Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

PK-Merz film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: amantadine sulphate.
Each film-coated tablet contains 100 mg of amantadine sulphate.

Excipients: Lactose monohydrate, Yellow Orange lacquer (E110): see also chapter 4.4.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Parkinsonian syndromes:

  treatment of symptoms of Parkinson's disease such as rigor, tremor, hypokinesia and akinesia.

4.2 Posology and method of administration

Dosage with single and daily doses:

An ECG (50 mm/s) should be recorded before and 1 and 3 weeks after commencing treatment and the Bazett frequency-corrected QT time (QTc) determined manually. Such an ECG should also be recorded before and 2 weeks after any subsequent dose increase. Further ECG check-ups should then take place at least once a year. Treatment must be avoided or discontinued in patients who show baseline QTc values above 420 ms, an increase of more than 60 ms during treatment with PK-Merz 100 mg film-coated tablets, or a QTc in excess of 480 ms during treatment with PK-Merz 100 mg film-coated tablets, and in patients who show discernible U waves.

By following the above precautions and taking the contraindications listed in section 4.3 into account, the very rare, but life-threatening, side effect torsade de pointes ventricular tachycardia can be prevented.

Treatment of patients with parkinsonian syndromes and drug-related movement disturbances should normally be introduced gradually, with the dose guided by the therapeutic effect.

Treatment should be commenced at a dose of 1 PK-Merz 100 mg film-coated tablet (equivalent to 100 mg amantadine sulphate per day) once daily for the first 4 to 7 days, followed by a once-weekly increase in daily dose of one tablet until the maintenance dose is reached.

The usual effective dose is 1 to 3 PK-Merz 100 mg film-coated tablets twice daily (equivalent to 200-600 mg amantadine sulphate per day).

In elderly patients, particularly those with states of agitation and confusion or delirious syndromes, treatment should be commenced at a lower dose.

If given in combination with other antiparkinsonian drugs, the dosage should be individually adjusted.

In patients previously treated with amantadine infusion solution, a higher starting dose can be chosen.

In the event of an acute worsening of parkinsonian symptoms in the sense of an akinetic crisis, amantadine infusion treatment should be administered.

Dosage in patients with renal impairment:

In patients with renal impairment the dosage must be tailored according to the extent of the decrease in renal clearance (measured as the glomerular filtration rate: GFR), as shown in the following table:

GFR (ml/min)	Dosage (amantadine sulphate)	Dosing interval
80-60	100 mg	every 12 hours
50-30	100 mg	once daily
30-20	200 mg	twice a week
20-10	100 mg	three times a week
< 10 and haemodialysis patients	200 mg and 100 mg	once a week or once every two weeks

* achieved by alternate administration of 1 × 1 and 1 × 2 tablets of 100 mg amantadine sulphate

The glomerular filtration rate (GFR) can be estimated according to the following approximation:

$$Cl_{cr} = \frac{(140 - age) \times weight}{72 \times creatinine}$$

where:

Cl_{cr} = creatinine clearance in ml/min and

creatinine = serum creatinine in mg/100 ml

The creatinine clearance calculated according to this expression applies to men only (the corresponding value in women is approximately 85% of this value) and can be equated to the inulin clearance for determination of the GFR (120 ml/min in adults).

Amantadine is dialysed only slightly (approx. 5%).

Method and duration of administration:

The film-coated tablets are to be taken with a little liquid, preferably in the morning and afternoon. The last daily dose should not be taken later than 4 p.m.

The duration of treatment is guided by the nature and severity of the disease course and is determined by the medical doctor giving treatment. Patients must not discontinue treatment unilaterally.

Abrupt discontinuation of PK-Merz 100 mg film-coated tablets must be avoided, as patients with Parkinson's disease may otherwise experience a severe intensification in extrapyramidal symptoms, sometimes including akinetic crisis, and withdrawal effects sometimes including delirium can occur.

