis/thromboembolism
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
Gastrointestinal disorders	Common	Constipation
	Uncommon	Vomiting
	Not known	Pancreatitis ²
Hepatobiliary disorders	Common	Elevated liver function test
	Not known	Hepatitis
General disorders and administration site conditions	Common	Headache
	Uncommon	Fatigue

¹ Hallucinations have mainly been observed in patients with severe Alzheimer's disease.

² Isolated cases reported in post-marketing experience

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 Axura.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Only limited experience with overdose is available from clinical studies and post-marketing experience.

Symptoms: Relative large overdoses (200 mg and 105 mg/day for 3 days, respectively) have been associated with either only symptoms of tiredness, weakness and/or diarrhoea or no symptoms. In the overdose cases below 140 mg or unknown dose the patients revealed symptoms from central nervous system (confusion, drowsiness, somnolence, vertigo, agitation, aggression, hallucination, and gait disturbance) and/or gastrointestinal origin (vomiting and diarrhoea).

In the most extreme case of overdose, the patient survived the oral intake of a total of 2000 mg memantine with effects on the central nervous system (coma for 10 days, and later diplopia and agitation). The patient received symptomatic treatment and plasmapheresis. The patient recovered without permanent sequelae.

In another case of a large overdose, the patient also survived and recovered. The patient had received 400 mg memantine orally. The patient experienced central nervous system symptoms such as restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor, and unconsciousness.

Treatment: In the event of overdose, treatment should be symptomatic. No specific antidote for intoxication or overdose is available. Standard clinical procedures to remove active substance material, e.g. gastric lavage, carbo medicinalis (interruption of potential entero-hepatic recirculation), acidification of urine, forced diuresis should be used as appropriate.

In case of signs and symptoms of general central nervous system (CNS) overstimulation, careful symptomatic clinical treatment should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other 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 modulates the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

Clinical studies:

A pivotal monotherapy study in a population of patients suffering from moderate to severe Alzheimer's disease (mini mental state examination (MMSE) total scores at baseline of 3 - 14)

included a total of 252 outpatients. The study showed beneficial effects of memantine treatment in comparison to placebo at 6 months (observed cases analysis for the clinician's interview based impression of change (CIBIC-plus): $p=0.025$; Alzheimer's disease cooperative study – activities of daily living (ADCS-ADLsev): $p=0.003$; severe impairment battery (SIB): $p=0.002$).

A pivotal monotherapy study of memantine in the treatment of mild to moderate Alzheimer's disease (MMSE total scores at baseline of 10 to 22) included 403 patients. Memantine-treated patients showed a statistically significantly better effect than placebo-treated patients on the primary endpoints: Alzheimer's disease assessment scale (ADAS-cog) ($p=0.003$) and CIBIC-plus ($p=0.004$) at week 24 last observation carried forward (LOCF). In another monotherapy study in mild to moderate Alzheimer's disease a total of 470 patients (MMSE total scores at baseline of 11-23) were randomised. In the prospectively defined primary analysis statistical significance was not reached at the primary efficacy endpoint at week 24.

A meta-analysis of patients with moderate to severe Alzheimer's disease (MMSE total scores < 20) from the six phase III, placebo-controlled, 6-month studies (including monotherapy studies and studies with patients on a stable dose of acetylcholinesterase inhibitors) showed that there was a statistically significant effect in favour of memantine treatment for the cognitive, global, and functional domains. When patients were identified with concurrent worsening in all three domains, results showed a statistically significant effect of memantine in preventing worsening, as twice as many placebo-treated patients as memantine-treated patients showed worsening in all three domains (21% vs. 11%, $p<0.0001$).

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.

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 cerebrospinal fluid (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.

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

Pharmacokinetic/pharmacodynamic relationship: At a dose of memantine of 20 mg per day the 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 active substances 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:

Microcrystalline cellulose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Tablet coating:

Hypromellose
Macrogol 400
Titanium dioxide (E 171)
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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 14, 28, 30, 42, 50, 56, 98, 100, 112 and multipacks containing 840 (20 x 42), 980 (10 x 98) or 1000 (20 x 50) tablets are presented.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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
EU/1/02/218/012
EU/1/02/218/013
EU/1/02/218/014
EU/1/02/218/015
EU/1/02/218/030

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 May 2002
Date of latest renewal: 17 May 2007

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Axura 5mg/pump actuation, oral solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of solution contains 10 mg of memantine hydrochloride equivalent to 8.31 mg memantine.

Each pump actuation delivers 0.5 ml solution which contains 5 mg of memantine hydrochloride which is equivalent to 4.16 mg memantine

Excipients: Each one millilitre of solution contains 100 mg sorbitol (E420) and 0.5 mg potassium, see section 4.4.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

The solution is clear and colourless to light yellowish.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

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 the intake of the medicinal product 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. 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:

Dose titration

The maximum daily dose is 20 mg once daily. In order to reduce the risk of undesirable effects the maintenance dose is achieved by upward titration of 5 mg per week over the first 3 weeks as follows:

Week 1 (day 1-7):

The patient should take 0.5 ml solution (5 mg) equivalent to one pump actuation per day for 7 days.

Week 2 (day 8-14):

The patient should take 1 ml solution (10 mg) equivalent to two pump actuations per day for 7 days.

Week 3 (day 15-21):

The patient should take 1.5 ml solution (15 mg) equivalent to three pump actuations per day for 7 days.

From Week 4 on:

The patient should take 2 ml solution (20 mg) equivalent to four pump actuations once a day.

Maintenance dose

The recommended maintenance dose is 20 mg (2 ml solution, equivalent to four pump actuations) per day.

Older people: On the basis of the clinical studies, the recommended dose for patients over the age of 65 years is 20 mg per day (2 ml solution, equivalent to four pump actuations) as described above.

Renal impairment: In patients with mildly impaired renal function (creatinine clearance 50 - 80 ml/min) no dose adjustment is required. In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) daily dose should be 10 mg (1 ml solution, equivalent to two pump actuations). If tolerated well after at least 7 days of treatment, the dose could be increased up to 20 mg/day according to standard titration scheme. In patients with severe renal impairment (creatinine clearance 5 – 29 ml/min) daily dose should be 10 mg (1 ml solution, equivalent to two pump actuations) per day.

Hepatic impairment: In patients with mild or moderate hepatic impaired function (Child-Pugh A and Child-Pugh B) no dose adjustment is needed. No data on the use of memantine in patients with severe hepatic impairment are available. Administration of Axura in patients with severe hepatic impairment is not recommended.

Children and adolescents: Axura is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Method of administration

Axura should be taken once daily at the same time each day. The solution can be taken with or without food. The solution must not be poured or pumped into the mouth directly from the bottle or the pump, but should be dosed onto a spoon or into a glass of water using the pump. For detailed instructions on the preparation and handling of the product see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

Concomitant use of other 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 reactions (mainly central nervous system (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), or uncontrolled hypertension were excluded. As a consequence, only limited data are available and patients with these conditions should be closely supervised.

Excipients: The oral solution contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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 dose 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 active substances 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.
- In post-marketing experience isolated cases with international normalized 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.

In single-dose pharmacokinetic (PK) studies in young healthy subjects no relevant active substance-active substance interaction of memantine with glyburide/metformin or donepezil was observed.

In a clinical study in young healthy subjects no relevant effect of memantine on the pharmacokinetics of galantamine was observed.

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

4.6 Fertility, 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.

Breast-feeding

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

Fertility

No adverse effects of memantine were noted on non-clinical male and female fertility studies.

4.7 Effects on ability to drive and use machines

Moderate to severe Alzheimer's disease usually causes impairment of driving performance and compromises the ability to use machinery. Furthermore, Axura has minor or moderate influence on the ability to drive and use machines such that outpatients should be warned to take special care.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials in mild to severe dementia, involving 1,784 patients treated with Axura and 1,595 patients treated with placebo, the overall incidence rate of adverse reactions with Axura did not differ from those with placebo; the adverse reactions were usually mild to moderate in severity. The most frequently occurring adverse reactions with a higher incidence in the Axura group than in the placebo group were dizziness (6.3% vs 5.6%, respectively), headache (5.2% vs 3.9%), constipation (4.6% vs 2.6%), somnolence (3.4% vs 2.2%) and hypertension (4.1% vs 2.8%).

The following Adverse Reactions listed in the Table below have been accumulated in clinical studies with Axura and since its introduction in the market. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

Adverse reactions are ranked according to system organ class, using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
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Psychiatric disorders	Common	Somnolence
	Uncommon	Confusion
	Uncommon	Hallucinations ¹
	Not known	Psychotic reactions ²
Nervous system disorders	Common	Dizziness
	Common	Balance disorder
	Uncommon	Gait abnormal
	Very rare	Seizures
Cardiac disorders	Uncommon	Cardiac failure
Vascular disorders	Common	Hypertension
	Uncommon	Venous thrombosis/thromboembolism
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
Gastrointestinal disorders	Common	Constipation
	Uncommon	Vomiting
	Not known	Pancreatitis ²
Hepatobiliary disorders	Common	Elevated liver function test
	Not known	Hepatitis
General disorders and administration site conditions	Common	Headache
	Uncommon	Fatigue

¹ Hallucinations have mainly been observed in patients with severe Alzheimer's disease.

