Physician's Prescribing Information

1. Name of the Medicinal Product

PK-Merz Infusion

0.4 mg/ml, Solution for injection

2. Qualitative and Quantitative Composition:

Active substance: Amantadine sulphate
One infusion bottle container of 500 ml solution for infusion contains:
200 mg Amantadine sulphate.
For a full list of excipiants: Sodium chloride, see section 6.1
Water for Injections

3. Pharmaceutical Form

Solution for infusion

4. Clinical Particulars

4.1 Therapeutic indications

For the treatment of parkinsonism which does not respond to oral treatment

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 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 of more than 60 ms during treatment with PK-Merz infusion, or a QTc time in excess of 480 ms during treatment with PK-Merz infusion, 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 the undesirable effect of Torsades-de-Pointes can be prevented.

Parkinson's syndromes:

In the event of an acute exacerbation in parkinsonian symptoms in the sense of an akinetic crisis, intravenous doses of 200 mg amantadine sulphate in 500 ml of solution should be administered 1-3 times a day.

The rate of infusion should not exceed 55 drops/min, equivalent to an infusion time of approximately 3 hours.

Decreased vigilance:

To improve vigilance in post-comatose states of varying aetiology, a therapy with a daily dose of 200 mg amantadine sulphate given as a slow infusion (> 3 hours) can be tried for an initial period of 3-5 days. Depending on the clinical course, treatment can then be continued –
if possible with oral dosage forms - for up to 4 weeks at a dose of 200 mg amantadine sulphate per day.

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 sulfate 200 mg/500 ml)	Dosing interval
80-60	100 mg	every 12 hours
60-50	200 mg and 100 mg	on alternate days
50-30	100 mg	once daily
30-20	200 mg	twice a week
20-10	100 mg	three times a week
< 10 and haemodialysis	200 mg and 100 mg	once a week or once every two weeks

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 dialyzed only slightly (approx. 5%).

Method and duration of administration:

Intravenous use:

Abrupt discontinuation of PK-Merz infusion must be avoided, as Parkinson patients may otherwise experience a severe intensification in extrapyramidal symptoms sometimes including akinetic crisis, and duration effects sometimes including delirium can occur.

The duration of use when continuing treatment with oral dosage forms, in patients with decreased vigilance, (See section 4.1 and 4.2) should not exceed 4 weeks**.**

Children:

There has been insufficient experience in children.

4.3 Contraindications

PK-Merz infusion must not be used in patients with:

- Hypersensitivity to amantadine or to any of the other constituents excipiants of the medicinal product
- Severe decompensated heart failure (NYHA stage IV)
- Cardiomyopathies and myocarditis
- Grade II or III AV block
- Existing bradycardia under 55 beats/minute
- Known prolonged QT interval (Bazett QTc > 420 ms) or discernible U waves or congenital QT syndrome in familial history
- History of serious ventricular arrhythmias including Torsades-de-Pointes
- Concurrent treatment with budipine or other drugs that prolong the QT interval (see section 4.5).

Reduced blood levels of Potassium or Magnesium.

PK-Merz infusion should not be used in:

- Severe renal insufficiency (creatinine clearance < 10 ml/min).

PK-Merz infusion may be used only with particular caution in patients with:

- Prostate hypertrophy

- Narrow angle glaucoma

-Renal insufficiency (of varying severity; risk of accumulation due to deterioration in renal

filtration performance (see section 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 special precautions for use

An ECG (50 mm/s) should be recorded before 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 under treatment with PK-Merz infusion, or a QTc time in excess of 480 ms during treatment with PK-Merz infusion, and in patients who show discernible U waves.

Patients at risk of electrolyte imbalances due to for example, treatment with diuretics, frequent vomiting and/or diarrhea, use of insulin in emergency situations, 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 infusion should be immediately discontinued and the patient checked within 24 hours for QT prolongation. If no QT prolongation is present, PK-Merz infusion can be recommenced, taking into account the contraindications and interactions.

In patients with cardiac pacemakers, exact determination of QT time is not possible, therefore the decision to use PK-Merz infusion must be made on an individual basis in consultation with the patient's cardiologist.

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

Special precautions for use:

Patients treated simultaneously with neuroleptic drugs and PK-Merz infusion are at risk of developing life-threatening malignant neuroleptic syndrome, if PK-Merz infusion is discontinued abruptly.

Intoxication may occur in patients with renal impairment.

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

Patients with known cardiovascular conditions must remain under regular clinical monitoring during treatment with PK-Merz infusion.

Patient with Parkinson often exhibit clinical symptoms such as low blood pressure, salivation, sweating, elevated body temperature, heat accumulation, fluid retention and depression. In such patient, due consideration should be given of the undesirable effects and interactions of PK-Merz infusion.

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 infusion should be discontinued if corneal oedema is diagnosed. Corneal oedema caused by PK-Merz infusion is generally reversible with a month.

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

An infusion bottle with 500 ml solution for infusion cantains 77 mmol Sodium (1770 mg Sodium). This should be taken into account in people on a low-salt diet.

