ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz 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 tablet.
Pale yellow to yellow, oval shaped film-coated tablet with imprint “M” on both sides right and left of the breakline and on the other side the imprints “1” and “0” left and right of the breakline. (tablet length: approx. 11.0 mm, tablet width: approx. 5.0 mm)
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

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer’s dementia.

Posology

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.

Elderly
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 Memantine Merz is not recommended in patients with severe hepatic impairment.

Paediatric population
Memantine Merz is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Method of administration

Memantine Merz 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 tubulary 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.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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, Memantine Merz 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 Memantine Merz and 1,595 patients treated with placebo, the overall incidence rate of adverse reactions with Memantine Merz 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 Memantine Merz 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 Memantine Merz 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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 systeme 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 Memantine Merz.

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 $t_{½}$ 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). Alkalisation of urine may result from drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or from the massive ingestion of alkalising gastric buffers.

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/1/12/799/001
EU/1/12/799/002
EU/1/12/799/003
EU/1/12/799/004
EU/1/12/799/005
EU/1/12/799/006
EU/1/12/799/007
EU/1/12/799/008
EU/1/12/799/009
EU/1/12/799/010
EU/1/12/799/011
EU/1/12/799/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 Nov 2012
Date of latest renewal: 13 July 2017

10. DATE OF REVISION OF THE TEXT

MM/YYYY

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

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz 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 (E 420), 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

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia.

Posology

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.

Elderly
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 Memantine Merz in patients with severe hepatic impairment is not recommended.

Paediatric population
Memantine Merz is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Method of administration

Memantine Merz 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 alkalising gastric buffers. Also, urine pH may be elevated by states of renal tubulary 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 hereditary fructose intolerance (HFI) should not take this medicinal product.Furthermore, this medicine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially potassium-free.

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, Memantine Merz 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 Memantine Merz and 1,595 patients treated with placebo, the overall incidence rate of adverse reactions with Memantine Merz 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 Memantine Merz 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 Memantine Merz 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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 systeme 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 Memantine Merz.

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 $t_{½}$ 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). Alkalisation of urine may result from drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or from the massive ingestion of alkalising gastric buffers.

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

Potassium sorbate
Sorbitol E 420
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 30ºC.

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

6.5 Nature and contents of container

50 ml (and 10 x 50 ml) in brown glass bottles (Hydrolytic Class II) and 100 ml in brown glass bottles (Hydrolytic Class III).

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.

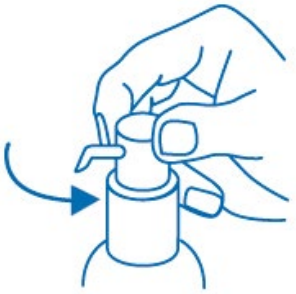
2.

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.

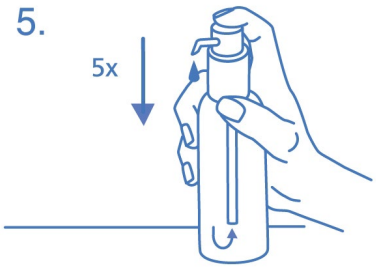


The dosing pump is then ready for use.

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).

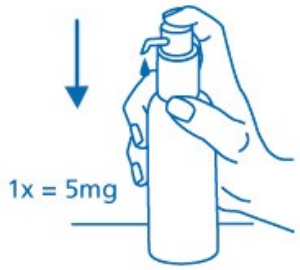
5.



