ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Memantine LEK 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, oval film-coated tablet scored in one side.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult 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. 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.

Posology

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.

Special populations

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 LEK is not recommended in patients with severe hepatic impairment.

Paediatric population
The safety and efficacy of Memantine LEK in children aged below 18 years has not been established. No data are available.

Method of administration

Memantine LEK is for oral use.
Memantine LEK 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 active substances 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 medicinal product 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 medicinal products, 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 active substances 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

There are no or limited amount of data from the use of memantine in pregnant women. 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 reactions 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 LEK 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 and 1,595 patients treated with placebo, the overall incidence rate of adverse reactions with memantine 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 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%).

Tabulated list of adverse reactions

The following Adverse Reactions listed in the Table below have been accumulated in clinical studies with memantine and since its introduction in the market.

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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Uncommon	Fungal infections
Immune system disorders	Common	Drug hypersensitivity
Psychiatric disorders	Common Uncommon Uncommon Not known	Somnolence Confusion Hallucinations[1] Psychotic reactions[2]
Nervous system disorders	Common Common Uncommon Very rare	Dizziness Balance disorders Gait abnormal Seizures
Cardiac disorders	Uncommon	Cardiac failure
Vascular disorders	Common Uncommon	Hypertension 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 reactions have been reported in patients treated with memantine.

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 of gastrointestinal origin (vomiting and diarrhoea).

In the most extreme case of overdose, the patient survived the oral intake of a total of 2,000 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.

Management

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: Psychoanaleptics; 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 events 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 coat

Polyvinyl alcohol
Macrogol 3350
Titanium dioxide (E 171)
Talc
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

Aluminium-PVC/PVDC blisters placed into cardboard boxes containing 28, 30, 42, 50, 56, 60, 98, 100 and 112 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pharmathen S.A.
6, Dervenakion str.
15351 Pallini, Attiki
Greece

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/826 /001
EU/1/13/826 /002
EU/1/13/826 /003
EU/1/13/826 /004
EU/1/13/826 /005
EU/1/13/826 /006
EU/1/13/826 /012
EU/1/13/826 /013
EU/1/13/826 /014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 April 2013
Date of latest renewal: 08 January 2018

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Memantine LEK 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Pale red, oval film-coated tablet scored in one side.
The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult 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. 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.

Posology

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 5 mg per day for 7 days.

Week 2 (day 8-14):
The patient should take 10 mg per day for 7 days.

Week 3 (day 15-21):
The patient should take 15 mg per day for 7 days.

From Week 4 on (day 22-28):
The patient should take one 20 mg film-coated tablet (20 mg) per day for 7 days.
The maximum daily dose is 20 mg per day.

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

Special populations
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 LEK is not recommended in patients with severe hepatic impairment.

Paediatric population
The safety and efficacy of Memantine LEK in children aged below 18 years has not been established. No data are available.

Method of administration

Memantine LEK is for oral use.
Memantine LEK 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 active substances 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 medicinal product 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 medicinal products, 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 active substances 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

There are no or limited amount of data from the use of memantine in pregnant women. 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 reactions 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 LEK 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 and 1,595 patients treated with placebo, the overall incidence rate of adverse reactions with memantine 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 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%).

Tabulated list of adverse reactions

The following Adverse Reactions listed in the Table below have been accumulated in clinical studies with memantine and since its introduction in the market.

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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Uncommon	Fungal infections
Immune system disorders	Common	Drug hypersensitivity
Psychiatric disorders	Common Uncommon Uncommon Not known	Somnolence Confusion Hallucinations[1] Psychotic reactions[2]
Nervous system disorders	Common Common Uncommon Very rare	Dizziness Balance disorders Gait abnormal Seizures
Cardiac disorders	Uncommon	Cardiac failure
Vascular disorders	Common Uncommon	Hypertension Venous thrombosis/thromboembolism
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
Hepatobiliary disorders	Common Not known	Elevated liver function test Hepatitis
Gastrointestinal disorders	Common Uncommon Not known	Constipation Vomiting Pancreatitis[2]
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 reactions have been reported in patients treated with memantine.

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 of gastrointestinal origin (vomiting and diarrhoea).

In the most extreme case of overdose, the patient survived the oral intake of a total of 2,000 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.

Management

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: Psychoanaleptics; 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 to100 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 events 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 coat

Polyvinyl alcohol
Macrogol 3350
Titanium dioxide (E 171)
Talc
Iron oxide yellow (E 172)
Iron oxide 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

Aluminium-PVC/PVDC blisters placed into cardboard boxes containing 28, 30, 42, 56, 98 and 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pharmathen S.A.
6, Dervenakion str.
15351 Pallini, Attiki
Greece

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/826 /007
EU/1/13/826 /008
EU/1/13/826 /009
EU/1/13/826 /010
EU/1/13/826 /011
EU/1/13/826 /015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 April 2013
Date of latest renewal: 08 January 2018

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURERS 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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Lek Pharmaceuticals d.d.
Verovškova 57, 1526 Ljubljana
Slovenia