² Isolated cases reported in post-marketing experience

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 Axura.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via **the national reporting system** listed in **Appendix V**

4.9 Overdose

Only limited experience with overdose is available from clinical studies and post-marketing experience.

Symptoms: Relative large overdoses (200 mg and 105 mg/day for 3 days, respectively) have been associated with either only symptoms of tiredness, weakness and/or diarrhoea or no symptoms. In the overdose cases below 140 mg or unknown dose the patients revealed symptoms from central nervous system (confusion, drowsiness, somnolence, vertigo, agitation, aggression, hallucination and gait disturbance) and/or gastrointestinal origin (vomiting and diarrhoea).

In the most extreme case of overdose, the patient survived the oral intake of a total of 2000 mg memantine with effects on the central nervous system (coma for 10 days, and later diplopia and agitation). The patient received symptomatic treatment and plasmapheresis. The patient recovered without permanent sequelae.

In another case of a large overdose, the patient also survived and recovered. The patient had received 400 mg memantine orally. The patient experienced central nervous system symptoms such as restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor, and unconsciousness.

Treatment: In the event of overdose, treatment should be symptomatic. No specific antidote for intoxication or overdose is available. Standard clinical procedures to remove active substance material, e.g. gastric lavage, carbo medicinalis (interruption of potential entero-hepatic recirculation), acidification of urine, forced diuresis should be used as appropriate.

In case of signs and symptoms of general central nervous system (CNS) overstimulation, careful symptomatic clinical treatment should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other 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 modulates the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

Clinical studies:

A pivotal monotherapy study in a population of patients suffering from moderate to severe Alzheimer's disease (mini mental state examination (MMSE) total scores at baseline of 3 - 14) included a total of 252 outpatients. The study showed beneficial effects of memantine treatment in comparison to placebo at 6 months (observed cases analysis for the clinician's interview based impression of change (CIBIC-plus): $p=0.025$; Alzheimer's disease cooperative study – activities of daily living (ADCS-ADLsev): $p=0.003$; severe impairment battery (SIB): $p=0.002$).

A pivotal monotherapy study of memantine in the treatment of mild to moderate Alzheimer's disease (MMSE total scores at baseline of 10 to 22) included 403 patients. Memantine-treated patients showed a statistically significantly better effect than placebo-treated patients on the primary endpoints: Alzheimer's disease assessment scale (ADAS-cog) ($p=0.003$) and CIBIC-plus ($p=0.004$) at week 24 last observation carried forward (LOCF). In another monotherapy study in mild to moderate Alzheimer's disease a total of 470 patients (MMSE total scores at baseline of 11-23) were randomised.

In the prospectively defined primary analysis statistical significance was not reached at the primary efficacy endpoint at week 24.

A meta-analysis of patients with moderate to severe Alzheimer's disease (MMSE total scores < 20) from the six phase III, placebo-controlled, 6-month studies (including monotherapy studies and studies with patients on a stable dose of acetylcholinesterase inhibitors) showed that there was a statistically significant effect in favour of memantine treatment for the cognitive, global, and functional domains. When patients were identified with concurrent worsening in all three domains, results showed a statistically significant effect of memantine in preventing worsening, as twice as many placebo-treated patients as memantine-treated patients showed worsening in all three domains (21% vs. 11%, $p < 0.0001$).

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.

Distribution: Daily doses of 20 mg lead to steady-state plasma concentrations of memantine ranging from 70 to 150 ng/ml (0.5 - 1 μ mol) with large interindividual variations. When daily doses of 5 to 30 mg were administered, a mean cerebrospinal fluid (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 m² and part of total renal clearance is achieved by tubular secretion.

Renal handling also involves tubular reabsorption, probably mediated by cation transport proteins. The renal elimination rate of memantine under alkaline urine conditions may be reduced by a factor of 7 to 9 (see 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.

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

Pharmacokinetic/pharmacodynamic relationship: At a dose of memantine of 20 mg per day the CSF levels match the k_i -value (k_i = inhibition constant) of memantine, which is 0.5 μ mol 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 active substances 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

Potassium sorbate
Sorbitol E420
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

The bottle with the mounted pump may only be kept and transported in a vertical position.

6.5 Nature and contents of container

Brown glass bottles (Hydrolytic Class III) containing either 50, 100 ml or 500ml (10 x 50 ml) solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Prior to first use the dosing pump has to be screwed on the bottle. For removing the screw cap from the bottle the cap must be turned anticlockwise and unscrewed completely (fig.1).

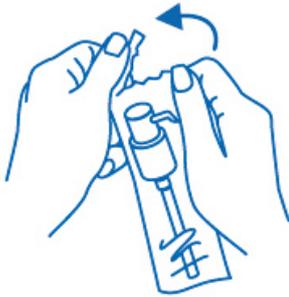
1.



Mounting the dosing pump on the bottle:

The dosing pump has to be removed from the plastic bag (fig. 2) and placed on top of the bottle, sliding the plastic dip tube carefully into the bottle. Then the dosing pump needs to be hold onto the neck of the bottle and screwed clockwise until it is firmly attached (fig 3). For the intended use the dosing pump is only screwed on once when starting the use, and should never be unscrewed.

2.



3.



Use of the dosing pump for dispensing:

The dosing pump head has two positions and is easy to turn – anticlockwise (unlocked position) and clockwise (locked position). The dosing pump head should not be pushed down while in the locked position. The solution may only be dispensed in the unlocked position. To do this, the dosing pump head has to be turned in the direction of the arrow about one eighth of a turn, until a resistance is felt (fig. 4)

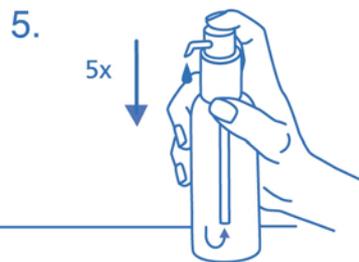
4.



The dosing pump is then ready for use.

Preparing the dosing pump:

When used for the first time, the dosing pump does not dispense the correct amount of oral solution. Therefore, the pump must be prepared (primed) by pushing the dosing pump head down completely five times in succession (fig. 5).



The solution thus dispensed is discarded. The next time the dosing pump head is pushed downwards completely (equivalent to one pump actuation), it dispenses the correct dose (1 pump actuation is equivalent to 0.5 ml oral solution, and contains 5 mg of the active substance memantine hydrochloride; fig. 6).

6.



Correct use of the dosing pump:

The bottle should be placed on a flat, horizontal surface, for example a table top, and only use it in a vertical position.. A glass with a little water or a spoon should be held below the nozzle and the dosing pump head has to be pushed down in a firm but calm and steady manner (not too slowly) right down to the stop (fig. 7, fig. 8).

7.



8.



The dosing pump head can then be released and is ready for the next pump actuation.

The dosing pump may only be used with the memantine hydrochloride solution in the bottle provided, not for other substances or containers. If the pump does not function as described during intended use and according to instruction, the patient should consult the treating physician or a pharmacist. The dosing pump should be locked after use.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 May 2002
Date of latest renewal: 17 May 2007

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Axura 5 mg film-coated tablets.
Axura 10 mg film-coated tablets
Axura 15 mg film-coated tablets.
Axura 20 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg of memantine hydrochloride equivalent to 4.15 mg memantine.
Each film-coated tablet contains 10 mg of memantine hydrochloride equivalent to 8.31 mg memantine.
Each film-coated tablet contains 15 mg of memantine hydrochloride equivalent to 12.46 mg memantine.
Each film-coated tablet contains 20 mg of memantine hydrochloride equivalent to 16.62 mg memantine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

The 5 mg film-coated tablets are white to off-white, oval-oblong film-coated tablets with imprint '5' on one side and imprint 'MEM' on the other side.

The 10 mg film-coated tablets are pale yellow to yellow, oval shaped film-coated tablet with breaking line and engravings "1-0" on one side and "M M" on the other side The tablet can be divided into equal halves.

The 15 mg film-coated tablets are orange to grey-orange, oval-oblong film-coated tablets with imprint '15' on one side and imprint 'MEM' on the other side.

The 20 mg film-coated tablets are pale red to grey-red, oval-oblong film-coated tablets with imprint '20' on one side and imprint 'MEM' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

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 the intake of the medicinal product 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. 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:

Dose titration

The recommended starting dose is 5 mg per day which is stepwise increased over the first 4 weeks of treatment reaching the recommended maintenance dose as follows:

Week 1 (day 1-7):

The patient should take one 5 mg film-coated tablet per day (white to off-white, oval-oblong) for 7 days.

Week 2 (day 8-14):

The patient should take one 10 mg film-coated tablet per day (pale yellow to yellow, oval shaped) for 7 days.

Week 3 (day 15-21):

The patient should take one 15 mg film-coated tablet per day (greyorange, oval-oblong) for 7 days.

Week 4 (day 22-28):

The patient should take one 20 mg film-coated tablet per day (grey-red, oval-oblong) for 7 days.

Maintenance dose

The recommended maintenance dose is 20 mg per day.

Older people: On the basis of the clinical studies, the recommended dose for patients over the age of 65 years is 20 mg per day (20 mg once a day) as described above.

Renal impairment: In patients with mildly impaired renal function (creatinine clearance 50 – 80 ml/min) no dose adjustment is required. In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) daily dose should be 10 mg per day. If tolerated well after at least 7 days of treatment, the dose could be increased up to 20 mg/day according to standard titration scheme. In patients with severe renal impairment (creatinine clearance 5 – 29 ml/min) daily dose should be 10 mg per day.