4.5 Interaction with other medicaments and other forms of interaction

The simultaneous use of Amantadine and drugs known to cause prolongation of the QT interval is contraindicated.
For example:

- Certain antiarrythmic agents of class 1A (e.g, quinidine, disopyramide and procainamide) and class 3 (e.g. amiodarone and sotalol)
- Certain antipsychotics (e.g. thioridazine, chlorpromazine, haloperidol and pimozide)
- Certain tricyclic and tetracyclic antidepressants (e.g. amitriptiline)
- Certain antihistamines (e.g. astemizole and terfenadine)
- Certain macrolide antibiotics (e.g. erythromycin and clarithromicin)
- Certain gyrase inhibitors (e.g. sparfloxacin)
- Azole antimycotics and other drugs such as budipine, halofantrine, co-trimoxazole, peptamidine, cisapride and bepridil)

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

Use of PK-Merz infusion in combination with other Parkinsonian drugs is possible. To avoid undesirable effects (such as psychotic reactions), it may be necessary to reduce the dosage of the other drug or of the combination.

There have been no specific studies of the occurrence of interactions after administration of PK-Merz infusion alongside other antiparkinsonian drugs (e.g. levodopa, bromocriptine, trihexyphenidyl, etc.) or memantine (see Undesirable effects, section 4.8).

Simultaneous treatment with PK-Merz infusion and any of the drug types or active substances listed below can result in the following interactions:

Anticholinergics:

Enhancement of the undesirable effects (confusion and hallucinations) of anticholinergics (e.g. trihexyphenidyl, benztropine, 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 with PK-Merz infusion.

Memantine (anti-dementa drug):

Memantine can potentiate the effect and side effects of PK-Merz infusion (See section 4.3).

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 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 Parkinson's syndrome – 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 applies in particular to use in conjunction with the consumption of alcohol.

4.8 Undesirable effects

Assessment of undesirable effects is based on the following frequencies:

Very common:	**(≥1/10)**
Common:	**(≥1/100, <1/10)**
Uncommon:	**(≥1/1000, <1/100)**
Rare:	**(≥1/10000, <1/1000)**
Very rare:	**(<1/10000), not known (cannot be estimated from the available data)**

Blood and lymphatic system disorders

Very rarely during treatment with amantadine, haematological side effects, such as leukopenia and thrombocytopenia, have been reported.

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 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 are 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 and dry mouth.

Cardiac disorders:
Very rare reports of 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.

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

The above undesirable effects have been reported less frequently following infusion therapy.

Immune system disorders:
Very rare: Anaphylactic reactions after infusion therapy have been reported.

4.9 Overdose

Emergency and lymphatic system disorders:

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 characterized by nausea, vomiting, hyperexcitability, tremor, ataxia, blurred vision, lethargy, depression, dysarthria, and cerebral seizures; 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 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, possibly sedation, anticonvulsive measures and antiarrhythmics (lidocaine i.v.).

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

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

It is advisable to monitor patients particularly closely for possible QT prolongation and for factors that promote the occurrence of Torsades-de-Pointes, e.g. electrolyte imbalances (particularly hypokalemia and hypomagnesemia) and bradycardia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Parkinson Drug ATC code: NO4BB01

Pharmacological properties:

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 rte-uptake into the presynaptic neurons. 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

Plasma concentration, elimination:

Pick plasma concentrations are reached about 2-8 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 h. In patients with renal insufficiency the terminal plasma half-life may be substantially prolonged, to 68 $\pm$ 10 h.

Administration as an infusion:
Infusion of 200 mg amantadine sulphate over a 3-hours period resulted in a mean plasma concentration of 0.54 µg/ml. After treatment at a dose of 200 mg/day a mean plasma concentration of 0.76 µg/ml was reached at the end of the infusion on day 6. The mean total clearance was calculated at 3.6 L/hours; the plasma half-life ranged from 7 to 23 hours with a mean of approximately 10 hours.

In vitro: Amantadine is approximately 67% plasma protein bound approximately 33% are present in plasma in an unbound form. It overcomes the blood-brain barrier by virtue of a saturatable transporter system.

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

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

Metabolism:

Amantadine is not metabolized 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 reveal evidence of any genotoxic potential of amantadine.

No long-term studies of the carcinogenicity of amantadine have been carried out.

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.

Local tolerability:
Local tolerability of the solution for infusion in humans is good.

6. Pharmaceutical Particulars

6.1 List of excipients

Sodium chloride

Water for injection

6.2 Incompetabilities

Compatibility studies have not been performed.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C

After opening, the solution remains should be discarded

6.5 Nature and contents of container

PK-Merz infusion is available in packs containing 2 X 500 ml solution for infusion.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. Manufacturer

Merz Pharma GmbH & CO KgaA,
Eckenheimer 100-104 Frankfurt am Main, Germany

8. Marketing Authorization Holder

Megapharm Ltd. POB 519 Hod Hasharon , 45105

9. Marketing Authorization Number

137 44 27102 00

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