Children:

There has been insufficient experience in children

4.3 Contraindications

PK-Merz 100 mg film-coated tablets must not be used in patients with:

- hypersensitivity to amantadine compounds, Yellow-orange lacquer (E 110) or to any of the excipients of the medicinal product
- severe decompensated heart failure (NYHA class IV)
- cardiomyopathies and myocarditis
- 2nd or 3rd degree AV block
- existing bradycardia under 55 beats/min

- known prolonged QT interval (Bazett QTc > 420 ms) or discernible U-waves or congenital QT syndrome in the family anamnesis
- history of serious ventricular arrhythmias including torsade de pointes
- simultaneous treatment with budipine or other drugs that prolong the QT interval (see section 4.5).
- reduced levels of potassium or magnesium in the blood

PK-Merz 100 mg film-coated tablets may be used only with particular caution in patients with:

- prostatic hypertrophy
- narrow-angle glaucoma
- renal insufficiency (of varying severity; there is a risk of accumulation due to deterioration in renal filtration performance, see also sections 4.2 and 4.4)
- states of agitation or confusion
- delirious syndromes or exogenous psychosis in the anamnesis
- simultaneous treatment with memantine (see section 4.5).

4.4 Special warnings and precautions for use

An ECG (50 mm/s) should be recorded before and 1 and 3 weeks after commencing treatment and the Bazett frequency-corrected QT time (QTc) determined manually. Such an ECG should also be recorded before and 2 weeks after any subsequent increase in dose. Further ECG check-ups should then take place at least once a year. Treatment must be avoided or discontinued in patients who show baseline QTc values above 420 ms, an increase in QTc of more than 60 ms during treatment with PK-Merz 100 mg film-coated tablets, or a QTc time in excess of 480 ms during treatment with PK-Merz 100 mg film-coated tablets, and in patients who show discernible U waves.

Patients at risk of electrolyte imbalances, owing e.g. to treatment with diuretics, frequent vomiting and/or diarrhoea, use of insulin in emergency situations or renal or anorectic conditions must undergo adequate monitoring of laboratory parameters and appropriate electrolyte replacement, particularly for potassium and magnesium.

In the event of symptoms such as palpitations, dizziness or syncope, treatment with PK-Merz 100 mg film-coated tablets must be immediately discontinued and the patient checked within 24 hours for QT prolongation. If no QT prolongation is present, treatment with PK-Merz 100 mg film-coated tablets can be recommenced, taking into account the contraindications and interactions.

In the case of patients with cardiac pacemakers, exact determination of QT times is not possible, therefore the decision on use of PK-Merz 100 mg film-coated tablets must be made on an individual basis in consultation with the patient's cardiologist.

Supplementary administration of amantadine for the prevention and treatment of influenza virus A infection is inadvisable and should be avoided on account of the danger of overdose.

Yellow-orange lacquer (E 110) can trigger allergic reactions.

Lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Special precautions for use:

Patients treated simultaneously with neuroleptic drugs and PK-Merz 100 mg film-coated tablets are at risk of developing life-threatening neuroleptic malignant syndrome if PK-Merz 100 mg film-coated tablets are discontinued abruptly.

Intoxication may occur in patients with renal impairment.

Particular caution is advisable when prescribing PK-Merz 100 mg film-coated tablets to patients with organic brain syndrome or to those who are prone to cerebral seizures, as seizures and intensification of individual symptoms may occur (see sections 4.2 and 4.8).

Patients with known cardiovascular conditions must remain under regular medical monitoring during treatment with PK-Merz 100 mg film-coated tablets.

Patients with Parkinson's disease often exhibit disease symptoms such as low blood pressure, salivation, sweating, elevated body temperature, heat accumulation, fluid retention and depression. In such patients, due consideration should be given to the undesirable effects and interactions of PK-Merz 100 mg film-coated tablets.