Hepatic impairment: In patients with mild or moderate hepatic impaired function (Child-Pugh A and Child-Pugh B) no dose adjustment is needed. No data on the use of memantine in patients with severe hepatic impairment are available. Administration of Axura in patients with severe hepatic impairment is not recommended.

Children and adolescents: Axura is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Method of administration

Axura should be administered once a day and should be taken at the same time every day. The film-coated tablets can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 reactions (mainly central nervous system (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), or 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 dose 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 active substances 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.
- In post-marketing experience isolated cases with international normalized 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.

In single-dose pharmacokinetic (PK) studies in young healthy subjects no relevant active substance-active substance interaction of memantine with glyburide/metformin or donepezil was observed.

In a clinical study in young healthy subjects no relevant effect of memantine on the pharmacokinetics of galantamine was observed.

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

4.6 Fertility, 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.

Breast-feeding

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

Fertility

No adverse effects of memantine were noted on non-clinical male and female fertility studies.

4.7 Effects on ability to drive and use machines

Moderate to severe Alzheimer's disease usually causes impairment of driving performance and compromises the ability to use machinery. Furthermore, Axura has minor or moderate influence on the ability to drive and use machines such that outpatients should be warned to take special care.

4.8 Undesirable effects

Summary of safety profile

In clinical trials in mild to severe dementia, involving 1,784 patients treated with Axura and 1,595 patients treated with placebo, the overall incidence rate of adverse reactions with Axura did not differ from those with placebo; the adverse reactions were usually mild to moderate in severity. The most frequently occurring adverse reactions with a higher incidence in the Axura group than in the placebo group were dizziness (6.3% vs 5.6%, respectively), headache (5.2% vs 3.9%), constipation (4.6% vs 2.6%), somnolence (3.4% vs 2.2%) and hypertension (4.1% vs 2.8%).

The following Adverse Reactions listed in the Table below have been accumulated in clinical studies with Axura and since its introduction in the market. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

Adverse reactions are ranked according to system organ class, using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Infections and infestations	Uncommon	Fungal infections
Immune system disorders	Common	Drug hypersensitivity
Psychiatric disorders	Common	Somnolence
	Uncommon	Confusion
	Uncommon	Hallucinations ¹
	Not known	Psychotic reactions ²
Nervous system disorders	Common	Dizziness
	common	Balance disorder
	Uncommon	Gait abnormal
	Very rare	Seizures
Cardiac disorders	Uncommon	Cardiac failure
Vascular disorders	Common	Hypertension
	Uncommon	Venous thrombosis/thromboembolism
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
Gastrointestinal disorders	Common	Constipation
	Uncommon	Vomiting
	Not known	Pancreatitis ²
Hepatobiliary disorders	Common	Elevated liver function test
	Not known	Hepatitis
General disorders and administration site conditions	Common	Headache
	Uncommon	Fatigue

¹ Hallucinations have mainly been observed in patients with severe Alzheimer's disease.

² Isolated cases reported in post-marketing experience

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 Axura.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via **the national reporting system** listed in **Appendix V**

4.9 Overdose

Only limited experience with overdose is available from clinical studies and post-marketing experience.

Symptoms: Relative large overdoses (200 mg and 105 mg/day for 3 days, respectively) have been associated with either only symptoms of tiredness, weakness and/or diarrhoea or no symptoms. In the overdose cases below 140 mg or unknown dose the patients revealed symptoms from central nervous system (confusion, drowsiness, somnolence, vertigo, agitation, aggression, hallucination, and gait disturbance) and/or gastrointestinal origin (vomiting and diarrhoea).

In the most extreme case of overdose, the patient survived the oral intake of a total of 2000 mg memantine with effects on the central nervous system (coma for 10 days, and later diplopia and agitation). The patient received symptomatic treatment and plasmapheresis. The patient recovered without permanent sequelae.

In another case of a large overdose, the patient also survived and recovered. The patient had received 400 mg memantine orally. The patient experienced central nervous system symptoms such as restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor, and unconsciousness.

Treatment: In the event of overdose, treatment should be symptomatic. No specific antidote for intoxication or overdose is available. Standard clinical procedures to remove active substance material, e.g. gastric lavage, carbo medicinalis (interruption of potential entero-hepatic recirculation), acidification of urine, forced diuresis should be used as appropriate.

In case of signs and symptoms of general Central Nervous System (CNS) overstimulation, careful symptomatic clinical treatment should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other 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 modulates the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

Clinical studies:

A pivotal monotherapy study in a population of patients suffering from moderate to severe Alzheimer's disease (mini mental state examination (MMSE) total scores at baseline of 3 - 14) included a total of 252 outpatients. The study showed beneficial effects of memantine treatment in comparison to placebo at 6 months (observed cases analysis for the clinician's interview based impression of change (CIBIC-plus): $p=0.025$; Alzheimer's disease cooperative study- activities of daily living (ADCS-ADLsev): $p=0.003$; severe impairment battery (SIB): $p=0.002$).

A pivotal monotherapy study of memantine in the treatment of mild to moderate Alzheimer's disease (MMSE total scores at baseline of 10 to 22) included 403 patients. Memantine-treated patients showed a statistically significantly better effect than placebo-treated patients on the primary endpoints: Alzheimer's disease assessment scale (ADAS-cog) ($p=0.003$) and CIBIC-plus ($p=0.004$) at week 24 last observation carried forward (LOCF). In another monotherapy study in mild to moderate Alzheimer's disease a total of 470 patients (MMSE total scores at baseline of 11-23) were randomised.

In the prospectively defined primary analysis statistical significance was not reached at the primary efficacy endpoint at week 24.

A meta-analysis of patients with moderate to severe Alzheimer's disease (MMSE total scores < 20) from the six phase III, placebo-controlled, 6-month studies (including monotherapy studies and studies with patients on a stable dose of acetylcholinesterase inhibitors) showed that there was a statistically significant effect in favour of memantine treatment for the cognitive, global, and functional domains. When patients were identified with concurrent worsening in all three domains, results showed a statistically significant effect of memantine in preventing worsening, as twice as many placebo-treated patients as memantine-treated patients showed worsening in all three domains (21% vs. 11%, $p < 0.0001$).

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.

Distribution: Daily doses of 20 mg lead to steady-state plasma concentrations of memantine ranging from 70 to 150 ng/ml (0.5 - 1 μ mol) with large interindividual variations. When daily doses of 5 to 30 mg were administered, a mean cerebrospinal fluid (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 m² and part of total renal clearance is achieved by tubular secretion.

Renal handling also involves tubular reabsorption, probably mediated by cation transport proteins. The renal elimination rate of memantine under alkaline urine conditions may be reduced by a factor of 7 to 9 (see 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.

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

Pharmacokinetic/pharmacodynamic relationship: At a dose of memantine of 20 mg per day the CSF levels match the k_i -value (k_i = inhibition constant) of memantine, which is 0.5 μ mol 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 active substances 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 cores for 5/10/15/20 mg film-coated tablets:

Microcrystalline cellulose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Tablet coating for 5/10/15/20 mg film-coated tablets:

Hypromellose
Macrogol 400
Titanium dioxide (E 171)

Additional for 10 mg film-coated tablets:

Iron oxide yellow (E 172)

Additional for 15 mg and 20 mg film-coated tablets:

Iron oxide yellow and red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Each pack contains 28 film-coated tablets in 4 PVDC/PE/PVC/Al-blister or PP/Al-blisters with 7 film-coated tablets of 5 mg, 7 film-coated tablets of 10 mg, 7 film-coated tablets of 15 mg and 7 film-coated tablets of 20 mg.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/016
EU/1/02/218/023

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 May 2002
Date of latest renewal: 17 May 2007

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Axura 20 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg of memantine hydrochloride equivalent to 16.62 mg memantine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pale red to grey-red, oval-oblong film-coated tablets with imprint “20” on one side and imprint “MEM” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with moderate to severe Alzheimer’s disease.

4.2 Posology and method of administration

Posology

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 the intake of the medicinal product 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. 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:

Dose titration

The maximum daily dose is 20 mg per day. In order to reduce the risk of undesirable effects the maintenance dose is achieved by upward titration of 5 mg per week over the first 3 weeks as follows. For up-titration other tablet strengths are available.

Week 1 (day 1-7):

The patient should take one 5 mg film-coated tablet per day for 7 days.

Week 2 (day 8-14):

The patient should take one 10 mg film-coated tablet per day for 7 days.

Week 3 (day 15-21):

The patient should take one 15 mg film-coated tablet per day for 7 days.

From Week 4 on:

The patient should take one 20 mg film-coated tablet per day.

Maintenance dose

The recommended maintenance dose is 20 mg per day.

Older people: On the basis of the clinical studies, the recommended dose for patients over the age of 65 years is 20 mg per day as described above.

Renal impairment: In patients with mildly impaired renal function (creatinine clearance 50 – 80 ml/min) no dose adjustment is required. In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) daily dose should be 10 mg per day. If tolerated well after at least 7 days of treatment, the dose could be increased up to 20 mg/day according to standard titration scheme. In patients with severe renal impairment (creatinine clearance 5 – 29 ml/min) daily dose should be 10 mg per day.