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 hold 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/1/12/799/027
EU/1/12/799/028

EU/1/12/799/029

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 Nov 2012
Date of latest renewal: 13 July 2017

10. DATE OF REVISION OF THE TEXT

MM/YYYY

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

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz 5 mg film-coated tablets
Memantine Merz 10 mg film-coated tablets
Memantine Merz 15 mg film-coated tablets
Memantine Merz 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 shaped film-coated tablets with engravings '5' on one side and 'MEM' on the other side. (tablet length: approx. 8.0 mm, tablet width: approx. 4.0 mm)
The 10 mg film-coated tablets are pale yellow to yellow, oval shaped film-coated tablet with imprint "M" on both sides right and left of the breakline and on the other side the imprints "1" and "0" left and right of the breakline. (tablet length: approx. 11.0 mm, tablet width: approx. 5.0 mm) The tablet can be divided into equal halves.
The 15 mg film-coated tablets are orange coloured, oval shaped film-coated tablets with engravings '15' on one side and 'MEM' on the other side. (tablet length: approx. 12.0 mm, tablet width: approx. 6.3 mm)
The 20 mg film-coated tablets are pink coloured, oval shaped film-coated tablets with engravings '20' on one side and 'MEM' on the other side. (tablet length: approx. 13.0 mm, tablet width: approx. 7.0 mm)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia.

Posology

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 shaped) 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 (orange, oval shaped) for 7 days.

Week 4 (day 22-28):
The patient should take one 20 mg film-coated tablet per day (pink, oval shaped) for 7 days.

Maintenance dose
The recommended maintenance dose is 20 mg per day.

Elderly
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 Memantine Merz in patients with severe hepatic impairment is not recommended.

Paediatric population
Memantine Merz is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Method of administration

Memantine Merz 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 tubulary 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.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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, Memantine Merz 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 Memantine Merz and 1,595 patients treated with placebo, the overall incidence rate of adverse reactions with Memantine Merz 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 Memantine Merz 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 Memantine Merz 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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 systeme 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 Uncommon Not known	Constipation Vomiting Pancreatitis[2]
Hepatobiliary disorders	Common Not known	Elevated liver function test Hepatitis
General disorders and administration site conditions	Common Uncommon	Headache 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 Memantine Merz.

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.

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Clinical studies

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Pharmacokinetic/pharmacodynamic relationship

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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/1/12/799/025
EU/1/12/799/026

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 Nov 2012

Date of latest renewal: 13 July 2017

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz 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.
Pink coloured, oval shaped film-coated tablets with engravings “20” on one side and “MEM” on the other side. (tablet length: approx. 13.0 mm, tablet width: approx. 7.0 mm)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer’s dementia.

Posology

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.

Elderly
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 Memantine Merz in patients with severe hepatic impairment is not recommended.

Paediatric population
Memantine Merz is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Method of administration

Memantine Merz 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 tubulary 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.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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, Memantine Merz 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 Memantine Merz and 1,595 patients treated with placebo, the overall incidence rate of adverse reactions with Memantine Merz 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 Memantine Merz 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 Memantine Merz 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 (≥1/10), common (≥1/100 to < 1/10), uncommon (≥1/1,000 to <1/100), rare (≥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 systeme 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 Memantine Merz.

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 $t_{½}$ 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). Alkalisation of urine may result from drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or from the massive ingestion of alkalising gastric buffers.

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/1/12/799/013
EU/1/12/799/014
EU/1/12/799/015
EU/1/12/799/016
EU/1/12/799/017
EU/1/12/799/018
EU/1/12/799/019
EU/1/12/799/020
EU/1/12/799/021
EU/1/12/799/022
EU/1/12/799/023
EU/1/12/799/024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 Nov 2012
Date of latest renewal: 13 July 2017

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal 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 Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.

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

Memantine Merz 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

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/1/12/799/001 14 film-coated tablets
EU/1/12/799/002 28 film-coated tablets
EU/1/12/799/003 30 film-coated tablets
EU/1/12/799/004 42 film-coated tablets
EU/1/12/799/005 50 film-coated tablets
EU/1/12/799/006 56 film-coated tablets
EU/1/12/799/007 98 film-coated tablets
EU/1/12/799/008 100 film-coated tablets
EU/1/12/799/009 112 film-coated tablets

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Memantine Merz 10 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

Memantine Merz 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

42 film-coated tablets
Component of a multipack, can't be sold separately.
50 film-coated tablets
Component of a multipack, can't be sold separately.
98 film-coated tablets
Component of a multipack, can't be sold separately.

