ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz Pharmaceuticals GmbH 10 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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

The tablets can be taken with or without food.

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

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

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

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

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

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

Based on pharmacological considerations and single case reports, caution is recommended with patients suffering from epilepsy.

Concomitant use of N-methyl-D-aspartate(NMDA)-antagonists such as amantadine, ketamine or dextromethorphan should be avoided. These compounds act at the same receptor system as memantine, and therefore adverse drug reactions (mainly CNS-related) may be more frequent or more pronounced (see also section 4.5).

Some factors that may raise urine pH (see section 5.2 “Elimination”) may necessitate careful monitoring of the patient. These factors include drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or a massive ingestion of 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, congestive heart failure (NYHA III-IV), and uncontrolled hypertension were excluded. As a consequence, only limited data are available and patients with these conditions should be closely supervised.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

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

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

4.9 Overdose

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

Treatment of overdosage should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

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

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

After 6 months, the rate of individual responders (response prospectively defined as stabilisation or improvement in two independent domains) was 29% for the memantine group versus 10% for placebo (p=0.004). With a triple criterion (response defined as stabilisation or improvement in all three domains: cognition, functional and global domain), there were 11% responders for memantine versus 6% for placebo (p=0.17).

5.2 Pharmacokinetic properties

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

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

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

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

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

Elimination: Memantine is eliminated in a monoexponential manner with a terminal $t_{½}$ 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.

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

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

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

5.3 Preclinical safety data

In short term studies in rats memantine like other NMDA-antagonists have induced neuronal vacuolisation and necrosis (Olney lesions) only after doses leading to very high peak serum concentrations. Ataxia and other preclinical signs have preceded the vacuolisation and necrosis. As the effects have neither been observed in long term studies in rodents nor in non-rodents, the clinical relevance of these findings is unknown.

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Colloidal anhydrous silica
Talc
Magnesium stearate

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Blister packs containing either 10 or 20 tablets per blister strip (Alu/PP). Pack sizes of 30, 50 or 100 tablets are presented.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Merz Pharmaceuticals GmbH
Eckenheimer Landstr. 100 - 104,
D-60318 Frankfurt/Main
Germany

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz Pharmaceuticals GmbH 10 mg/g oral drops, solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

Oral drops, solution.
The solution is clear and colourless to light yellowish.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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

The drops can be taken with or without food.

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

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

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

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

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

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

Based on pharmacological considerations and single case reports, caution is recommended with patients suffering from epilepsy.

Concomitant use of N-methyl-D-aspartate(NMDA)-antagonists such as amantadine, ketamine or dextromethorphan should be avoided. These compounds act at the same receptor system as memantine, and therefore adverse drug reactions (mainly CNS-related) may be more frequent or more pronounced (see also section 4.5).

Some factors that may raise urine pH (see section 5.2 “Elimination”) may necessitate careful monitoring of the patient. These factors include drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or a massive ingestion of 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, congestive heart failure (NYHA III-IV), and uncontrolled hypertension were excluded. As a consequence, only limited data are available and patients with these conditions should be closely supervised.

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

- The mode of action suggests that the effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with NMDA-antagonists such as memantine. The effects of barbiturates and neuroleptics may be reduced. Concomitant administration of memantine with the antispasmodic agents, dantrolene or baclofen, can modify their effects and a dosage adjustment may be necessary.
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- Other drugs such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine that use the same renal cationic transport system as amantadine may also possibly interact with memantine leading to a potential risk of increased plasma levels.
- There may be a possibility of reduced excretion of hydrochlorothiazide (HCT) when memantine is co-administered with HCT or any combination with HCT.

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

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Preferred term (WHO ART)	*Memantine n=299*	*Placebo n=288*
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Urinary Incontinence	*17 (5.7%)*	*21 (7.3%)*
Diarrhoea	*16 (5.4%)*	*14 (4.9%)*
Insomnia	*16 (5.4%)*	*14 (4.9%)*
Dizziness	*15 (5.0%)*	*8 (2.8%)*
Headache	*15 (5.0%)*	*9 (3.1%)*
Hallucination	*15 (5.0%)*	*6 (2.1%)*
Fall	*14 (4.7%)*	*14 (4.9%)*
Constipation	*12 (4.0%)*	*13 (4.5%)*
Coughing	*12 (4.0%)*	*17 (5.9%)*

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

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

4.9 Overdose

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

Treatment of overdosage should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-dementia drugs, ATC code: N06DX01.
There is increasing evidence that malfunctioning of glutamatergic neurotransmission, in particular at NMDA-receptors, contributes to both expression of symptoms and disease progression in neurodegenerative dementia.

