1. NAME OF THE DRUG

AMANDIN 100
Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Amantadine-hemisulphate

AMANDIN100:
1 film-coated tablet contains 100mg Amantadine-hemisulphate

Other ingredients: Lactose monohydrate, Orange-yellow S (E 110)

For the complete list of the other ingredients, see Section 6.1

3. DOSAGE FORM

Film-coated tablets
AMANDIN 100

Film coated tablets are round, orange and biconvex with a score on one side. The film-coated tablet can be divided in two equal halves.

4. CLINICAL INFORMATION

4.1 Indication

Parkinson's syndromes:

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

4.2 Dosage, type and duration of treatment

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 AMANDIN 100 film-coated tablets, or a QTc in excess of 480 ms during treatment with AMANDIN 100 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.

Amantadine-hemisulphate tablets are not interchangeable with Amantadine hydrochloride tablets.
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 AMANDIN 100 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 AMANDIN100 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
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 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:

Amandin- 100 can be divided into halves.

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 AMANDIN 100 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

- Hypersensitivity to Amantadine compounds, Orange-yellow S (E 110) or any of the other ingredients (see section 6.1).

- Severe uncompensated heart failure (NYHA class IV),
- Cardiomyopathies and myocarditis,
- 2nd or 3rd degree AV block,
- Previously known bradycardia below 55 beats/min,
- Known prolonged QT interval (QTc according to Bazett > 420 ms) or detectable U-waves or congenital QT syndrome in the family anamnesis,
- History of major ventricular arrhythmias including TdP (“twisting of the peaks”),
- Concomitant treatment with budipine or other QT-prolonging drugs (see Section 4.5),
- Reduction of potassium and magnesium in the blood.

4.4 Special warnings and precautions for use

- AMANDIN 100 should be used only with extreme caution in patients with:
- Prostatic hypertrophy,
- Narrow-angle glaucoma,
- Renal insufficiency (different degrees of severity, there is a risk of accumulation due to a deterioration in the filtration performance of the kidneys, see dosage and other information),
- State of excitement and confusion,
- Delirious syndromes, as well as exogenous psychoses in the anamnesis.
- AMANDIN 100 should be used with particular caution in patients treated with memantine (see Section 4.5).

Other notes:

Special precautions for use:

- Patients treated with neuroleptics and AMANDINE 100 concurrently are at risk of developing a life-threatening neuroleptic malignant syndrome, if AMANDIN 100 is suddenly discontinued.
- Disturbed kidney function can lead to intoxication.
- In patients with an organic brain psycho-syndrome, as well as cerebral seizure disorders in the anamnesis, the use of AMANDIN 100 requires special care, as individual disease symptoms may worsen and seizures may occur (see side effects, dosage).
- Patients with known cardiovascular disease should be under regular medical supervision during concomitant treatment with AMANDIN 100. As soon as symptoms such as palpitations, dizziness or syncope appear, amantadine must be discontinued and the patient should be examined within 24 hours for a possible QT prolongation. If there is no QT prolongation, amantadine can be resumed taking into account contraindications and interactions (see Section 4.8).
- In patients with Parkinson's disease, symptoms, such as low blood pressure, salivation, sweating, increased body temperature, heat congestion, water retention and depressive mood are often observed. They should be treated with Amantadine-neuraxpharm 100 mg AMANDIN 100, taking into account the side effects and interactions.
- Patients should be asked to consult the doctor if they experience any discomfort during urination.

***Impulse control disorders*:**

Patients should be monitored regularly for the development of impulse control disorders. Patients and their caregivers should be advised that behavioral symptoms of impulse control disorders, including gambling addiction, increased libido, hyper-sexuality, the compulsive spending of

money or shopping addiction, as well as binge eating and compulsive eating, may occur in patients on treatment with dopaminergic drugs, including AMANDIN 100. When developing these symptoms, consider reducing the dose or tapering the treatment.

If blurred vision or other visual disturbances occur, an ophthalmologist should be consulted to rule out corneal edema. If corneal edema is diagnosed, treatment with amantadine should be discontinued

Driving and using machines:

Effects on the attention and alertness (vigilance) and adjustment of the eye with regard to the eyesight (accommodation) cannot be ruled out, also in conjunction with other means for the treatment of Parkinson's syndrome. At the beginning of the treatment, it may therefore come - in addition to the illness-related restrictions - to a reduction in the ability to drive and the ability to operate machines.

