130 mm

PK-Merz® Tablet 100 mg

AMANTADINE SULPHATE 100 mg

Direction for use, please read carefully!

Composition:
One film-coated tablet contains:
Active ingredient: Amantadine sulphate 100 mg.
Excipients: Lactose monohydrate, microcrystalline cellulose, potato starch, gelatine, povidone, talc, colloidal silicon dioxide, magnesium stearate, croscarmellose sodium, eudragit E, yellow-orange S and titanium dioxide.

Product Description:
Biconvex film-coated tablet with dividing groove on one side.

Route of administration:
Oral route

Pharmacodynamics:

Pharmacotherapeutic group:
Anti-Parkinson Drug

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 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.

Pharmacokinetics:

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

Plasma concentration, elimination:
Maximum plasma concentration are reached about 2 and 8 hours (tmax) 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 (Cmax) is reached later than that of the hydrochloride. After a single oral dose of 250 mg amantadine hydrochloride, a Cmax of 0.5 mcg/ml is attained. At a dose of 200 mcg/ml steady state is reached after 4 – 7 days, with plasma concentration of 400 – 900 ng /ml. After administration of 100 mg amantadine sulphate Cmax is 0.15 mcg/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 ± 10 l/h in healthy elderly volunteers. The apparent volume of distribution (4.2 ± 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, on average 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 ± 10 hours.

Amantadine is bound to plasma proteins at approximately 67 % (in vitro); approximately 33 % are present in plasma in the unbound form. It overcomes the blood-brain barrier by virtue of a saturatable transporter system.

Amantadine is excreted with the urine almost completely unchanged (90 % of a single dose), small amounts being excreted with the faeces.
The dialysability of amantadine hydrochloride is low, at some 5 % for a single dialysis.

Metabolism:
Amantadine is not metabolized in humans.

Indications:
PK-Merz film-coated tablet is effective against all symptoms of Parkinson's disease such as rigidity, tremor and hypo- or akinesia as well as against residual symptoms and complaints after stereotactic operations.

Contra-indications:
PK-Merz film-coated tablets must not be used in patients with:
– hypersensitivity to amantadine compound, Yellow-orange S (E 110) or to any of the excipients.
– severe decompensated heart failure (stage NYHA IV),
– cardiomyopathies and myocarditis (disease of the cardiac muscles),
– 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 torsades de pointes and
– reduced levels of potassium or magnesium in the blood.
PK-Merz film-coated tablets may be used only with particular caution in patients with:
– prostatic hypertrophy,
– narrow angle glaucoma,
– renal insufficiency (of varying severity; risk of accumulation due to deterioration in renal filtration performance),
– states of agitation or confusion and
– delirious syndromes or exogenous psychosis in the anamnesis.
– simultaneous treatment with memantine.

Warning and Precautions

Warnings:
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 under treatment with PK-Merz 100 mg film-coated tablets, or a QTc time in excess of 480 ms under 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, the 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 prevention and treatment of influenza virus A infection is inadvisable and should be avoided on account of the danger of overdose.

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

Lactose: Patients with rare hereditary problems of galactose intolerance, total 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 malignant neuroleptic 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 who are prone to seizures, as seizures and intensification of individual symptoms may occur.

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

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

If blurred vision or other visual problems occur an ophthalmologist should be contacted to exclude corneal oedema. In case that corneal oedema is diagnosed treatment with amantadine should be discontinued.

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

Cases of suicidal ideation and behaviour have been reported during treatment with amantadine. Patients should be monitored for signs of suicidal ideation and behaviour and treatment initiated as needed. Patients (and caregivers of patients) should be advised to seek medical advice if any signs of suicidal ideation or behaviour emerge.

Impulse control disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders, including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with products with a dopaminergic effect, including PK-Merz 100 mg film-coated tablets. Dose reduction or tapered discontinuation should be considered if such symptoms develop.

Side effects:
The following table is used to explain this section:

Very common	More than 1 from 10 patients
Common	More than 1 from 100 patients
Uncommon	More than 1 from 1000 patients
Rare	More than 1 from 10000 patients
Very rare	1 or less from 10000 patients and in very rare cases
Not known	(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 is given in combination with other antiparkinsonian drugs (e.g. levodopa, bromocriptine) or memantine.