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

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

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

After 6 months, the rate of individual responders (response prospectively defined as stabilisation or improvement in two independent domains) was 29% for the memantine group versus 10% for placebo (p=0.004). With a triple criterion (response defined as stabilisation or improvement in all three domains: cognition, functional and global domain), there were 11% responders for memantine versus 6% for placebo (p=0.17).

5.2 Pharmacokinetic properties

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

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

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

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

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

Elimination: Memantine is eliminated in a monoexponential manner with a terminal $t_{½}$ 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.

Specific patient population: In elderly volunteers with normal and reduced renal function (creatinine clearance of 50 - 100 ml/min/1.73 m²), a significant correlation was observed between creatinine clearance and total renal clearance of memantine (see section 4.2).

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

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

5.3 Preclinical safety data

In short term studies in rats memantine like other NMDA-antagonists have induced neuronal vacuolisation and necrosis (Olney lesions) only after doses leading to very high peak serum concentrations. Ataxia and other preclinical signs have preceded the vacuolisation and necrosis. As the effects have neither been observed in long term studies in rodents nor in non-rodents, the clinical relevance of these findings is unknown.

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potassium sorbate
Sorbitol
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

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

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Merz Pharmaceuticals GmbH
Eckenheimer Landstr. 100 - 104,
D-60318 Frankfurt/Main
Germany

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Merz Pharma GmbH & Co. KGaA
Eckenheimer Landstr. 100 - 104,
D-60318 Frankfurt/Main,
Germany.

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

  Medicinal product subject to medical prescription

- **OTHER CONDITIONS**

  The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

CARTON FOR 30 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz Pharmaceuticals GmbH 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

30 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the enclosed leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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
Postfach 11 13 53,
D-60048 Frankfurt
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

CARTON FOR 50 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz Pharmaceuticals GmbH 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

50 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the enclosed leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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
Postfach 11 13 53,
D-60048 Frankfurt
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

CARTON FOR 100 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz Pharmaceuticals GmbH 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

100 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the enclosed leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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
Postfach 11 13 53,
D-60048 Frankfurt
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz Pharmaceuticals GmbH 10 mg film-coated tablets
Memantine hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Merz Pharmaceuticals GmbH

3. EXPIRY DATE

EXP {MM/YYYY}
See margin stamp.

4. BATCH NUMBER

Lot {number}
See margin stamp.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR 20 g BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz Pharmaceuticals GmbH 10 mg/g oral drops, solution
Memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 g solution (20 drops) contains 10 mg memantine hydrochloride (equivalent to 8.31 mg memantine).

3. LIST OF EXCIPIENTS

The solution also contains potassium sorbate.

4. PHARMACEUTICAL FORM AND CONTENTS

20 g. Oral drops, solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the enclosed leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

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
Postfach 11 13 53,
D-60048 Frankfurt
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR 50 g BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz Pharmaceuticals GmbH 10 mg/g oral drops, solution
Memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 g solution (20 drops) contains 10 mg memantine hydrochloride (equivalent to 8.31 mg memantine).

3. LIST OF EXCIPIENTS

The solution also contains potassium sorbate.

4. PHARMACEUTICAL FORM AND CONTENTS

50 g. Oral drops, solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the enclosed leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

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
Postfach 11 13 53,
D-60048 Frankfurt
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

CARTON AND LABEL FOR 100 g BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Memantine Merz Pharmaceuticals GmbH 10 mg/g oral drops, solution
Memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 g solution (20 drops) contains 10 mg memantine hydrochloride (equivalent to 8.31 mg memantine).

3. LIST OF EXCIPIENTS

The solution also contains potassium sorbate.

4. PHARMACEUTICAL FORM AND CONTENTS

100 g. Oral drops, solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the enclosed leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

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
Postfach 11 13 53,
D-60048 Frankfurt
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Memantine Merz Pharmaceuticals GmbH 10 mg film-coated tablets
Memantine hydrochloride

The active substance is memantine hydrochloride.

The other ingredients are lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, talc and magnesium stearate, all in the tablet core; and methacrylic acid - ethyl acrylate copolymer (1:1), sodium lauryl sulphate, polysorbate 80, talc, triacetin and simethicone emulsion, all in the tablet coating.

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.

1. WHAT MEMANTINE MERZ PHARMACEUTICALS GMBH IS AND WHAT IT IS USED FOR

What Memantine Merz Pharmaceuticals GmbH is:
Memantine Merz Pharmaceuticals GmbH tablets are presented as white to off-white, long shaped, film-coated tablets with a single breakline on both sides. Each tablet contains 10 mg of memantine hydrochloride.