You might not be able to react promptly and efficiently enough to unexpected or sudden events. Hence, you should not drive a car or other vehicles and/or operate electrical equipment or machinery without prior consultation with your doctor. Please note in particular that alcohol further reduces your ability to drive.

Warnings:

This medicine contains lactose. Patients with rare hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take AMANDIN 100.

Orange-yellow S (E 110) can cause an allergic reaction.

4.5 Interactions with other drugs and other interactions

- Concomitant use of Amantadine with other known drugs known to prolong the QT intervals is contraindicated. Examples are:
- Certain class I A antiarrhythmic drugs (such as quinidine, disopyramide, procainamide) and of class III (such as amiodarone, sotalol),
- Certain antipsychotics (such as thioridazine, chlorpromazine, haloperidol, pimozide),
- Certain tri- and tetracyclic antidepressants (such as, for example, amitriptyline),
- Certain antihistamines (such as, for example, astemizole, terfenadine),
- Certain macrolide antibiotics (such as erythromycin, clarithromycin),
- Certain gyrase inhibitors (such as, for example, sparfloxacin),
- Azole antimycotics and other drugs such as budipine, halofantrine, cotrimoxazole, pentamidine, cisapride or bepridil.

This list cannot be complete. Before the concomitant use of Amantadine with another drug, its Subject Information should be reviewed for possible interaction by QT prolongation between this medication and Amantadine.

It is possible to combine AMANDIN 100 with other anti-Parkinson drugs. To avoid side effects (such as psychotic reactions), a dose reduction of the other drugs or the combination may become necessary.

There are no specific studies on the occurrence of interactions following the administration of Amantadine with other anti-Parkinson drugs (for example levodopa, bromocriptine, memantine, trihexyphenidyl, etc.) (Check side effects).

Concomitant therapy with AMANDIN 100 and the drug groups or active substances listed below, may cause the following interactions:

Anticholinergics:

Increase of side effects of the anticholinergic drugs (states of confusion and hallucinations) in combination with, for example, trihexyphenidyl, benzatropine, scopolamine, biperiden, orphenadrine, etc.

Indirect centrally active sympathomimetics:

Increase of the central effect of Amantadine.

Alcohol:

Decreased alcohol tolerance.

Levodopa (anti-Parkinson drug):

Mutual increase of the therapeutic effect. Levodopa can therefore be combined with AMANDIN 100.

Other anti-Parkinson drugs:

Memantine can increase the effect and side effects of AMANDIN100 (see Contraindications).

Other drugs:

Concomitant administration of diuretics of the triamterene /hydrochlorothiazide combination type can decrease the plasma clearance of Amantadine and lead to toxic plasma concentrations. A concomitant administration should therefore be avoided.

4.6 Pregnancy and Breast-feeding

Pregnancy

No data is available on placental transfer. There is no adequate data concerning the use of Amantadine in pregnant women. There are some case reports of healthy children, but also pregnancy complications and five malformations (cardiovascular defects, limb reduction) have been reported. Amantadine has been shown to be embryo-toxic and teratogenic in animal studies (see Section 5.3). The potential risk for humans is unknown.

Therefore, Amantadine may only be taken during pregnancy, if this is absolutely necessary. If therapy is given in the 1st trimester, thorough ultrasound evaluation should be performed.

If Amantadine is prescribed to a woman with childbearing potential, she should be advised to contact her doctor immediately, if she wishes to get pregnant or suspects a pregnancy.

Breast-feeding

Amantadine is transferred to breast milk. If medication is mandatory during breastfeeding, the infant should be monitored for possible drug effects (skin rash, urinary retention, vomiting). If necessary, weaning should be considered.

4.7 Effects on the ability to drive and using machines

Effects on alertness and accommodation cannot be excluded - also in conjunction with other means for the treatment of Parkinson's syndrome. At the beginning of the treatment, it may therefore come - in addition to the illness-related restrictions - to a reduction in the ability to drive and the ability to operate machines.

This is especially true in combination with alcohol.