Hepatic impairment: In patients with mild or moderate hepatic impaired function (Child-Pugh A and Child-Pugh B) no dose adjustment is needed. No data on the use of memantine in patients with severe hepatic impairment are available. Administration of Axura in patients with severe hepatic impairment is not recommended.

Children and adolescents: Axura is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Method of administration

Axura should be administered once a day and should be taken at the same time every day. The film-coated tablets can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 reactions (mainly central nervous system (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), or 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 dose 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 active substances 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.
- In post-marketing experience isolated cases with international normalized 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.

In single-dose pharmacokinetic (PK) studies in young healthy subjects no relevant active substance-active substance interaction of memantine with glyburide/metformin or donepezil was observed.

In a clinical study in young healthy subjects no relevant effect of memantine on the pharmacokinetics of galantamine was observed.

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

4.6 Fertility, 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.

Breast-feeding

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

Fertility

No adverse effects of memantine were noted on non-clinical male and female fertility studies.

4.7 Effects on ability to drive and use machines

Moderate to severe Alzheimer's disease usually causes impairment of driving performance and compromises the ability to use machinery. Furthermore, Axura has minor or moderate influence on the ability to drive and use machines such that outpatients should be warned to take special care.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials in mild to severe dementia, involving 1,784 patients treated with Axura and 1,595 patients treated with placebo, the overall incidence rate of adverse reactions with Axura did not differ from those with placebo; the adverse reactions were usually mild to moderate in severity. The most frequently occurring adverse reactions with a higher incidence in the Axura group than in the placebo

group were dizziness (6.3% vs 5.6%, respectively), headache (5.2% vs 3.9%), constipation (4.6% vs 2.6%), somnolence (3.4% vs 2.2%) and hypertension (4.1% vs 2.8%).

The following Adverse Reactions listed in the Table below have been accumulated in clinical studies with Axura and since its introduction in the market. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

Adverse reactions are ranked according to system organ class, using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Infections and infestations	Uncommon	Fungal infections
Immune system disorders	Common	Drug hypersensitivity
Psychiatric disorders	Common	Somnolence
	Uncommon	Confusion
	Uncommon	Hallucinations ¹
	Not known	Psychotic reactions ²
Nervous system disorders	Common	Dizziness
	Common	Balance disorder
	Uncommon	Gait abnormal
	Very rare	Seizures
Cardiac disorders	Uncommon	Cardiac failure
Vascular disorders	Common	Hypertension
	Uncommon	Venous thrombosis/thromboembolism
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
Gastrointestinal disorders	Common	Constipation
	Uncommon	Vomiting
	Not known	Pancreatitis ²
Hepatobiliary disorders	Common	Elevated liver function test
	Not known	Hepatitis
General disorders and administration site conditions	Common	Headache
	Uncommon	Fatigue

¹ Hallucinations have mainly been observed in patients with severe Alzheimer's disease.

² Isolated cases reported in post-marketing experience

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 Axura.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V

4.9 Overdose

Only limited experience with overdose is available from clinical studies and post-marketing experience.

Symptoms: Relative large overdoses (200 mg and 105 mg/day for 3 days, respectively) have been associated with either only symptoms of tiredness, weakness and/or diarrhoea or no symptoms. In the overdose cases below 140 mg or unknown dose the patients revealed symptoms from central nervous system (confusion, drowsiness, somnolence, vertigo, agitation, aggression, hallucination, and gait disturbance) and/or gastrointestinal origin (vomiting and diarrhoea).

In the most extreme case of overdose, the patient survived the oral intake of a total of 2000 mg memantine with effects on the central nervous system (coma for 10 days, and later diplopia and agitation). The patient received symptomatic treatment and plasmapheresis. The patient recovered without permanent sequelae.

In another case of a large overdose, the patient also survived and recovered. The patient had received 400 mg memantine orally. The patient experienced central nervous system symptoms such as restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor, and unconsciousness.

Treatment: In the event of overdose, treatment should be symptomatic. No specific antidote for intoxication or overdose is available. Standard clinical procedures to remove active substance material, e.g. gastric lavage, carbo medicinalis (interruption of potential entero-hepatic recirculation), acidification of urine, forced diuresis should be used as appropriate.

In case of signs and symptoms of general central nervous system (CNS) overstimulation, careful symptomatic clinical treatment should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other 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 modulates the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

Clinical studies:

A pivotal monotherapy study in a population of patients suffering from moderate to severe Alzheimer's disease (mini mental state examination (MMSE) total scores at baseline of 3 - 14) included a total of 252 outpatients. The study showed beneficial effects of memantine treatment in

comparison to placebo at 6 months (observed cases analysis for the clinician's interview based impression of change (CIBIC-plus): $p=0.025$; Alzheimer's disease cooperative study – activities of daily living (ADCS-ADLsev): $p=0.003$; severe impairment battery (SIB): $p=0.002$).

A pivotal monotherapy study of memantine in the treatment of mild to moderate Alzheimer's disease (MMSE total scores at baseline of 10 to 22) included 403 patients. Memantine-treated patients showed a statistically significantly better effect than placebo-treated patients on the primary endpoints: Alzheimer's disease assessment scale (ADAS-cog) ($p=0.003$) -and CIBIC-plus ($p=0.004$) at week 24 last observation carried forward (LOCF). In another monotherapy study in mild to moderate Alzheimer's disease a total of 470 patients (MMSE total scores at baseline of 11-23) were randomised. In the prospectively defined primary analysis statistical significance was not reached at the primary efficacy endpoint at week 24.

A meta-analysis of patients with moderate to severe Alzheimer's disease (MMSE total scores < 20) from the six phase III, placebo-controlled, 6-month studies (including monotherapy studies and studies with patients on a stable dose of acetylcholinesterase inhibitors) showed that there was a statistically significant effect in favour of memantine treatment for the cognitive, global, and functional domains. When patients were identified with concurrent worsening in all three domains, results showed a statistically significant effect of memantine in preventing worsening, as twice as many placebo-treated patients as memantine-treated patients showed worsening in all three domains (21% vs. 11%, $p<0.0001$).

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.

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 cerebrospinal fluid (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.

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

Pharmacokinetic/pharmacodynamic relationship: At a dose of memantine of 20 mg per day the (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 active substances 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:

Microcrystalline cellulose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Tablet coating:

Hypromellose
Macrogol 400
Titanium dioxide (E 171)
Iron oxide yellow and red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister packs containing 14 film-coated tablets per PVDC/PE/PVC/Al-blister or PP/Al-blister strip. Pack sizes of 14, 28, 42, 56, 98 or multipacks containing 840 (20 x 42) film-coated tablets are presented.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/017
EU/1/02/218/018
EU/1/02/218/019
EU/1/02/218/020
EU/1/02/218/021
EU/1/02/218/022
EU/1/02/218/024
EU/1/02/218/025
EU/1/02/218/026
EU/1/02/218/027
EU/1/02/218/028
EU/1/02/218/029

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 May 2002
Date of latest renewal: 17 May 2007

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Merz Pharma GmbH & Co. KGaA
Eckenheimer Landstr. 100
D-60318 Frankfurt/Main
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Periodic Safety Update Report

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON FOR BLISTER PACK**

1. NAME OF THE MEDICINAL PRODUCT

Axura 10 mg film-coated tablets
Memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg memantine hydrochloride equivalent to 8.31 mg memantine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets.
14 film-coated tablets.
28 film-coated tablets.
30 film-coated tablets.
42 film-coated tablets.
50 film-coated tablets.
56 film-coated tablets.
98 film-coated tablets.
100 film-coated tablets.
112 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/012 14 film-coated tablets.
EU/1/02/218/007 28 film-coated tablets.
EU/1/02/218/001 30 film-coated tablets.
EU/1/02/218/013 42 film-coated tablets.
EU/1/02/218/002 50 film-coated tablets.
EU/1/02/218/008 56 film-coated tablets.
EU/1/02/218/014 98 film-coated tablets.
EU/1/02/218/003 100 film-coated tablets.
EU/1/02/218/009 112 film-coated tablets.

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Axura 10 mg tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 42, 50 AND 98 TABLETS AS INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Axura 10 mg film-coated tablets
Memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg memantine hydrochloride equivalent to 8.31 mg memantine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets. 42 film-coated tablets.

Component of a multipack comprising 20 packs, each containing 42 film-coated tablets. Not for separate sale.

Film-coated tablets. 50 film-coated tablets.

Component of a multipack comprising 20 packs, each containing 50 film-coated tablets. Not for separate sale.

Film-coated tablets. 98 film-coated tablets.

Component of a multipack comprising 10 packs, each containing 98 film-coated tablets. Not for separate sale.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/010 1000 film-coated tablets (20 packs of 50)
EU/1/02/218/015 980 film-coated tablets (10 packs of 98)
EU/1/02/218/030 840 film-coated tablets (20 packs of 42)

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Axura 10 mg tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**OUTER WRAPPER LABEL ON MULTIPACKS (20 x 42 TABLETS, 20 x 50 TABLETS AND 10 x 98 TABLETS)
WRAPPED IN FOIL (INCLUDING BLUE BOX)**

1. NAME OF THE MEDICINAL PRODUCT

Axura 10 mg film-coated tablets
Memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg memantine hydrochloride equivalent to 8.31 mg memantine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack comprising
20 packs, each containing 42 film-coated tablets.
20 packs, each containing 50 film-coated tablets.
10 packs, each containing 98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/010 1000 (20 packs of 50 film-coated tablets)
EU/1/02/218/015 980 (10 packs of 98 film-coated tablets)
EU/1/02/218/030 840 (20 packs of 42 film-coated tablets)

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Axura 10 mg film-coated tablets
Memantine hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Merz Pharmaceuticals GmbH

3. EXPIRY DATE

EXP {MM/YYYY}
See embossed stamp.