The patient should be examined by an ophthalmologist as soon as symptoms such as loss of visual acuity or blurred vision occur, in order to rule out corneal oedema as a possible cause. PK-Merz 100 mg film-coated tablets should be discontinued if corneal oedema is diagnosed. Corneal oedema caused by PK-Merz 100 mg film-coated tablets is generally reversible within a month.

Patients should be asked to consult their doctor if they experience problems when passing urine.

4.5 Interaction with other medicinal products and other forms of interaction

The simultaneous use of amantadine and drugs known to cause prolongation of the QT interval is contraindicated. Examples are:

- certain antiarrhythmic agents of class I A (e.g. quinidine, disopyramide, procainamide) and class III (e.g. amiodarone, sotalol)
- certain antipsychotics (e.g. thioridazine, chlorpromazine, haloperidol, pimozide)
- certain tricyclic and tetracyclic antidepressants (e.g. amitriptyline)
- certain antihistamines (e.g. astemizole, terfenadine)
- certain macrolide antibiotics (e.g. erythromycin, clarithromycin)
- certain gyrase inhibitors (e.g. sparfloxacin)
- azole antimycotics and other drugs such as budipine, halofantrine, co-trimoxazole, pentamidine, cisapride and bepridil.

This list cannot be exhaustive. Before commencing use of amantadine concomitantly with another drug, the SPC of the latter should be checked for potential interactions, due to QT prolongation, between the drug and amantadine.

Use of PK-Merz 100 mg film-coated tablets in combination with other antiparkinsonian drugs is possible. To avoid undesirable effects (such as psychotic reactions), it may be necessary to reduce the dosage of the other drugs or of the combination.

There have been no specific studies on the occurrence of interactions after administration of PK-Merz 100 mg film-coated tablets concomitantly with other antiparkinsonian drugs (e.g. levodopa, bromocriptine, trihexyphenidyl, etc.) or memantine (take note of undesirable effects 4.8).

Simultaneous treatment with PK-Merz 100 mg film-coated tablets and any of the drug types or active substances listed below may lead to the following interactions:

Anticholinergics:
Enhancement of the undesirable effects (confusion and hallucinations) of anticholinergics (e.g. trihexyphenidyl, benzatropine, scopolamine, biperiden, orphenadrine, etc.).

Indirectly CNS-active sympathomimetics:
Potentiation of the central effects of amantadine.

Alcohol:
Lowering of alcohol tolerance.

Levodopa (antiparkinsonian drug):
Mutual potentiation of the therapeutic action. Levodopa can therefore be given concomitantly with PK-Merz 100 mg film-coated tablets.

Memantine (anti-dementia drug):
Memantine can potentiate the effect and undesirable effects of PK-Merz 100 mg film-coated tablets (see section 4.4).

Other drugs:

The simultaneous use of diuretics of the triamterene/hydrochlorothiazide combination type can result in a decrease in the plasma clearance of amantadine, leading to toxic plasma concentrations. Simultaneous use should therefore be avoided.

4.6 Pregnancy and lactation

Pregnancy:

No data are available on placental transfer. There are no adequate data from the use of amantadine in pregnant women. There have been some case reports of healthy births but also of pregnancy complications and five cases of birth defects (cardiovascular defects, limb anomalies). In animal studies, amantadine was shown to be embryotoxic and teratogenic (see section 5.3). The potential risk for humans is not known.
Amantadine may therefore only be used during pregnancy if considered absolutely essential. If therapy is carried out during the 1st trimester, ultrasonography should be performed.
If amantadine is prescribed to a woman of child-bearing age, the patient should be instructed to contact her doctor immediately if she wishes to become pregnant or suspects that she is pregnant.

Lactation:

Amantadine is excreted into the breast milk. If use during lactation is considered absolutely essential, the infant should be kept under observation, due to possible drug-related symptoms (skin rash, urinary retention, vomiting) and weaned if necessary.

4.7 Effects on ability to drive and use machines

Effects on vigilance and accommodation, particularly in association with the effects of other drugs used to treat parkinsonian syndromes, cannot be ruled out. At the beginning of treatment there may consequently be a further deterioration in the ability to drive and operate machinery over and above any impairment caused by the condition itself.