Memantine Merz Pharmaceuticals GmbH tablets are available in blister packs of 30 tablets, 50 tablets or 100 tablets.

What Memantine Merz Pharmaceuticals GmbH is used for:
Memantine Merz Pharmaceuticals GmbH is used for the treatment of patients with moderately severe to severe Alzheimer’s disease.

Memory loss in Alzheimer’s disease is due to a disturbance of message signals in the brain. The brain contains so-called NMDA-receptors that are involved in transmitting nerve signals important in learning and memory. Memantine Merz Pharmaceuticals GmbH belongs to a group of medicines called NMDA-receptor antagonists. Memantine Merz Pharmaceuticals GmbH acts on these NMDA-receptors improving the transmission of nerve signals and the memory.

2. BEFORE YOU TAKE MEMANTINE MERZ PHARMACEUTICALS GMBH

Before taking Memantine Merz Pharmaceuticals GmbH it is important that you read the following sections and discuss any questions you might have with your doctor. Your caregiver may be able to assist you with any details you wish to discuss.

Do not take Memantine Merz Pharmaceuticals GmbH:
- if you are hypersensitive (allergic) to memantine hydrochloride or any of the other ingredients of Memantine Merz Pharmaceuticals GmbH tablets listed above.

Take special care with Memantine Merz Pharmaceuticals GmbH:
- 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.

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

If you suffer from moderate renal impairment, your doctor should closely monitor your kidney function and adapt the memantine doses accordingly. For patients with severe renal impairment, the use of memantine is not recommended.

The use of medicinal products called amantadine, ketamine, dextromethorphan and other NMDA-antagonists at the same time should be avoided.

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

Taking Memantine Merz Pharmaceuticals GmbH 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) or severe infections of the urinary tract, as your doctor may need to adjust the dose of your 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 Pharmaceuticals GmbH 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 Pharmaceuticals GmbH may change your reactivity, making driving or operating machinery inappropriate.

Taking other medicines:
Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines, even those obtained without a prescription.

In particular, the effects of the following medicines may be changed by Memantine Merz Pharmaceuticals GmbH 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).

If you go into hospital, let your doctor know that you are taking Memantine Merz Pharmaceuticals GmbH.

3. HOW TO TAKE MEMANTINE MERZ PHARMACEUTICALS GMBH

Always take Memantine Merz Pharmaceuticals GmbH exactly as your doctor has instructed you. To benefit from your medicine you should take it regularly every day. You should check with your doctor or pharmacist if you are unsure.

Dosage:
The recommended dose of Memantine Merz Pharmaceuticals GmbH for adults and elderly patients is 20 mg (2x 1 tablet) daily. In order to reduce the risk of side effects this dose is achieved gradually by the following daily treatment scheme:

	morning	afternoon or evening
week 1	½ tablet	none
week 2	½ tablet	½ tablet
week 3	1 tablet	½ tablet
week 4 and beyond	1 tablet	1 tablet

The usual starting dose is half a tablet once daily (1x 5 mg) for the first week. This is increased to half a tablet twice a day (2x 5 mg) in the second week and to 1 tablet (1x 10 mg) and half a tablet (1x 5 mg) daily taken in separate doses in the third week. From the fourth week on, the usual dose is 1 tablet twice a day (2x 10 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 Pharmaceuticals GmbH should be administered orally twice a day (except for the first week of treatment). 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 Pharmaceuticals GmbH as long as it is of benefit to you and you do not experience any unacceptable side effects. Your doctor should assess your treatment on a regular basis.

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

If you forget to take Memantine Merz Pharmaceuticals GmbH:
- If you find you have forgotten to take your dose of Memantine Merz Pharmaceuticals GmbH, wait and take your next dose at the usual time.
- Do not take a double dose to make up for the forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Memantine Merz Pharmaceuticals GmbH can have side effects.

In general, observed side effects are mild to moderate. The most common side effects (frequency 2% and less) are hallucinations, confusion, dizziness, headache and tiredness. Uncommon side effects are anxiety, hypertonia (increased muscle tone), vomiting, bladder infections and increased sexual drive.

If you have experienced epileptic seizures, there is a slight possibility that Memantine Merz Pharmaceuticals GmbH may increase the chances of one occurring.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING MEMANTINE MERZ PHARMACEUTICALS GMBH

- Keep out of the reach and sight of children.
- There are no special storage instructions.

Do not use after the expiry date stated on the carton and the blister.