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/1/12/799/010 840 film-coated tablets (20 packs of 42)
EU/1/12/799/011 980 film-coated tablets (10 packs of 98)
EU/1/12/799/012 1000 film-coated tablets (20 packs of 50)

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Memantine Merz 10 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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

Memantine Merz 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 840 (20 packs of 42) film-coated tablets
Multipack 980 (10 packs of 98) film-coated tablets
Multipack 1000 (20 packs of 50) 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/1/12/799/010 840 film-coated tablets (20 packs of 42)
EU/1/12/799/011 980 film-coated tablets (10 packs of 98)
EU/1/12/799/012 1000 film-coated tablets (20 packs of 50)

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz 10 mg film-coated tablets
Memantine hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Merz Pharmaceuticals GmbH

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz 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 sorbitol (E 420).
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 30ºC.

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/1/12/799/027 50 ml
EU/1/12/799/029 100 ml

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Memantine Merz 5 mg/pump actuation, oral solution

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

Memantine Merz 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 sorbitol (E 420).
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

50 ml oral solution
Component of a multipack, can't be sold separately.

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 sightand reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

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/1/12/799/028 500 ml (10 bottles of 50 ml)

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Memantine Merz 5 mg/pump actuation, oral solution

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz 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 sorbitol (E 420).
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack 500 ml, 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 30ºC.
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/1/12/799/028 500 ml (10 bottles of 50 ml)

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz 5 mg film-coated tablets
Memantine Merz 10 mg film-coated tablets
Memantine Merz 15 mg film-coated tablets
Memantine Merz 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 Memantine Merz 5 mg
7 x Memantine Merz 10 mg
7 x Memantine Merz 15 mg
7 x Memantine Merz 20 mg

One tablet daily

Week 1
Day 1, 2, 3, 4, 5, 6, 7
7 film-coated tablets. Memantine Merz 5 mg

Week 2
Day 8, 9, 10, 11, 12, 13, 14
7 film-coated tablets. Memantine Merz 10 mg

Week 3
Day 15, 16, 17, 18, 19, 20, 21
7 film-coated tablets. Memantine Merz 15 mg

Week 4
Day 22, 23, 24, 25, 26, 27, 28
7 film-coated tablets. Memantine Merz 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/1/12/799/025 28 film-coated tablets
EU/1/12/799/026 28 film-coated tablets

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Memantine Merz 5 mg, 10 mg, 15 mg, 20 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz5 mg, 10 mg, 15 mg, 20 mg film-coated tablets
Memantine hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Merz Pharmaceuticals GmbH

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz 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

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/1/12/799/013 14 film-coated tablets
EU/1/12/799/014 28 film-coated tablets
EU/1/12/799/015 42 film-coated tablets
EU/1/12/799/016 56 film-coated tablets
EU/1/12/799/017 98 film-coated tablets
EU/1/12/799/019 14 film-coated tablets
EU/1/12/799/020 28 film-coated tablets
EU/1/12/799/021 42 film-coated tablets
EU/1/12/799/022 56 film-coated tablets
EU/1/12/799/023 98 film-coated tablets

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Memantine Merz 20 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

Memantine Merz 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

42 film-coated tablets
Component of a multipack, can't be sold separately.

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/1/12/799/018 840 film-coated tablets (20 packs of 42)
EU/1/12/799/024 840 film-coated tablets (20 packs of 42)

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Memantine Merz 20 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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

Memantine Merz 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 (20 packs of 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/1/12/799/018 840 film-coated tablets (20 packs of 42)
EU/1/12/799/024 840 film-coated tablets (20 packs of 42)

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz 20 mg film-coated tablets
Memantine hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Merz Pharmaceuticals GmbH

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

5. OTHER

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

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Memantine Merz 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 Memantine Merz is and what it is used for

How does Memantine Merz work
Memantine Merz contains the active substance memantine hydrochloride.
Memantine Merz 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. Memantine Merz belongs to a group of medicines called NMDA-receptor antagonists. Memantine Merz acts on these NMDA-receptors improving the transmission of nerve signals and the memory.