This impairment is further intensified in combination with alcohol.

4.8 Undesirable effects

Assessment of undesirable effects is based on the following frequencies:

Very common:	(≥10%)
Common:	(≥1%, <10%)
Uncommon:	(≥0.1%, <1%)
Rare:	(≥0.01%, <0.1%)
Very rare:	Frequency cannot be estimated from the available data)

Nervous system disorders:
Common: Dizziness
Very rare: Epileptic fits, usually after treatment in excess of the recommended dose; myoclonus, symptoms of peripheral neuropathy

Psychiatric disorders:
Common: Sleep disturbances, motor and psychiatric agitation. Particularly in predisposed elderly patients, paranoid exogenous psychoses accompanied by visual hallucinations may be triggered. Adverse reactions of this type may occur with greater frequency when PK-Merz infusion is given in combination with other antiparkinsonian drugs (e.g. levodopa, bromocriptine) or memantine.

Renal and urinary disorders:
Common: Urinary retention in case of prostatic hypertrophy.

Skin and subcutaneous tissue disorders:
Common: Livedo reticularis (marble skin), sometimes associated with lower-leg and ankle oedema

Gastrointestinal disorders:

Common: Nausea, dry mouth

Cardiac disorders:
Very rare: Cardiac arrhythmias such as ventricular tachycardia, ventricular fibrillation, torsade de pointes and QT prolongation. Most of these cases occurred after overdose or in association with certain drugs or other risk factors for cardiac arrhythmias (see sections 4.3 and 4.5). Cardiac arrhythmias with tachycardia.

Vascular disorders:
Common: Orthostatic dysregulation

Eye disorders:
Rare: Blurred vision*
Very rare: Temporary loss of vision*, increased photosensitivity
Not known: Corneal oedema, reversible after discontinuation
* The patient should be examined by an ophthalmologist as soon as loss of visual acuity or blurred vision occur, in order to rule out corneal oedema as a possible cause (see section 4.4).

Blood and lymphatic system disorders:
Very rare: Haematological side-effects such as leukopenia and thrombocytopenia

Yellow orange lacquer (E 110) may trigger allergic reactions.

4.9 Overdose

Emergency measures, symptoms and antidotes

The possibility of multiple intoxication must always be considered, for example ingestion of more than one drug with suicidal intention.

a) Symptoms of overdose

Acute intoxication is characterised by nausea, vomiting, hyperexcitability, tremor, ataxia, blurred vision, lethargy, depression, dysarthria and cerebral seizures; a malignant cardiac arrhythmia has been reported in one case.

Acute toxic psychoses in the form of states of confusion with visual hallucinations sometimes including coma and myoclonus have been observed after simultaneous administration of amantadine and other antiparkinsonian drugs.

b) Management of overdose

There is no known specific drug treatment or antidote. In the event of intoxication with film-coated tablets, vomiting should be induced and/or gastric lavage performed.

In the event of life-threatening intoxication, intensive care is necessary additionally. Therapeutic measures to be considered include fluid intake and acidification of the urine for more rapid excretion of the substance, and possibly sedation, anticonvulsive measures, and antiarrhythmic agents (lidocaine i.v.).

For the treatment of neurotoxic symptoms (such as those described above), intravenous administration of physostigmine can be tried in adults at a dose of 1-2 mg every 2 hours and in children 2 $\times$ 0.5 mg at intervals of 5-10 minutes up to a maximum dose of 2 mg.

Because of the low dialysability of amantadine (approx. 5%), haemodialysis is not an option.