4.8 Side effects

The evaluation of side effects is based on the following frequencies.:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1000 to <1/100)
Rare (≥ 1/10, 000 to < 1/1000)
Very rare (<1/10,000) and not known (frequency cannot be estimated using the available

Frequently, sleep disorders, motor and mental restlessness, urinary retention in prostatic hypertrophy may occur.

Particularly in elderly predisposed patients, delusional (paranoid) exogenous psychoses associated with visual hallucinations, can be elicited. These undesirable effects can occur more *frequently* when AMANDIN 100 is combined with other anti-Parkinson drugs (e.g. levodopa, bromocriptine, memantine).

Frequently, the development of a livedo reticularis (picture of a "marbled skin"), sometimes associated with accumulations of water in the ankle and lower leg area, can also be observed.

Frequent events are nausea, dizziness, dry mouth, orthostatic deregulation.

Occasional: blurred vision

Rare cases of transient visual loss and blurred vision have been reported, caused by corneal edema. In such cases, treatment with Amantadine should be stopped.

Rare: corneal lesion, e.g. punctate, sub-epithelial clouding, which might be associated with superficial punctate keratitis, corneal epithelium edema, and markedly reduced visual acuity.

Very rare are hematological side effects, such as leukopenia and thrombocytopenia reported during treatment with amantadine.

Very rare reports included cardiac arrhythmias, such as ventricular tachycardia, ventricular fibrillation, TdP and QT prolongation. In most of these cases, overdoses, certain co-medications or risk factors for cardiac arrhythmias were present (see Sections 4.3 and 4.5).

Very rarely reported are increased photosensitivity and cardiac arrhythmias with increased heart rate. Furthermore, isolated cases of epileptic seizures, usually associated with higher doses than recommended, were reported.

Very rarely, myoclonus and symptoms of peripheral neuropathy have been described.

Very rarely, suicide attempts have been reported in amantadine treated patients - even in the case of short-term prophylaxis or treatment of viral influenza A.

Unknown (frequency cannot be estimated from the available data)

Impulse control disorders:

Gambling addiction, increased libido, hyper-sexuality, compulsive spending of money or shopping addiction, and binge eating and compulsive eating may occur in patients on dopamine-mediated drugs, including AMANDIN 100 (see Section 4.4).

Orange yellow S (E 110) can cause an allergic reaction.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Emergency measures, symptoms and antidotes:

In principle, the possibility of multiple intoxication should always be considered, for example, if several drugs are used with suicidal intention.

a) Symptoms of overdose:

The acute intoxication is characterized by nausea, vomiting, hyper-excitability, tremor, ataxia, blurred vision, lethargy, depression, dysarthria and cerebral seizures; in one case, malignant cardiac arrhythmia has been reported.

Acute toxic psychoses ranging from confusion with visual hallucinations to coma and myoclonus have been reported with concomitant administration of amantadine with other anti-Parkinson drugs.

b) Therapeutic measures in case of overdose:

A specific drug therapy or antidote is not known. In case of intoxication through the ingestion of film-coated tablets, induce vomiting or gastric lavage.

In addition, intensive monitoring measures are necessary for vitally threatening intoxications.. Therapeutically, liquid intake, acidification of the urine for the faster excretion of the substance, possibly sedation, anticonvulsive measures and anti-arrhythmic drugs (lidocaine i.v.) are also suitable.

For the treatment of neurotoxic symptoms (as described above), intravenous administration of 1-2 mg physostigmine in adults may be attempted every 2 hours, in children 0.5 mg twice in intervals of 5 to 10 minutes, to a maximum dose of 2 mg. Due to the low dialyzability of Amantadine (about 5%) hemodialysis does not make sense.

It is recommended to especially monitor patients for possible QT prolongation and factors that favor the onset of TdP, e.g. electrolyte disorders (in particular hypokalemia and hypomagnesemia) or bradycardia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Virustatic agent and antiparkinsonian agent

ATC code: N04BB01

Amantadine has many pharmacological effects. Amantadine has an indirect agonistic effect on the striatal dopamine receptor. Animal studies have shown that Amantadine increases the extracellular dopamine concentration by increasing dopamine release, as well as by inhibiting reuptake in presynaptic neurons. Amantadine inhibits NMDA receptor-mediated release of acetylcholine at therapeutic levels and may induce anticholinergic effects.. With L-Dopa it shows synergistic effects.