4. BATCH NUMBER

Lot {number}
See embossed stamp.

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Axura 5 mg/pump actuation, oral solution
Memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pump actuation delivers 0.5 ml solution which contains 5 mg of memantine hydrochloride which is equivalent to 4.16 mg memantine

3. LIST OF EXCIPIENTS

The solution also contains potassium sorbate and sorbitol (E420).
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution.
50 ml.
100 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.
Once daily.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

When opened, use within 3 months.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/005 50 ml.
EU/1/02/218/006 100 ml

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Axura 5 mg/pump actuation, oral solution

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR 50 ml BOTTLE AS INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Axura 5 mg/pump actuation, oral solution
memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pump actuation delivers 0.5 ml solution which contains 5 mg of memantine hydrochloride which is equivalent to 4.16 mg memantine

3. LIST OF EXCIPIENTS

The solution also contains potassium sorbate and sorbitol (E420).
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution. 50 ml.
Component of a multipack comprising 10 packs, each containing 1 bottle with 50 ml oral solution. Not for separate sale.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

Once daily.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
When opened, use within 3 months.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/011 500ml (10 bottles of 50ml)

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Axura 5 mg/pump actuation, oral solution

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**OUTER WRAPPER LABEL ON MULTIPACKS (10x 50 ml) WRAPPED IN FOIL
(INCLUDING BLUE BOX)**

1. NAME OF THE MEDICINAL PRODUCT

Axura 5 mg/pump actuation, oral solution
memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pump actuation delivers 0.5 ml solution which contains 5 mg of memantine hydrochloride which is equivalent to 4.16 mg memantine

3. LIST OF EXCIPIENTS

The solution also contains potassium sorbate and sorbitol (E420).
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution
Multipack 500ml, comprising 10 packs, each containing 1 bottle with 50 ml) oral solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

Once daily.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
When opened, use within 3 months.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/011 500ml (10 bottles of 50ml)

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 28 TABLETS - TREATMENT INITIATION PACK – 4 WEEK TREATMENT SCHEDULE

1. NAME OF THE MEDICINAL PRODUCT

Axura 5 mg film-coated tablets.
Axura 10 mg film-coated tablets.
Axura 15 mg film-coated tablets.
Axura 20 mg film-coated tablets.
Memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 5 mg of memantine hydrochloride equivalent to 4.15 mg memantine.
Each film-coated tablet contains 10 mg of memantine hydrochloride equivalent to 8.31 mg memantine.
Each film-coated tablet contains 15 mg of memantine hydrochloride equivalent to 12.46 mg memantine.
Each film-coated tablet contains 20 mg of memantine hydrochloride equivalent to 16.62 mg memantine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Each pack of 28 film-coated tablets for a 4 week treatment schedule contains:
7 x Axura 5 mg
7 x Axura 10 mg
7 x Axura 15 mg
7 x Axura 20 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

Once daily

For continuation of your treatment please consult your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/016 28 film-coated tablets
EU/1/02/218/023 28 film-coated tablets

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Axura 5 mg, 10 mg, 15 mg, 20 mg tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON FOR BLISTER PACK; front and backside

1. NAME OF THE MEDICINAL PRODUCT

Axura 5mg,
Axura 10 mg
Axura 15 mg
Axura 20 mg

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Memantine hydrochloride

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets. Axura 5 mg
7 film-coated tablets. Axura 10 mg
7 film-coated tablets. Axura 15 mg
7 film-coated tablets. Axura 20 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

One tablet daily

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Week 1, 2, 3, 4

Day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28,

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON FOR BLISTER PACK; frontside

1. NAME OF THE MEDICINAL PRODUCT

Axura 5mg,
Axura 10 mg
Axura 15 mg
Axura 20 mg
film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Memantine hydrochloride

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Each pack of 28 film- coated tablets for a 4 week treatment schedule contains:

7 x Axura 5 mg
7 x Axura 10 mg
7 x Axura 15 mg
7 x Axura 20 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Once daily

For continuation of your treatment please consult your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/016 28 film-coated tablets

EU/1/02/218/023 28 film-coated tablets

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Axura 5mg, 10mg, 15mg, 20 mg film-coated tablets
Memantine hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Merz Pharmaceuticals GmbH

3. EXPIRY DATE

EXP {MM/YYYY}
See embossed stamp.

4. BATCH NUMBER

Lot {number}
See embossed stamp.

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Axura 20 mg film-coated tablets
Memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg memantine hydrochloride equivalent to 16.62 mg memantine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets.
14 film-coated tablets.
28 film-coated tablets.
42 film-coated tablets.
56 film-coated tablets.
98 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

Once daily

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/017 14 film-coated tablets
EU/1/02/218/018 28 film-coated tablets
EU/1/02/218/019 42 film-coated tablets
EU/1/02/218/020 56 film-coated tablets
EU/1/02/218/021 98 film-coated tablets
EU/1/02/218/024 14 film-coated tablets
EU/1/02/218/025 28 film-coated tablets
EU/1/02/218/026 42 film-coated tablets
EU/1/02/218/027 56 film-coated tablets
EU/1/02/218/028 98 film-coated tablets

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Axura 20 mg tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 42 TABLETS AS INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Axura 20 mg film-coated tablets
Memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg memantine hydrochloride equivalent to 16.62 mg memantine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets. 42 film-coated tablets.
Component of a multipack comprising 20 packs, each containing 42 film-coated tablets. Not for separate sale.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

Once daily

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/022 840 film-coated tablets (20 packs of 42)
EU/1/02/218/029 840 film-coated tablets (20 packs of 42)

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Axura 20 mg tablets

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER WRAPPER LABEL ON MULTIPACKS (20x 42 TABLETS) WRAPPED IN FOIL
(INCLUDING BLUE BOX)**

1. NAME OF THE MEDICINAL PRODUCT

Axura 20 mg film-coated tablets
Memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg memantine hydrochloride equivalent to 16.62 mg memantine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack 840 film-coated tablets, comprising 20 packs, each containing 42 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

Once daily

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS
OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF
APPROPRIATE**

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/022 840 film-coated tablets (20 packs of 42)
EU/1/02/218/029 840 film-coated tablets (20 packs of 42)

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Axura 20 mg film-coated tablets
Memantine hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Merz Pharmaceuticals GmbH

3. EXPIRY DATE

EXP {MM/YYYY}
See embossed stamp.

4. BATCH NUMBER

Lot {number}
See embossed stamp.

5. OTHER

Mon → Tue → Wed → Thu → Fri → Sat → Sun

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Axura 10 mg film-coated tablets Memantine hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
-

What is in this leaflet:

1. What Axura is and what it is used for
2. What you need to know before you take Axura
3. How to take Axura
4. Possible side effects
5. How to store Axura
6. Content of the pack and other information

1. What Axura is and what it is used for

How does Axura work

Axura contains the active substance memantine hydrochloride.

Axura belongs to a group of medicines known as anti-dementia medicines.

Memory loss in Alzheimer's disease is due to a disturbance of message signals in the brain. The brain contains so-called N-methyl-D-aspartate (NMDA)-receptors that are involved in transmitting nerve signals important in learning and memory. Axura belongs to a group of medicines called NMDA-receptor antagonists. Axura acts on these NMDA-receptors improving the transmission of nerve signals and the memory.

What is Axura used for

Axura is used for the treatment of patients with moderate to severe Alzheimer's disease.

2. What you need to know before you take Axura

Do not take Axura

- if you are allergic (hypersensitive) to memantine hydrochloride or any of the other ingredients of Axura tablets (listed in section 6).

Warning and precautions

Talk to your doctor or pharmacist before taking Axura

- if you have a history of epileptic seizures
- if you have recently experienced a myocardial infarction (heart attack), or if you are suffering from congestive heart failure or from an uncontrolled hypertension (high blood pressure).

In these situations the treatment should be carefully supervised, and the clinical benefit of Axura reassessed by your doctor on a regular basis.

If you suffer from renal impairment (kidney problems), your doctor should closely monitor your kidney function and if necessary adapt the memantine doses accordingly.

The use of medicinal products called amantadine (for the treatment of Parkinson's disease), ketamine (a substance generally used as an anaesthetic), dextromethorphan (generally used to treat cough) and other NMDA-antagonists at the same time should be avoided.

Axura is not recommended for children and adolescents under the age of 18 years.

Other medicines and Axura

Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, Axura may change the effects of the following medicines and their dose may need to be adjusted by your doctor:

amantadine, ketamine, dextromethorphan
dantrolene, baclofen
cimetidine, ranitidine, procainamide, quinidine, quinine, nicotine
hydrochlorothiazide (or any combination with hydrochlorothiazide)
anticholinergics (substances generally used to treat movement disorders or intestinal cramps)
anticonvulsants (substances used to prevent and relieve seizures)
barbiturates (substances generally used to induce sleep)
dopaminergic agonists (substances such as L-dopa, bromocriptine)
neuroleptics (substances used in the treatment of mental disorders)
oral anticoagulants

If you go into hospital, let your doctor know that you are taking Axura.

Axura with food and drink

You should inform your doctor if you have recently changed or intend to change your diet substantially (e.g. from normal diet to strict vegetarian diet) or if you are suffering from states of renal tubular acidosis (RTA, an excess of acid-forming substances in the blood due to renal dysfunction (poor kidney function)) or severe infections of the urinary tract (structure that carries urine), as your doctor may need to adjust the dose of your medicine.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy: The use of memantine in pregnant women is not recommended.

Breast-Feeding: Women taking Axura should not breast-feed.

Driving and using machines

Your doctor will tell you whether your illness allows you to drive and to use machines safely. Also, Axura may change your reactivity, making driving or operating machinery inappropriate.

3. How to take Axura

Always take Axura exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dosage

The recommended dose of Axura for adults and older people is 20 mg once a day. In order to reduce the risk of side effects this dose is achieved gradually by the following daily treatment scheme:

week 1	half a 10 mg tablet
week 2	one 10 mg tablet
week 3	one and a half 10 mg tablet
week 4 and beyond	two 10 mg tablets once a day

The usual starting dose is half a tablet once a day (1x 5 mg) for the first week. This is increased to one tablet once a day (1x 10 mg) in the second week and to 1 and a half tablet once a day in the third week. From the fourth week on, the usual dose is 2 tablets once a day (1x 20 mg).

Dosage in patients with impaired kidney function

If you have impaired kidney function, your doctor will decide upon a dose that suits your condition. In this case, monitoring of your kidney function should be performed by your doctor at specified intervals.

Administration

Axura should be administered orally once a day. To benefit from your medicine you should take it regularly every day at the same time of the day. The tablets should be swallowed with some water. The tablets can be taken with or without food.

Duration of treatment

Continue to take Axura as long as it is of benefit to you. Your doctor should assess your treatment on a regular basis.

If you take more Axura than you should

- In general, taking too much Axura should not result in any harm to you. You may experience increased symptoms as described in section 4. „Possible side effects“.
- If you take a large overdose of Axura, contact your doctor or get medical advice, as you may need medical attention.

If you forget to take Axura

- If you find you have forgotten to take your dose of Axura, wait and take your next dose at the usual time.
- Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

In general, the observed side effects are mild to moderate.

Common (affects 1 to 10 users in 100):

- Headache, sleepiness, constipation, elevated liver function tests, dizziness, balance disorders, shortness of breath, high blood pressure and drug hypersensitivity

Uncommon (affects 1 to 10 users in 1,000):

- Tiredness, fungal infections, confusion, hallucinations, vomiting, abnormal gait, heart failure and venous blood clotting (thrombosis/thromboembolism).

Very Rare (affects less than 1 user in 10,000):

- Seizures

Not known (frequency cannot be estimated from the available data):

- Inflammation of the pancreas, inflammation of the liver (hepatitis) and psychotic reactions

Alzheimer's disease has been associated with depression, suicidal ideation and suicide. These events have been reported in patients treated with Axura.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Axura

Keep out of the sight and reach of children.

Do not use Axura after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Content of the pack and other information

What Axura contains

- The active substance is memantine hydrochloride. Each film-coated tablet contains 10 mg of memantine hydrochloride equivalent to 8.31 mg memantine.
- The other ingredients are microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, and magnesium stearate, all in the tablet core; and hypromellose, macrogol 400, titanium dioxide (E171) and iron oxide yellow (E172) all in the tablet coating.

What Axura looks like and contents of the pack

Axura film-coated tablets are presented as pale yellow to yellow, oval shaped film-coated tablet with breaking line and engravings "1-0" on one side and "M M" on the other side

Axura film-coated tablets are available in blister packs of 14 tablets, 28 tablets, 30 tablets, 42 tablets, 50 tablets, 56 tablets, 98 tablets, 100 tablets, 112 tablets and multipacks of 840 (20 packs of 42) tablets, 980 (10 packs of 98) tablets or 1000 (20 packs of 50) tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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

Manufacturer

Merz Pharma GmbH + Co. KGaA
Eckenheimer Landstr. 100
D-60318 Frankfurt/Main
Germany.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Tel: +49 (0)69 1503 – 0

United Kingdom

Merz Pharmaceuticals GmbH
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This leaflet was last revised in MM/YYYY.

Detailed information on this medicine is available on the European Medicines Agency (EMA) web side: <http://www.ema.europa.eu>

Package leaflet: Information for the user

Axura 5 mg/pump actuation, oral solution Memantine hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Axura is and what it is used for
2. What you need to know before you take Axura
3. How to take Axura
4. Possible side effects
5. How to store Axura
6. Content of the pack and other information

1. What Axura is and what it is used for

How does Axura work

Axura contains the active substance memantine hydrochloride.

Axura belongs to a group of medicines known as anti-dementia medicines.

Memory loss in Alzheimer's disease is due to a disturbance of message signals in the brain. The brain contains so-called N-methyl-D-aspartate (NMDA)-receptors that are involved in transmitting nerve signals important in learning and memory. Axura belongs to a group of medicines called NMDA-receptor antagonists. Axura acts on these NMDA-receptors improving the transmission of nerve signals and the memory.

What is Axura used for

Axura is used for the treatment of patients with moderate to severe Alzheimer's disease.

2. What you need to know before you take Axura

Do not take Axura

- if you are allergic (hypersensitive) to memantine hydrochloride or any of the other ingredients of Axura oral solution (listed in section 6).

Warning and precautions Talk to your doctor or pharmacist before taking Axura

- if you have a history of epileptic seizures
- if you have recently experienced a myocardial infarction (heart attack), or if you are suffering from congestive heart failure or from an uncontrolled hypertension (high blood pressure).

In these situations the treatment should be carefully supervised, and the clinical benefit of Axura reassessed by your doctor on a regular basis.

- If you suffer from renal impairment (kidney problems), your doctor should closely monitor your kidney function and if necessary adapt the memantine doses accordingly.

- The use of medicinal products called amantadine (for the treatment of Parkinson's disease), ketamine (a substance generally used as an anaesthetic), dextromethorphan (generally used to treat cough) and other NMDA-antagonists at the same time should be avoided.

Axura is not recommended for children and adolescents under the age of 18 years.

Other medicines and Axura

Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, Axura may change the effects of the following medicines and their dose may need to be adjusted by your doctor:

amantadine, ketamine, dextromethorphan
dantrolene, baclofen
cimetidine, ranitidine, procainamide, quinidine, quinine, nicotine
hydrochlorothiazide (or any combination with hydrochlorothiazide)
anticholinergics (substances generally used to treat movement disorders or intestinal cramps)
anticonvulsants (substances used to prevent and relieve seizures)
barbiturates (substances generally used to induce sleep)
dopaminergic agonists (substances such as L-dopa, bromocriptine)
neuroleptics (substances used in the treatment of mental disorders)
oral anticoagulants

If you go into hospital, let your doctor know that you are taking Axura.

Axura with food and drink

You should inform your doctor if you have recently changed or intend to change your diet substantially (e.g. from normal diet to strict vegetarian diet) or if you are suffering from states of renal tubular acidosis (RTA, an excess of acid-forming substances in the blood due to renal dysfunction (poor kidney function)) or severe infections of the urinary tract (structure that carries urine), as your doctor may need to adjust the dose of your medicine.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy: The use of memantine in pregnant women is not recommended.

Breast-Feeding: Women taking Axura should not breast-feed.

Driving and using machines

Your doctor will tell you whether your illness allows you to drive and to use machines safely. Also, Axura may change your reactivity, making driving or operating machinery inappropriate.

Axura contains sorbitol

This medicinal product contains sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product. Your doctor will advise you.

Furthermore, this medicine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially potassium-free.

3. How to take Axura

Always take Axura exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dosage

One pump actuation contains 5mg memantine hydrochloride.

The recommended dose of Axura for adults and older people is four pump actuations, equivalent to 20 mg once a day.

In order to reduce the risk of side effects this dose is achieved gradually by the following daily treatment scheme:

week 1	one pump actuation.
week 2	two pump actuations.
week 3	three pump actuations
week 4 and beyond	four pump actuations

The usual starting dose is one pump actuation (1 x 5 mg) once daily for the first week. This dose is increased in the second week to two pump actuations once daily (1 x 10 mg), and in the third week to three pump actuations (1 x 15 mg) once daily. From the fourth week the recommended dose is four pump actuations once daily (1 x 20mg)

Dosage in patients with impaired kidney function

If you have impaired kidney function, your doctor will decide upon a dose that suits your condition. In this case, monitoring of your kidney function should be performed by your doctor at specified intervals.

Administration

Axura should be administered orally once a day. To benefit from your medicine you should take it regularly every day at the same time of the day. The solution should be taken with a little water. The solution can be taken with or without food.

For detailed instructions on the preparation and handling of the product see end of this leaflet.

Duration of treatment

Continue to take Axura as long as it is of benefit to you. Your doctor should assess your treatment on a regular basis.