It is advisable to monitor patients particularly closely for possible QT prolongation and for factors that promote the occurrence of torsade de pointes, e.g. electrolyte imbalances (particularly hypokalaemia and hypomagnesaemia) or bradycardia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-parkinson drugs, *ATC code:* N04BB01

Amantadine has various pharmacological effects. The agent has an indirectly agonistic effect at the striatal dopamine receptor. Animal studies have shown that amantadine increases the extracellular

dopamine concentration both by increased dopamine release and through blockade of re-uptake into the presynaptic neurones. At therapeutic concentrations, amantadine inhibits the release of acetylcholine mediated by NMDA receptors and can thus trigger anticholinergic effects. The agent has synergistic effects with L-dopa.

5.2 Pharmacokinetic properties

Absorption:

Amantadine hydrochloride undergoes rapid and complete absorption from the gastrointestinal tract after oral administration.

Plasma concentration, elimination:

Peak plasma concentrations are reached approximately 2 and 8 hours (t_{max}) after administration of a single dose. The freely soluble amantadine hydrochloride gives higher peak plasma amantadine concentrations than the more sparingly soluble amantadine sulphate, for which the peak plasma concentration (C_{max}) is reached later than that of the hydrochloride. After a single oral dose of 250 mg amantadine hydrochloride, a C_{max} of 0.5 µg/ml is attained.

At a dosage of 200 mg/day steady state is reached after 4-7 days, with plasma concentrations of 400-900 ng/ml. After administration of 100 mg amantadine sulphate C_{max} is 0.15 µg/ml.

The total amount of active substance absorbed (AUC) is the same for the two amantadine salts. Plasma clearance was found to be identical to renal clearance, at 17.7 $\pm$ 10 L/h in healthy elderly volunteers. The apparent volume of distribution (4.2 $\pm$ 1.9 L/kg) is age-dependent; in the elderly it is 6.0 L/kg.

The elimination half-life is between 10 and 30 hours, with a mean of approximately 15 hours, and is largely dependent on the age of the patient. Elderly male patients (62-72 years) show an elimination half-life of 30 hours. In patients with renal insufficiency, the terminal plasma half-life may be substantially prolonged, to 68 $\pm$ 10 hours.
In vitro, amantadine is approximately 67% plasma-protein bound; approximately 33% is present in plasma in the unbound form. It overcomes the blood-brain barrier by virtue of a saturatable transporter system.

Amantadine is excreted in the urine almost completely unchanged (90% of a single dose), small amounts being excreted in the faeces.

The dialysability of amantadine hydrochloride is low, at some 5% for a single dialysis.

Metabolism:

Amantadine is not metabolised in humans.

5.3 Preclinical safety data

Amantadine has effects on cardiac electrophysiology, including prolongation of the action potential duration through inhibition of the influx of repolarising potassium ions. In humans too, in rare cases, these effects can result in particular types of cardiac arrhythmia (apical reciprocating tachycardia or torsade de pointes arrhythmia).

Chronic toxicity studies primarily revealed CNS-stimulating effects. In dogs and monkeys extrasystoles were observed in isolated cases and in dogs slight fatty infiltration of the myocardium was also seen.

A mutagenicity study with established in-vitro and in-vivo tests did not produce evidence of any genotoxic potential of amantadine.

No long-term carcinogenicity studies have been performed for amantadine.

In embryotoxicity studies in rats, mice and rabbits, only rats showed embryolethal effects and malformations at high doses. Oedema, malposition of the back legs and skeletal abnormalities were observed with increased frequency. Effects on fertility have been insufficiently investigated; there is evidence in rats of impairment of fertility.

No investigations have been performed into the perinatal/postnatal period.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Potato starch
Gelatin
Povidone
Talc
silica, colloidal anhydrous
Magnesium stearate
Croscarmellose sodium
Butylmethacrylat-(2-dimethyl-aminoethyl)-methacrylate-methyl-methacrylate-copolymer (1:2:1)
Yellow-orange lacquer (E 110)
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.
This medicine should not be used after the expiry date

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

Polypropylene/Aluminium blisters containing 10, 30, or 100 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Megapharm Ltd. P.O.Box 519 Hod Hasharon 45105 Israel

8. MANUFACTURER

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9. MARKETING AUTHORISATION NUMBER

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