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

2. What you need to know before you take Memantine Merz

Do not take Memantine Merz
- if you are allergic (hypersensitive) to memantine hydrochloride or any of the other ingredients of Memantine Merz tablets (listed in section 6).

Warning and precautions
Talk to your doctor or pharmacist before taking Memantine Merz
- 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 Memantine Merz 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.

Children and adolescents
Memantine Merz is not recommended for children and adolescents under the age of 18 years.

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

In particular, Memantine Merz 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 Memantine Merz.

Memantine Merz 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 tubulary 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 Memantine Merz 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, Memantine Merz may change your reactivity, making driving or operating machinery inappropriate.

Memantine Merz contains Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Memantine Merz

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

Dosage
The recommended dose of Memantine Merz 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
Memantine Merz 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 Memantine Merz as long as it is of benefit to you. Your doctor should assess your treatment on a regular basis.

If you take more Memantine Merz than you should
- In general, taking too much Memantine Merz 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 Memantine Merz, contact your doctor or get medical advice, as you may need medical attention.

If you forget to take Memantine Merz
- If you find you have forgotten to take your dose of Memantine Merz, 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 (may affect up to 1 in 10 users):

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

Uncommon (may affect up to 1 in 100 users):
- Tiredness, fungal infections, confusion, hallucinations, vomiting, abnormal gait, heart failure and venous blood clotting (thrombosis/thromboembolism)

Very rare (may affect up to 1 in 10,000 users):
- 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 Memantine Merz.

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 Memantine Merz

Keep out of the sight and reach of children.

Do not use Memantine Merz 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 Memantine Merz 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 (E 171) and iron oxide yellow (E 172) all in the tablet coating.

What Memantine Merz looks like and contents of the pack
Memantine Merz film-coated tablets are presented as pale yellow to yellow, oval shaped film-coated tablets with imprint “M” on both sides right and left of the breakline and on the other side the imprints “1” and “0” left and right of the breakline. The tablet is approximately 11.0 mm long, and 5.0 mm wide.

Memantine Merz 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 multipscks 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.

België/Belgique/Belgien
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

България
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

Česká republika
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Danmark
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Deutschland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Eesti
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Ελλάδα
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

España
Merz Therapeutics Iberia, S.L.U.
Tel. +34 91 117 89 17

France
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Hrvatska
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Ireland

Lietuva
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Luxembourg/Luxemburg
HANFF Global Health Solutions s.à r.l.
Tél: +352 45 07 07-1

Magyarország
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Malta
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

Nederland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Norge
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Österreich
Merz Pharma Austria GmbH
Tel.: +43 1 865 88 95

Polska
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

Portugal
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

România
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Slovenija

Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Ísland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Italia
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Κύπρος
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Latvija
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Slovenská republika
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Suomi/Finland
Oy H. Lundbeck Ab
Puh/Tel: +358 2 276 5000

Sverige
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

This leaflet was last revised in MM/YYYY.
Detailed information on this medicine is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu.

Package leaflet: Information for the user

Memantine Merz 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 Memantine Merz is and what it is used for

How does Memantine Merz work
Memantine Merz contains the active substance memantine hydrochloride.
Memantine Merz 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. Memantine Merz belongs to a group of medicines called NMDA-receptor antagonists. Memantine Merz acts on these NMDA-receptors improving the transmission of nerve signals and the memory.

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

2. What you need to know before you take Memantine Merz

Do not take Memantine Merz
- if you are allergic (hypersensitive) to memantine hydrochloride or any of the other ingredients of Memantine Merz oral solution (listed in section 6).

Warning and precautions
Talk to your doctor or pharmacist before taking Memantine Merz
- 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 Memantine Merz 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.

Children and adolescents
Memantine Merz is not recommended for children and adolescents under the age of 18 years.

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

In particular, Memantine Merz 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 Memantine Merz.

Memantine Merz 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 tubulary 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 Memantine Merz 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, Memantine Merz may change your reactivity, making driving or operating machinery inappropriate.