If you take more Axura than you should

- In general, taking too much Axura should not result in any harm to you. You may experience increased symptoms as described in section 4. „Possible side effects“.
- If you take a large overdose of Axura, contact your doctor or get medical advice, as you may need medical attention.

If you forget to take Axura

- If you find you have forgotten to take your dose of Axura, wait and take your next dose at the usual time.
- Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

In general, the observed side effects are mild to moderate.

Common (affects 1 to 10 users in 100):

- Headache, sleepiness, constipation, elevated liver function tests, dizziness, balance disorder, shortness of breath, high blood pressure and drug hypersensitivity

Uncommon (affects 1 to 10 users in 1,000):

- Tiredness, fungal infections, confusion, hallucinations, vomiting, abnormal gait, heart failure and venous blood clotting (thrombosis/thromboembolism)

Very Rare (affects less than 1 user in 10,000):

- Seizures

Not known (frequency cannot be estimated from the available data):

- Inflammation of the pancreas, inflammation of the liver (hepatitis) and psychotic reactions

Alzheimer's disease has been associated with depression, suicidal ideation and suicide. These events have been reported in patients treated with Axura.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Axura

- Keep out of the sight and reach of children.

Do not use Axura after the expiry date which is stated on the carton and the bottle label after the EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

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

The bottle with the mounted pump must be kept and transported in an upright position only.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Content of the pack and other information

What Axura contains

The active substance is memantine hydrochloride.

Each pump actuation delivers 0.5 ml solution which contains 5 mg of memantine hydrochloride which is equivalent to 4.16 mg memantine.

The other ingredients are: potassium sorbate, sorbitol (E420) and purified water.

What Axura looks like and contents of the pack

Axura oral solution is presented as a clear, colourless to light yellowish solution.

Axura oral solution is available in bottles of 50 ml, 100 ml or a multipack of 500ml (10 x 50 ml).

Not all pack sizes may be marketed.

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Manufacturer

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This leaflet was last revised in MM/YYYY.

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.ema.europa.eu>

Instruction for proper use of the pump

The solution must not be poured or pumped directly into the mouth from the bottle or pump. Measure the dose onto a spoon or into a glass of water, using the pump.

Take the screw cap off the bottle:

The cap must be turned anticlockwise, unscrewed completely and removed (fig. 1).

1.



Mounting the dosing pump on the bottle:

Take the dosing pump out of the plastic bag (fig. 2) and place it on top of the bottle. Slide the plastic dip tube carefully into the bottle. Hold the dosing pump onto the neck of the bottle and screw it clockwise until it fits firmly (fig. 3). The dosing pump is only screwed on once when starting the use, and should never be unscrewed.

2.



3.



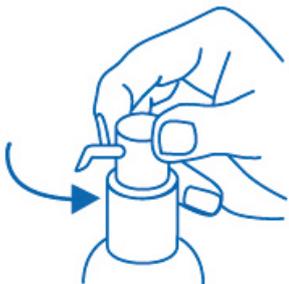
How the dosing pump works:

The dosing pump head has two positions and is easy to turn:

- anticlockwise to unlock and
- clockwise to lock.

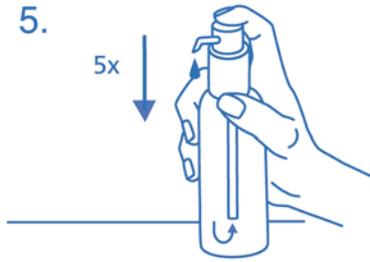
The dosing pump head should not be pushed down while in the locked position. The solution may only be dispensed in the unlocked position. To unlock, turn the pump head in the direction of the arrow until it cannot be turned any further (about one eighth of a turn, fig. 4). The dosing pump is then ready for use.

4.



Preparing the dosing pump:

When used for the first time, the dosing pump does not dispense the correct amount of oral solution. Therefore, the pump must be prepared (primed) by pushing the dosing pump head down completely five times in succession (fig. 5).



The solution thus dispensed is discarded. The next time the dosing pump head is pushed downwards completely (equivalent to one pump actuation), it dispenses the correct dose (fig. 6).

6.



Correct use of the dosing pump:

Place the bottle on a flat, horizontal surface, for example a table top, and only use it in a upright position. Hold a glass with a little water or a spoon below the nozzle. Push down the dosing pump head in a firm but calm and steady manner - not too slowly (fig. 7, fig. 8).

7.



8.



The dosing pump head can then be released and is ready for the next pump actuation.

The dosing pump must only be used with the Axura solution in the bottle provided, not for other substances or containers. If the pump does not function properly, consult your doctor or a pharmacist. Lock the dosing pump after using Axura.

Package leaflet: Information for the user

Axura 5 mg film-coated tablets
Axura 10 mg film-coated tablets
Axura 15 mg film-coated tablets
Axura 20 mg film-coated tablets
Memantine hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
-

What is in this leaflet:

1. What Axura is and what it is used for
2. What you need to know before you take Axura
3. How to take Axura
4. Possible side effects
5. How to store Axura
6. Content of the pack and other information

1. What Axura is and what it is used for

How does Axura work

Axura contains the active substance memantine hydrochloride.

Axura belongs to a group of medicines known as anti-dementia medicines.

Memory loss in Alzheimer's disease is due to a disturbance of message signals in the brain. The brain contains so-called N-methyl-D-aspartate (NMDA)-receptors that are involved in transmitting nerve signals important in learning and memory. Axura belongs to a group of medicines called NMDA-receptor antagonists. Axura acts on these NMDA-receptors improving the transmission of nerve signals and the memory.

What is Axura used for

Axura is used for the treatment of patients with moderate to severe Alzheimer's disease.

2. What you need to know before you take Axura

Do not take Axura

- if you are allergic (hypersensitive) to memantine hydrochloride or any of the other ingredients of Axura tablets (listed in section 6).

Warning and precautions Talk to your doctor or pharmacist before taking Axura

- if you have a history of epileptic seizures
- if you have recently experienced a myocardial infarction (heart attack), or if you are suffering from congestive heart failure or from an uncontrolled hypertension (high blood pressure).

In these situations the treatment should be carefully supervised, and the clinical benefit of Axura reassessed by your doctor on a regular basis.

If you suffer from renal impairment (kidney problems), your doctor should closely monitor your kidney function and if necessary adapt the memantine doses accordingly.

The use of medicinal products called amantadine (for the treatment of Parkinson's disease), ketamine (a substance generally used as an anaesthetic), dextromethorphan (generally used to treat cough) and other NMDA-antagonists at the same time should be avoided.

Axura is not recommended for children and adolescents under the age of 18 years.

Other medicines and Axura

Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, Axura may change the effects of the following medicines and their dose may need to be adjusted by your doctor:

amantadine, ketamine, dextromethorphan
dantrolene, baclofen
cimetidine, ranitidine, procainamide, quinidine, quinine, nicotine
hydrochlorothiazide (or any combination with hydrochlorothiazide)
anticholinergics (substances generally used to treat movement disorders or intestinal cramps)
anticonvulsants (substances used to prevent and relieve seizures)
barbiturates (substances generally used to induce sleep)
dopaminergic agonists (substances such as L-dopa, bromocriptine)
neuroleptics (substances used in the treatment of mental disorders)
oral anticoagulants

If you go into hospital, let your doctor know that you are taking Axura.

Axura with food and drink

You should inform your doctor if you have recently changed or intend to change your diet substantially (e.g. from normal diet to strict vegetarian diet) or if you are suffering from states of renal tubular acidosis (RTA, an excess of acid-forming substances in the blood due to renal dysfunction (poor kidney function)) or severe infections of the urinary tract (structure that carries urine) as your doctor may need to adjust the dose of your medicine.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy: The use of memantine in pregnant women is not recommended.

Breast-Feeding: Women taking Axura should not breast-feed.

Driving and using machines

Your doctor will tell you whether your illness allows you to drive and to use machines safely. Also, Axura may change your reactivity, making driving or operating machinery inappropriate.

3. How to take Axura

The Axura treatment initiation pack is only to be used for the beginning of the treatment with Axura.

Always take Axura exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dosage

The recommended treatment dose of 20 mg per day is achieved by a gradual increase of the Axura dose during the first 3 weeks of treatment. The treatment scheme is also indicated on the treatment initiation pack. Take one tablet once a day.

Week 1 (day 1-7):

Take one 5 mg tablet once a day (white to off-white, oval-oblong) for 7 days.

Week 2 (day 8-14):

Take one 10 mg tablet once a day (pale yellow to yellow, oval shaped) for 7 days.

Week 3 (day 15-21):

Take one 15 mg tablet once a day (grey-orange, oval-oblong) for 7 days.

Week 4 (day 22-28):

Take one 20 mg tablet per day (grey-red, oval-oblong) for 7 days.

week 1	5 mg tablet
week 2	10 mg tablet
week 3	15 mg tablet
week 4 and beyond	20 mg tablets once a day

Maintenance dose

The recommended daily dose is 20 mg once a day.

For continuation of the treatment please consult your doctor.

Dosage in patients with impaired kidney function

If you have impaired kidney function, your doctor will decide upon a dose that suits your condition. In this case, monitoring of your kidney function should be performed by your doctor at specified intervals.

Administration

Axura should be administered orally once a day. To benefit from your medicine you should take it regularly every day at the same time of the day. The tablets should be swallowed with some water. The tablets can be taken with or without food.