Not known: Impulse control disorders e.g. pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with products with a dopaminergic effect, including PK-Merz 100 mg film-coated tablets

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. Cardiac arrhythmias with tachycardia.

Vascular disorders:
Common: Orthostatic dysregulation

Eye disorders:
Uncommon: Blurred vision
Rare: Corneal lesion, e.g. punctate subepthelial opacities which might be associated with superficial punctate keratitis, corneal epithelial oedema, and markedly reduced visual acuity.

Very rare: Temporary loss of vision*, increased photosensitivity

*) The patient should be examined by an ophthalmologist as soon as loss of visual acuity or blurred vision occurs, 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
Yellow orange S (E 110) may trigger allergic reactions.

MC 306

75 mm

594 mm

75 mm

MC 306

units: mm
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140

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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.

Interaction with other drugs:
The simultaneous use of amantadine and drugs known to cause prolongation of the QT interval is contra-indicated. 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) and
– azole antimycotics and other drugs such as budipine, halofantrine, co-trimoxazole, pentamidine, cisapride, and bepridil.

This list may be in-exhaustive. Before commencing use of another drug concomitantly with amantadine, this patients information leaflet should be thoroughly checked for potential interactions due to QT prolongation, between the drug and amantadine.
Use of PK-Merz film-coated tablets in combination with other antiparkinsonian drugs is possible. To avoid side 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 on the occurrence of interactions after administration of PK-Merz film-coated tablets concomitantly with other antiparkinsonian drugs (e.g. levodopa, bromocriptine, trihexyphenidyl, etc.) or memantine (take note of side effects).
Simultaneous treatment with PK-Merz 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, benztropine, scopolamine, biperiden, orphenadrine, etc.) may be intensified if they are administered concomitantly with PK-Merz film-coated tablets.
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 PK-Merz film-coated tablets.
Memantine: Memantine can potentiate the effect and side effects of PK-Merz film-coated tablets.
Other drugs: The simultaneous use of diuretics of the triamterene/hydrochlorothiazide type can result in a decrease in the plasma clearance of amantadine, leading to toxic plasma concentrations. Simultaneous use should therefore be avoided.

Precautionary measures for application and warning:
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 under treatment with PK-Merz film-coated tablets, or a QTc time in excess of 480 ms under treatment with PK-Merz, 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 film-coated tablets must be immediately discontinued and the patient checked within 24 hours for QT prolongation. If no QT prolongation is present, the treatment with PK-Merz 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 film-coated tablets 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.

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. On commencement 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.

Pregnancy and Lactation

Pregnancy:
Fertility
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.

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. 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.

Breast-feeding:
Amantadine is excreted into 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.

Dosage and method of administration:
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).

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

Combination therapy
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
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 patients	200 mg and 100 mg	once a week or once every two weeks

*) achieved by administering 1 × 1 and 1 × 2 tablets of 100 mg amantadine sulphate alternately

The following approximation may be used to estimate the glomerular filtration rate (GFR):

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

where Cl_{cr} = creatinine clearance in ml/min and
creatinine = serum creatinine in mg/100 ml

The creatinine clearance value calculated in this way applies to men (the corresponding value for women is approx. 85 % of this value) and may be equated to inulin clearance for GFR calculations (120 ml/min in adults). Amantadine is only partially dialyzable (approx. 5 %).

Method 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.

Paedatric population
The safety and efficacy of PK-Merz 100 mg film-coated tablets in children has not been established. No data are available.

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

Symptoms of overdose:
Acute intoxication is characterized by nausea, vomiting, hyper-excitability, 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.

Management of overdose:
There is no known specific drug treatment or antidote. In the event of intoxication with PK-Merz 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 antiarrhythmics (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 x 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 %), 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) or bradycardia.

Note:
Do not store above 25 °C.
Do not use PK-Merz film-coated tablets after the expiry date stated on the carton and the blister.

Keep all drugs out of the reach of children!

Manufacturer:
Merz Pharma GmbH & Co. KGaA
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64354 Reinheim, Germany

Legal address:
Eckenheimer Landstraße 100
60318 Frankfurt/Main, Germany

Presentation and package size:
Packs of 30 and 100 film-coated tablets.

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