Pharmathen International S.A.
Industrial Park Sapes
Rodopi Prefecture
Block No 5
EL-69300 Rodopi
Greece

Pharmathen S.A.
6 Dervenakion str.
15351 Pallini, Attiki
Greece

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKING

1. NAME OF THE MEDICINAL PRODUCT

Memantine LEK 10 mg film-coated tablets
memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral 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

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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6, Dervenakion str.
15351 Pallini, Attiki
Greece
Tel.: +30 210 66 65 067
Email: info@pharmathen.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/826 /001 28 film-coated tabletsEU/1/13/826 /002 30 film-coated tablets
EU/1/13/826 /003 42 film-coated tablets
EU/1/13/826 /004 50 film-coated tablets
EU/1/13/826 /005 56 film-coated tablets
EU/1/13/826 /006 60 film-coated tablets
EU/1/13/826 /012 98 film-coated tablets
EU/1/13/826 /013 100 film-coated tablets
EU/1/13/826 /014 112 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Memantine LEK 10 mg

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 LEK 10 mg film-coated tablets
memantine hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pharmathen S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKING

1. NAME OF THE MEDICINAL PRODUCT

Memantine LEK 20 mg film-coated tablets
memantine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet.
28 film-coated tablets
30 film-coated tablets
42 film-coated tablets
56 film-coated tablets
98 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral 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

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmathen S.A.
6, Dervenakion str.
15351 Pallini, Attiki
Greece
Tel.: +30 210 66 65 067
Email: info@pharmathen.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/826 /007 28 film-coated tablets
EU/1/13/826 /008 30 film-coated tablets
EU/1/13/826 /009 42 film-coated tablets
EU/1/13/826 /010 56 film-coated tablets
EU/1/13/826 /011 98 film-coated tablets
EU/1/13/826 /015 100 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Memantine LEK 20 mg

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 LEK 20 mg film-coated tablets
memantine hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pharmathen S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Memantine LEK 10 mg film-coated tablets
Memantine LEK 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 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 LEK is and what it is used for

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

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

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

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

Warnings and precautions
Talk to your doctor or pharmacist before taking Memantine LEK
- 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 LEK 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 LEK is not recommended for children and adolescents under the age of 18 years.

Other medicines and Memantine LEK
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription.

In particular, Memantine LEK 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 LEK.

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

Memantine LEK 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 LEK

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

Dose
The recommended dose of Memantine LEK 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:

week 1	half 10 mg tablet
week 2	one 10 mg tablet
week 3	one and a half 10 mg tablets
week 4 and beyond	two 10 mg tablets or one 20 mg tablet once a day

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

Dose 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 LEK 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 LEK as long as it is of benefit to you. Your doctor should assess your treatment on a regular basis.

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

If you forget to take Memantine LEK
- If you find you have forgotten to take your dose of Memantine LEK, 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 people*):*
- 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 people*):*
- 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 people*):*
- 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.

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 LEK

Keep this medicine out of the sight and reach of children.

Do not use this medicine 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 medicine 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. Contents of the pack and other information

What Memantine LEK contains
- The active substance is memantine hydrochloride.
  Each 10 mg tablet contains 10 mg of memantine hydrochloride equivalent to 8.31 mg memantine.
  Each 20 mg tablet contains 20 mg of memantine hydrochloride equivalent to 16.62 mg memantine.

- The other ingredients are:
  Tablet core: croscarmellose sodium, colloidal anhydrous silica, microcrystalline cellulose, magnesium stearate

  10 mg:
  Film-coating: polyvinyl alcohol, titanium dioxide (E-171), talc, macrogol 3350 and iron oxide yellow (E-172)

  20 mg:
  Film-coating: polyvinyl alcohol, titanium dioxide (E-171), talc, macrogol 3350, iron oxide yellow (E-172) and iron oxide red (E-172)

What Memantine LEK looks like and contents of the pack
Memantine LEK 10 mg film-coated tablets are presented as yellow, oval film-coated tablet scored in one side. The tablet can be divided into equal doses.
Memantine LEK 20 mg film-coated tablets are presented as pale red, oval film-coated tablet scored in one side. The score line is not intended for breaking the tablet.

Memantine LEK 10 mg film-coated tablets are available in PVC/PVDC–Aluminium blister packs of 28, 30, 42, 50, 56, 60, 98, 100 and 112 tablets.

Memantine LEK 20 mg film-coated tablets are available in PVC/PVDC–Aluminium blister packs of 28, 30, 42, 56, 98 and 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Pharmathen S.A., 6, Dervenakion str., 15351 Pallini, Attiki, Greece

Manufacturers
Pharmathen S.A , 6, Dervenakion str., 15351 Pallini, Attiki, Greece

Pharmathen International S.A., Industrial Park Sapes, Rodopi Prefecture, Block No 5, Rodopi 69300, Greece
Lek Pharmaceuticals d.d., Verovškova 57, 1526 Ljubljana, Slovenia

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This leaflet was last revised in .

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