Duration of treatment

Continue to take Axura as long as it is of benefit to you. Your doctor should assess your treatment on a regular basis.

If you take more Axura than you should

- In general, taking too much Axura should not result in any harm to you. You may experience increased symptoms as described in section 4. „Possible side effects“.
- If you take a large overdose of Axura, contact your doctor or get medical advice, as you may need medical attention.

If you forget to take Axura

- If you find you have forgotten to take your dose of Axura, wait and take your next dose at the usual time.

- Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

In general, the observed side effects are mild to moderate.

Common (affects 1 to 10 users in 100):

- Headache, sleepiness, constipation, elevated liver function tests, dizziness, balance disorders, shortness of breath, high blood pressure and drug hypersensitivity

Uncommon (affects 1 to 10 users in 1,000):

- Tiredness, fungal infections, confusion, hallucinations, vomiting, abnormal gait, heart failure and venous blood clotting (thrombosis/thromboembolism)

Very Rare (affects less than 1 user in 10,000):

- Seizures

Not known (frequency cannot be estimated from the available data):

- Inflammation of the pancreas, inflammation of the liver (hepatitis) and psychotic reactions

Alzheimer's disease has been associated with depression, suicidal ideation and suicide. These events have been reported in patients treated with Axura.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly **the national reporting system listed in Appendix V**. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Axura

- Keep out of the sight and reach of children.

Do not use Axura after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Content of the pack and other information

What Axura contains

The active substance is memantine hydrochloride. Each tablet contains 5/10/15/20 mg of memantine hydrochloride equivalent to 4.15/8.31/12.46/16.62 mg memantine.

The other ingredients for Axura 5/10/15 and 20 mg film-coated tablets are microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, all in the tablet core; and hypromellose, macrogol 400, titanium dioxide (E 171) and additional for Axura 10 mg film-coated

tablets is iron oxide yellow (E172) and for Axura 15 mg and Axura 20 mg film-coated tablets are iron oxide yellow and red (E 172), all in the tablet coating.

What Axura looks like and contents of the pack

Axura 5 mg film-coated tablets are presented as white to off-white, oval-oblong with imprint '5' on one side and imprint 'MEM' on the other side.

Axura 10 mg film-coated tablets are presented as pale yellow to yellow, oval shaped film-coated tablet with breaking line and engravings "1-0" on one side and "M M" on the other side. The tablet can be divided into equal halves.

Axura 15 mg film-coated tablets are presented as orange to grey-orange, oval-oblong with imprint '15' on one side and imprint 'MEM' on the other side.

Axura 20 mg film-coated tablets are presented as pale red to grey-red, oval-oblong with imprint '20' on one side and imprint 'MEM' on the other side.

One treatment initiation pack contains 28 tablets in 4 blisters with 7 tablets of Axura 5 mg, 7 tablets of Axura 10 mg, 7 tablets of Axura 15 mg and 7 tablets of Axura 20 mg.

Marketing Authorisation Holder

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Manufacturer

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in MM/YYYY.

Detailed information on this medicine is available on the European Medicines Agency (EMA) web side: <http://www.ema.europa.eu>

Package leaflet: Information for the user

Axura 20 mg film-coated tablets Memantine hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any the side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
-

In this leaflet:

1. What Axura is and what it is used for
2. What you need to know before you take Axura
3. How to take Axura
4. Possible side effects
5. How to store Axura
6. Content of the pack and other information

1. What Axura is and what it is used for

How does Axura work

Axura contains the active substance memantine hydrochloride.

Axura belongs to a group of medicines known as anti-dementia medicines.

Memory loss in Alzheimer's disease is due to a disturbance of message signals in the brain. The brain contains so-called N-methyl-D-aspartate (NMDA)-receptors that are involved in transmitting nerve signals important in learning and memory. Axura belongs to a group of medicines called NMDA-receptor antagonists. Axura acts on these NMDA-receptors improving the transmission of nerve signals and the memory.

What is Axura used for

Axura is used for the treatment of patients with moderate to severe Alzheimer's disease.

2. What you need to know before you take Axura

Do not take Axura

- if you are allergic (hypersensitive) to memantine hydrochloride or any of the other ingredients of Axura tablets (listed in section 6).

Warning and precautions

Talk to your doctor or pharmacist before taking Axura

- if you have a history of epileptic seizures
- if you have recently experienced a myocardial infarction (heart attack), or if you are suffering from congestive heart failure or from an uncontrolled hypertension (high blood pressure).

In these situations the treatment should be carefully supervised, and the clinical benefit of Axura reassessed by your doctor on a regular basis.

If you suffer from renal impairment (kidney problems), your doctor should closely monitor your kidney function and if necessary adapt the memantine doses accordingly.

The use of medicinal products called amantadine (for the treatment of Parkinson's disease), ketamine (a substance generally used as an anaesthetic), dextromethorphan (generally used to treat cough) and other NMDA-antagonists at the same time should be avoided.

Axura is not recommended for children and adolescents under the age of 18 years.

Other medicines and Axura

Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, Axura may change the effects of the following medicines and their dose may need to be adjusted by your doctor:

amantadine, ketamine, dextromethorphan
dantrolene, baclofen
cimetidine, ranitidine, procainamide, quinidine, quinine, nicotine
hydrochlorothiazide (or any combination with hydrochlorothiazide)
anticholinergics (substances generally used to treat movement disorders or intestinal cramps)
anticonvulsants (substances used to prevent and relieve seizures)
barbiturates (substances generally used to induce sleep)
dopaminergic agonists (substances such as L-dopa, bromocriptine)
neuroleptics (substances used in the treatment of mental disorders)
oral anticoagulants

If you go into hospital, let your doctor know that you are taking Axura.

Axura with food and drink

You should inform your doctor if you have recently changed or intend to change your diet substantially (e.g. from normal diet to strict vegetarian diet) or if you are suffering from states of renal tubular acidosis (RTA, an excess of acid-forming substances in the blood due to renal dysfunction (poor kidney function)) or severe infections of the urinary tract (structure that carries urine), as your doctor may need to adjust the dose of your medicine.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy: The use of memantine in pregnant women is not recommended.

Breast-Feeding: Women taking Axura should not breast-feed.

Driving and using machines

Your doctor will tell you whether your illness allows you to drive and to use machines safely. Also, Axura may change your reactivity, making driving or operating machinery inappropriate.

3. How to take Axura

Always take Axura exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dosage

The recommended dose of Axura for adults and older people is 20 mg once a day.

In order to reduce the risk of side effects this dose is achieved gradually by the following daily treatment scheme. For up-titration other tablet strengths are available.

At the beginning of treatment you will start by using Axura 5 mg film-coated tablets once a day. This dose will be increased weekly by 5 mg until the recommended (maintenance) dose is reached. The recommended maintenance dose is 20 mg once a day, which is reached at the beginning of the 4th week.

Dosage in patients with impaired kidney function

If you have impaired kidney function, your doctor will decide upon a dose that suits your condition. In this case, monitoring of your kidney function should be performed by your doctor at specified intervals.

Administration

Axura should be administered orally once a day. To benefit from your medicine you should take it regularly every day at the same time of the day. The tablets should be swallowed with some water. The tablets can be taken with or without food.

Duration of treatment

Continue to take Axura as long as it is of benefit to you. Your doctor should assess your treatment on a regular basis.

If you take more Axura than you should

- In general, taking too much Axura should not result in any harm to you. You may experience increased symptoms as described in section 4. „Possible side effects“.
- If you take a large overdose of Axura, contact your doctor or get medical advice, as you may need medical attention.

If you forget to take Axura

- If you find you have forgotten to take your dose of Axura, wait and take your next dose at the usual time.
- Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

In general, the observed side effects are mild to moderate.

Common (affects 1 to 10 users in 100):

- Headache, sleepiness, constipation, elevated liver function tests, dizziness, balance disorders, shortness of breath, high blood pressure and drug hypersensitivity

Uncommon (affects 1 to 10 users in 1,000):

- Tiredness, fungal infections, confusion, hallucinations, vomiting, abnormal gait, heart failure and venous blood clotting (thrombosis/thromboembolism)

Very Rare (affects less than 1 user in 10,000):

- Seizures

Not known (frequency cannot be estimated from the available data):

- Inflammation of the pancreas, inflammation of the liver (hepatitis) and psychotic reactions

Alzheimer's disease has been associated with depression, suicidal ideation and suicide. These events have been reported in patients treated with Axura.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#)

listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Axura

Keep out of the sight and reach of children.

Do not use Axura after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Content of the pack and other information

What Axura contains

The active substance is memantine hydrochloride. Each film-coated tablet contains 20 mg of memantine hydrochloride equivalent to 16.62 mg memantine.

The other ingredients are microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, all in the tablet core; and hypromellose, macrogol 400, titanium dioxide (E 171), iron oxide yellow and red (E 172), all in the tablet coating.

What Axura looks like and contents of the pack

Axura film-coated tablets are presented as pale red to grey-red, oval-oblong film-coated tablets with imprint '20' on one side and imprint 'MEM' on the other side.

Axura film-coated tablets are available in blister packs of 14 tablets, 28 tablets, 42 tablets, 56 tablets, 98 tablets or in multipacks of 840 (20 x 42) tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Detailed information on this medicine is available on the European Medicines Agency (EMA) website: <http://www.ema.europa.eu>