Amantadine inhibits the proton pump activity of the influenza A matrix protein 2 (M2). This inhibits the release of the nucleic acids of already invading viruses and thus the uptake of the viral ribonucleic complex in the cell nucleus of the target cell, as well as blocking the release of infectious particles from infected cells.

The protection rate prior to infection varies between 50 and 95%. Amantadine may reduce the duration and severity of the disease by 50%, if therapy is started in a timely manner..

Under therapy with amantadine, stable mutations leading to resistant phenotypes are selected. After 5-7 days, 50% of all isolates are resistant. Resistant strains can be transmitted from person to person.

5.2 Pharmacokinetic properties

Absorption:

Amantadine hydrochloride is rapidly and completely absorbed from the gastrointestinal tract after oral administration.

Plasma concentration, elimination:

Maximum plasma concentrations are reached approximately 2 and 8 hours (tmax) after the administration of a single dose.

The readily soluble Amantadine hydrochloride gives a higher concentration of Amantadine plasma peak than the less soluble Amantadine-hemisulphate, for which the maximum plasma peak concentration (Cmax) occurs later than that of the hydrochloride. After a single oral dose of 250 mg Amantadine-hydrochloride, Cmax of 0.5 µg/mL is achieved.

At a dosage of 200 mg/day, a steady-state is reached after 4-7 days, with plasma concentrations between 400 and 900 ng/mL. After administration of 100 mg Amantadine-hemisulphate, the Cmax is 0.15 µg/mL.

The total amount of absorbed active substance (AUC value) does not differ for both salt types of Amantadine.

The plasma clearance was identical to renal clearance and was 17.7 ± 10 L/h in healthy elderly volunteers.

The apparent distribution volume (4.2 ± 1.9 L/kg) is age-dependent; it is 6.0 L/kg in the elderly.

The *elimination half-life time*

Amounts to between 10 and 30 hours, in average approximately 15 hours. It is heavily dependent on the age of the patient. Older male patients (62 to 72 years) show elimination half-life of 30 h. For renal insufficiency patients there is a considerable prolongation of the terminal plasma half-life, to 68 ± 10 hours.

Amantadine is bound to about 67% (in vitro) of plasma proteins, about 33% are in plasma as a free fraction. The blood-brain barrier is overcome by means of a saturable transport system.

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

The dialyzability of Amantadine is low and is 5% for single dialysis.

Metabolism:

In humans, Amantadine is not metabolized.

5.3 Pre-clinical safety data

Amantadine has effects on the electrophysiology of the heart; it prolongs - among others - the action potential duration via an inhibition of repolarizing potassium currents. In rare cases, these effects can also to certain cases of cardiac arrhythmias in humans (tip reversal tachycardia or TdP arrhythmias).

In studies of chronic toxicity, CNS-stimulating effects were seen first and foremost.. In dogs and monkeys some extra-systoles were observed, in the dog also slight fatty infiltrations on the heart muscle.

In a mutagenicity test with established in vitro and in vivo tests, there was no evidence of genotoxic potential for Amantadine.

Long-term studies on the carcinogenicity of Amantadine are not available.

Embryo toxicity studies in rats, mice and rabbits have shown embryo-lethal effects and high-dose malformations only in rats. Increased edema, malposition of the hind legs and skeletal abnormalities were observed. Effects on fertility have been insufficiently studied; there is evidence of fertility impairment in rats. Studies on the peri/postnatal period have not been carried out.

6. PHARMACEUTICAL DETAILS

6.1 List of other ingredients

Lactose monohydrate, microcrystalline cellulose, povidone (K 28/32), croscarmellose sodium, maize starch, talc, magnesium stearate (Ph. Eur.), polyacrylate dispersion 30%, titanium dioxide (E 171), orange yellow (E 110), macrogol 6000, hypromellose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

No special storage conditions are required for these drugs.
Store below 25°C.

6.5 Type and content of container

Blisters made of aluminum / PVC / PVdC foil
Packs of 20, 30, 60 and 100 film-coated tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. OWNER OF THE AUTHORIZATION

Megapharm Ltd
POBox 519, Hod Hasharon, 4510501 Israel

8. MANUFACTURER

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9. SALE RESTRICTIONS

By prescription only

Approved on 20.05.2019