This leaflet was last approved in {MM/YYYY}

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Memantine Merz Pharmaceuticals GmbH 10 mg/g oral drops, solution
Memantine hydrochloride

The active substance is memantine hydrochloride.

The other ingredients are: potassium sorbate, sorbitol, purified water.

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.

1. WHAT MEMANTINE MERZ PHARMACEUTICALS GMBH IS AND WHAT IT IS USED FOR

What Memantine Merz Pharmaceuticals GmbH is:
Memantine Merz Pharmaceuticals GmbH solution is presented as a clear, colourless to light yellowish solution. Each one gram of solution contains 10 mg of memantine hydrochloride.

Memantine Merz Pharmaceuticals GmbH solution is available in bottles of 20 g, 50 g or 100 g.

What Memantine Merz Pharmaceuticals GmbH is used for:
Memantine Merz Pharmaceuticals GmbH is used for the treatment of patients with moderately severe to severe Alzheimer's disease.

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

2. BEFORE YOU TAKE MEMANTINE MERZ PHARMACEUTICALS GMBH

Before taking Memantine Merz Pharmaceuticals GmbH it is important that you read the following sections and discuss any questions you might have with your doctor. Your caregiver may be able to assist you with any details you wish to discuss.

Do not take Memantine Merz Pharmaceuticals GmbH:
- if you are hypersensitive (allergic) to memantine hydrochloride or any of the other ingredients of Memantine Merz Pharmaceuticals GmbH solution listed above.

Take special care with Memantine Merz Pharmaceuticals GmbH:
- 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.

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

If you suffer from moderate renal impairment, your doctor should closely monitor your kidney function and adapt the memantine doses accordingly. For patients with severe renal impairment, the use of memantine is not recommended.

The use of medicinal products called amantadine, ketamine, dextromethorphan and other NMDA-antagonists at the same time should be avoided.

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

Taking Memantine Merz Pharmaceuticals GmbH 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) or severe infections of the urinary tract, as your doctor may need to adjust the dose of your 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 Pharmaceuticals GmbH 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 Pharmaceuticals GmbH may change your reactivity, making driving or operating machinery inappropriate.

Taking other medicines:
Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines, even those obtained without a prescription.

In particular, the effects of the following medicines may be changed by Memantine Merz Pharmaceuticals GmbH 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).

If you go into hospital, let your doctor know that you are taking Memantine Merz Pharmaceuticals GmbH.

3. HOW TO TAKE MEMANTINE MERZ PHARMACEUTICALS GMBH

Always take Memantine Merz Pharmaceuticals GmbH exactly as your doctor has instructed you. To benefit from your medicine you should take it regularly every day. You should check with your doctor or pharmacist if you are unsure.

Dosage:
The recommended dose of Memantine Merz Pharmaceuticals GmbH for adults and elderly patients is 20 mg (2x 20 drops) daily. In order to reduce the risk of side effects this dose is achieved gradually by the following daily treatment scheme:

	morning	afternoon or evening
week 1	10 drops	none
week 2	10 drops	10 drops
week 3	20 drops	10 drops
week 4 and beyond	20 drops	20 drops

The usual starting dose is 10 drops once daily (1x 5 mg) for the first week. This is increased to 10 drops twice a day (2x 5 mg) in the second week and to 20 drops (1x 10 mg) and 10 drops (1x 5 mg) daily taken in separate doses in the third week. From the fourth week on, the usual dose is 20 drops twice a day (2x 10 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 Pharmaceuticals GmbH should be administered orally twice a day (except for the first week of treatment). The drops should be swallowed with some water. The drops can be taken with or without food.

Duration of treatment:
Continue to take Memantine Merz Pharmaceuticals GmbH as long as it is of benefit to you and you do not experience any unacceptable side effects. Your doctor should assess your treatment on a regular basis.

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

If you forget to take Memantine Merz Pharmaceuticals GmbH:

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Memantine Merz Pharmaceuticals GmbH can have side effects.

In general, observed side effects are mild to moderate. The most common side effects (frequency 2% and less) are hallucinations, confusion, dizziness, headache and tiredness. Uncommon side effects are anxiety, hypertonia (increased muscle tone), vomiting, bladder infections and increased sexual drive.

If you have experienced epileptic seizures, there is a slight possibility that Memantine Merz Pharmaceuticals GmbH may increase the chances of one occurring.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING MEMANTINE MERZ PHARMACEUTICALS GMBH

- Keep out of the reach and sight of children.
- Do not store above 30ºC.

Do not use after the expiry date stated on the carton and the bottle label.

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

This leaflet was last approved in {MM/YYYY}