Memantine Merz contains sorbitol
This medicine contains 100 mg sorbitol in each gram which is equivalent to 200 mg /4 pump actuation. Sorbitol is a source of fructose. If your doctor told you that you have an intolerance to some sugars, or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you take or receive this medicine.

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

3. How to take Memantine Merz

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

If you take more Memantine Merz than you should
- In general, taking too much Memantine Merz 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 Memantine Merz, contact your doctor or get medical advice, as you may need medical attention.

If you forget to take Memantine Merz
- If you find you have forgotten to take your dose of Memantine Merz, 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 (may affect up to 1 in 10 users):
- Headache, sleepiness, constipation, elevated liver function tests, dizziness, balance disorder, shortness of breath, high blood pressure and drug hypersensitivity

Uncommon (may affect up to 1 in 100 users):
- Tiredness, fungal infections, confusion, hallucinations, vomiting, abnormal gait, heart failure and venous blood clotting (thrombosis/thromboembolism)

Very rare (may affect up to 1 in 10,000 users):
- 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 Memantine Merz.

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 Memantine Merz

Keep out of the sight and reach of children.

Do not use Memantine Merz 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 Memantine Merz 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 (E 420) and purified water.

What Memantine Merz looks like and contents of the pack
Memantine Merz oral solution is presented as a clear, colourless to light yellowish solution.

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

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.

België/Belgique/Belgien
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

България
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

Česká republika
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Danmark
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Deutschland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Eesti
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Ελλάδα
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

España
Merz Therapeutics Iberia, S.L.U.
Tel. +34 91 117 89 17

Lietuva
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Luxembourg/Luxemburg
HANFF Global Health Solutions s.à r.l.
Tél: +352 45 07 07-1

Magyarország
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Malta
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

Nederland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Norge
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Österreich
Merz Pharma Austria GmbH
Tel.: +43 1 865 88 95

Polska
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

France
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Hrvatska
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Ireland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Ísland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Italia
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Κύπρος
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Latvija
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Portugal
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

România
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Slovenija
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Slovenská republika
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Suomi/Finland
Oy H. Lundbeck Ab
Puh/Tel: +358 2 276 5000

Sverige
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

This leaflet was last revised in MM/YYYY.
Detailed information on this medicine is available on the website of the European Medicines Agency (EMA) 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:

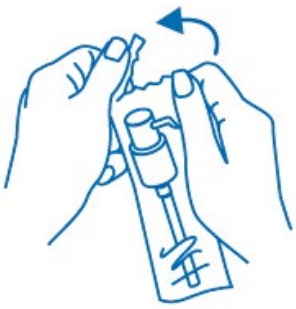
The cap must be turned anticlockwise, unscrewed completely and removed (fig. 1).

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.

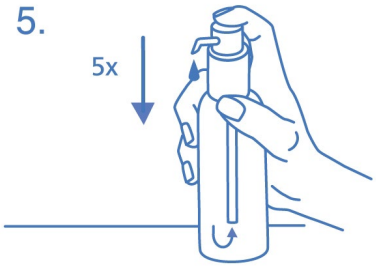
The dosing pump head should not be pushed down while in the locked position. The solution may only be dispensed in the unlocked position. To unlock, turn the pump head in the direction of the arrow until it cannot be turned any further (about one eighth of a turn, fig. 4). The dosing pump is then ready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

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 Memantine Merz 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 Memantine Merz.

Package leaflet: Information for the user

Memantine Merz 5 mg film-coated tablets
Memantine Merz 10 mg film-coated tablets
Memantine Merz 15 mg film-coated tablets
Memantine Merz 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 Memantine Merz is and what it is used for

How does Memantine Merz work
Memantine Merz contains the active substance memantine hydrochloride.
Memantine Merz 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. Memantine Merz belongs to a group of medicines called NMDA-receptor antagonists. Memantine Merz acts on these NMDA-receptors improving the transmission of nerve signals and the memory.

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

2. What you need to know before you take Memantine Merz

Do not take Memantine Merz
- if you are allergic (hypersensitive) to memantine hydrochloride or any of the other ingredients of Memantine Merz tablets (see section 6).

Warning and precautions
Talk to your doctor or pharmacist before taking Memantine Merz
- 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 Memantine Merz 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.

Children and adolescents
Memantine Merz is not recommended for children and adolescents under the age of 18 years.

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

In particular, Memantine Merz 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 Memantine Merz.

Memantine Merz 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 tubulary 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 Memantine Merz 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, Memantine Merz may change your reactivity, making driving or operating machinery inappropriate.

Memantine Merz contains Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Memantine Merz

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

Always take Memantine Merz 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 Memantine Merz 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 shaped) 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 (orange, oval shaped) for 7 days.

Week 4 (day 22-28):
Take one 20 mg tablet per day (pink, oval shaped) 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
Memantine Merz 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 Memantine Merz as long as it is of benefit to you. Your doctor should assess your treatment on a regular basis.

If you take more Memantine Merz than you should
- In general, taking too much Memantine Merz 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 Memantine Merz, contact your doctor or get medical advice, as you may need medical attention.

If you forget to take Memantine Merz
- If you find you have forgotten to take your dose of Memantine Merz, 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 (may affect up to 1 in 10 users):
- Headache, sleepiness, constipation, elevated liver function tests, dizziness, balance disorders, shortness of breath, high blood pressure and drug hypersensitivity

Uncommon (may affect up to 1 in 100 users):
- Tiredness, fungal infections, confusion, hallucinations, vomiting, abnormal gait, heart failure and venous blood clotting (thrombosis/thromboembolism)

Very rare (may affect up to 1 in 10,000 users):
- Seizures

Not known (frequency cannot be estimated from the available data):
- Inflammation of the pancreas, inflammation of the liever (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 Memantine Merz.

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 Memantine Merz

Keep out of the sight and reach of children.

Do not use Memantine Merz 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 notthrow 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 Memantine Merz 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 Memantine Merz 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 Memantine Merz 10 mg film-coated tablets is iron oxide yellow (E172) and for Memantine Merz 15 mg and Memantine Merz 20 mg film-coated tablets are iron oxide yellow and red (E 172), all in the tablet coating.

What Memantine Merz looks like and contents of the pack
Memantine Merz 5 mg film-coated tablets are presented as white to off-white, oval shaped with engravings '5' on one side and 'MEM' on the other side. The tablet is approximately 8.0 mm long, and 4.0 mm wide.
Memantine Merz 10 mg film-coated tablets are presented as pale yellow to yellow, oval shaped film-coated tablets with with imprint "M" on both sides right and left of the breakline and on the other side the imprints "1" and "0" left and right of the breakline. The tablet is approximately 11.0 mm long, and 5.0 mm wide. The tablet can be divided into equal halves.
Memantine Merz 15 mg film-coated tablets are presented as orange coloured, oval shaped with engravings '15' on one side and 'MEM' on the other side. The tablet is approximately 12.0 mm long, and 6.3 mm wide.
Memantine Merz 20 mg film-coated tablets are presented as pink coloured, oval shaped with engravings '20' on one side and 'MEM' on the other side. The tablet is approximately 13.0 mm long, and 7.0 mm wide.

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

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.

België/Belgique/Belgien
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

България
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

Česká republika
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Danmark
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Lietuva
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Luxembourg/Luxemburg
HANFF Global Health Solutions s.à r.l.
Tél: +352 45 07 07-1

Magyarország
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Malta
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

Deutschland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Eesti
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Ελλάδα
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

España
Merz Therapeutics Iberia, S.L.U.
Tel. +34 91 117 89 17

France
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Hrvatska
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Ireland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Ísland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Italia
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Κύπρος
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Latvija
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Nederland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Norge
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Österreich
Merz Pharma Austria GmbH
Tel.: +43 1 865 88 95

Polska
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

Portugal
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

România
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Slovenija
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Slovenská republika
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Suomi/Finland
Oy H. Lundbeck Ab
Puh/Tel: +358 2 276 5000

Sverige
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

This leaflet was last revised in MM/YYYY.
Detailed information on this medicine is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu.

Package leaflet: Information for the user

Memantine Merz 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.

What is in this leaflet

1. What Memantine Merz is and what it is used for

How does Memantine Merz work
Memantine Merz contains the active substance memantine hydrochloride.
Memantine Merz 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. Memantine Merz belongs to a group of medicines called NMDA-receptor antagonists. Memantine Merz acts on these NMDA-receptors improving the transmission of nerve signals and the memory.

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

2. What you need to know before you take Memantine Merz

Do not take Memantine Merz
- if you are allergic (hypersensitive) to memantine hydrochloride or any of the other ingredients of Memantine Merz tablets (see section 6).

Warning and precautions
Talk to your doctor or pharmacist before taking Memantine Merz
- 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 Memantine Merz 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.

Children and adolescents
Memantine Merz is not recommended for children and adolescents under the age of 18 years.

Other medicines and Memantine Merz
Please tell your doctor or pharmacist if you are taking have recently taken or might takeany other medicines.

In particular, Memantine Merz 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 Memantine Merz.

Memantine Merz 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 tubulary 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
Tell your doctor if you are pregnant or planning to become pregnant. The use of memantine in pregnant women is not recommended.

Breast-Feeding
Women taking Memantine Merz 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, Memantine Merz may change your reactivity, making driving or operating machinery inappropriate.

Memantine Merz contains Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Memantine Merz

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

Dosage
The recommended dose of Memantine Merz for adults and elderly patients 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 Memantine Merz 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
Memantine Merz 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 Memantine Merz as long as it is of benefit to you. Your doctor should assess your treatment on a regular basis.

If you take more Memantine Merz than you should
- In general, taking too much Memantine Merz 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 Memantine Merz, contact your doctor or get medical advice, as you may need medical attention.

If you forget to take Memantine Merz
- If you find you have forgotten to take your dose of Memantine Merz, 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 (may affect up to 1 in 10 users):
- Headache, sleepiness, constipation, elevated liver function tests, dizziness, balance disorders, shortness of breath, high blood pressure and drug hypersensitivity

Uncommon (may affect up to 1 in 100 users):
- Tiredness, fungal infections, confusion, hallucinations, vomiting, abnormal gait, heart failure and venous blood clotting (thrombosis/thromboembolism)

Very rare (may affect up to 1 in 10,000 users):

- 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 Memantine Merz.

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 Memantine Merz

Keep out of the sight and reach of children.

Do not use Memantine Merz 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Content of the pack and other information

What Memantine Merz 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 Memantine Merz looks like and contents of the pack
Memantine Merz film-coated tablets are presented as pink coloured, oval shaped film-coated tablets with engravings ‘20’ on one side and ‘MEM’ on the other side. The tablet is approximately 13.0 mm long, and 7.0 mm wide.

Memantine Merz 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
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.

België/Belgique/Belgien
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

България
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

Česká republika
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Danmark
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Deutschland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Eesti
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Ελλάδα
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

España
Merz Therapeutics Iberia, S.L.U.
Tel. +34 91 117 89 17

France
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Hrvatska
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Ireland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Ísland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Italia
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Lietuva
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Luxembourg/Luxemburg
HANFF Global Health Solutions s.à r.l.
Tél: +352 45 07 07-1

Magyarország
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Malta
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

Nederland
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Norge
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Österreich
Merz Pharma Austria GmbH
Tel.: +43 1 865 88 95

Polska
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

Portugal
Merz Pharmaceuticals GmbH
Tel.: +49 (0)69 1503-0

România
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Slovenija
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Slovenská republika
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Suomi/Finland
Oy H. Lundbeck Ab
Puh/Tel: +358 2 276 5000

Κύπρος
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Latvija
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

Sverige
Merz Pharmaceuticals GmbH
Tel: +49 (0)69 1503-0

This leaflet was last revised in MM/YYYY.
Detailed information on this medicine is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu.