

Ministry of Health of the Republic of Belarus

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PACKAGE LEAFLET

Capreocin

Powder for solution for intravenous and intramuscular injection

500 mg, 750 mg and 1000 mg.

Trade name: Capreocin

International non-proprietary name: Capreomycin

Dosage form: Powder for solution intravenous and intramuscular injection 500 mg, 750 mg and 1000 mg

Appearance: white or near white powder

Composition per 1 bottle:

Capreomycin – 500 mg or 750 mg or 1000 mg (in the form of capreomycin sulfate)

ATC code: Jo4AB30

Pharmacological properties.

Pharmacodynamics.

Capreocin is a polypeptide antibiotic produced by *Streptomyces capreolus*. Capreocin is a complex of 4 microbiologically active components. The drug inhibits protein synthesis in a bacterial cell producing bacteriostatic action. Capreocin is selectively active in relation to *Mycobacterium tuberculosis* localized outside and inside the cell.

Treatment with this drug alone rapidly induces emergence of resistant strains, cross resistance to canamycin, viomycin and, in some cases, to amikacin and neomycin is noted. There was no cross resistance between capreomycin and isoniazide, aminosalicylic acid, cyloserine, streptomycin, ethionamide and ethambutol.

Pharmacokinetics

Absorption

Capreocin is practically non-absorbable from GIT (less than 1%). Peak plasma concentration 20-47 mg/l is reached in 1-2 hours after 1000 mg intramuscular injection. After 10 hours concentration is 4 mg/l. After 1 hour of 1000 mg intravenous infusion the maximal concentration is 30-50 mg/l.

Distribution and metabolism

Capreocin does not cross the blood-brain barrier and crosses the placental barrier.

The drug is non-metabolized. About 50-60% of the dose is excreted by glomerular filtration leading to high urine concentration of active and unchangeable antibiotic. This amount is predominantly excreted during first 12 hours after dose administration. Slight amount of the drug can be excreted in bile.

Urine concentration during 6 hours after 1000 mg administration is averaged to 1.68 mg/ml. Elimination half-life is 3-6 hours. The drug is not accumulated by daily administration in the dose of 1000 mg for 30 days.

By renal impairment Capreocin elimination half-life is prolonged and a tendency to accumulation appears.

Indications for use

Treatment of pulmonary tuberculosis caused by *Mycobacterium tuberculosis* strains sensitive to the drug, in case the first-line antitubercular drugs (isoniazide, rifampicin, ethambutol, aminosalicylic acid, streptomycin) are ineffective or cannot be used because of toxic action or presence of resistant tuberculous bacteria.

To prove presence of *Mycobacterium tuberculosis* strain sensitive to Capreocin a sensitivity test must be performed.

Contraindications.

Capreocin is contraindicated to children (under 12 years – safety and efficiency are not established), to patients with hypersensitivity to capreomycin, pregnant women and nursing mothers.

Precautions

With extreme caution Capreocin should be prescribed to patients with renal insufficiency and pre-existent hearing disorders excluding cases when the expected benefit of the treatment justifies the potential risk of additional dysfunction of VIII pair of cerebral nerves and renal injury.

Before start and regularly during Capreocin treatment it is necessary to perform audiometry and evaluation of vestibular function as well as to control renal function (weekly).

Renal injury associated with Capreocin treatment is accompanied by necrosis of tubules, increase in urea nitrogen or serum creatinine levels, emergence of pathological urinary sediment.

By increase in urea nitrogen level by more than 30 mg/100 ml and any other signs of decrease in renal function with/without increase of urea nitrogen level as well as by suspicion of renal function failure a careful examination of the patient, decrease in dose or withdrawal of the drug is required.

Capreocin (as any antibiotics) is prescribed with caution to patients with any forms of allergy, especially with drug allergy.

Capreocin shall be used with caution during and after surgery associated with drugs causing neuromuscular blockade (especially upon high possibility of incomplete postoperative cessation of neuromuscular blockade).

As hypokalaemia can developed during treatment it is necessary to perform frequent measurements of serum potassium.

A constant control of dosage regimen and treatment schedules as well as accuracy and regularity of compliance is required during treatment. In case of omitting an injection the drug is injected as soon as possibly unless it is time for the next dose.

In the absence of improvement during 2-3 weeks or upon emergence of new symptoms of the disease it is required to consult a doctor.

Route of administration and posology.

Capreocin is used i.m. and i.v.

Before treatment an analysis is performed to proved presence of *Mycobacterium tuberculosis* strain sensitive to Capreocin.

Capreocin is to be combined with at least one more antituberculous drug which is active against the *Mycobacterium tuberculosis* strain present in the patient.

Average dose is 1000 mg/day not exceeding 20 mg/kg/day. The drug is injected intramuscular or intravenous daily during 60-120 days, than – 1000 mg by any of the two methods 2-3 times a week.

Tuberculosis treatment is continued for 12-24 months. In absence of possibility of parenteral administration of drugs, at hospital discharge they are replaced by the drugs for oral administration.

Patients with renal impairment require dose reduction in accordance with recommendations in the table 1 presented below. With these doses average concentration of capreomycin 10 mg/l is reached.

| Creatinine clearance (ml/min) | Capreomycin clearance (l/kg/hx10 ²) | Elimination half-life (h) | Dose (mg/kg) for the following intervals between injections | | |
|-------------------------------|---|---------------------------|---|------|------|
| | | | 24 h | 48 h | 72 h |
| 0 | 0.54 | 55.5 | 1.29 | 2.58 | 3.87 |
| 10 | 1.01 | 29.4 | 2.43 | 4.87 | 7.3 |
| 20 | 1.49 | 20 | 3.58 | 7.16 | 10.7 |
| 30 | 1.97 | 15.1 | 4.72 | 9.45 | 14.2 |
| 40 | 2.45 | 12.2 | 5.87 | 11.7 | |
| 50 | 2.92 | 10.2 | 7.01 | 14 | |
| 60 | 3.4 | 8.8 | 8.16 | | |
| 80 | 4.35 | 6.8 | 10.4 | | |
| 100 | 5.31 | 5.6 | 12.7 | | |
| 110 | 5.78 | 5.2 | 13.9 | | |

Solution preparation and injection rules

For intramuscular and intravenous injection 1000 mg of the drug (content of 1 bottle) are dissolved in 2 ml of sodium chloride solution for injections or water for injections. The contents of the bottle are completely dissolved during 2-3 minutes.

For intravenous infusion dissolved Capreocin is diluted in 100 ml of 0.9% of sodium chloride solution for injections and injected during 60 minutes by drop infusion.

For intramuscular injection dissolved Capreocin is injected deeply in the muscle as interfacial injection can cause increased soreness and development of aseptic abscesses.

To inject 1000 mg it is necessary to use all contents of the bottle. To inject less than 1000 mg it is recommended to use the following table of dilutions:

| Amount of solvent added into the 10 ml bottle containing 1000 mg | Volume of Capreocin solution for injection | Concentration* of solution (approx) |
|--|--|-------------------------------------|
| 2.15 ml | 2.85 ml | 350 mg*/ml |
| 2.63 ml | 3.33 ml | 300 mg*/ml |
| 3.3 ml | 4 ml | 250 mg*/ml |
| 4.3 ml | 5 ml | 200 mg*/ml |

* Equivalent of Capreocin activity.

The solution can become slightly yellow and eventually dark, but it is not accompanied by loss of activity or emergence of toxicity,

Adverse reactions.

Urinary system disorders: renal toxicity – toxic nephritis, renal injury with tubule necrosis, dysuria (increase/decrease in urinary frequency or urinary amount), renal insufficiency, increase in urea nitrogen for more than 20-30 mg/100 ml (46%) and serum creatinine levels, emergence of abnormal sediment in urea or blood corpuscles.

Nervous system and sense organ disorders: unusual fatigue or weakness, drowsiness; ototoxicity – hearing decrease, including nonreversible, buzzing, tinnitus or congestion feeling; vestibular toxicity – dystaxia; walking lability; neuromuscular blockage.

Gastrointestinal disorders: nausea, vomiting, anorexia, thirst, hepatotoxicity, with liver disorder (especially associated with liver diseases in past medical history).

Allergic reactions: rash, pruritus, erythema, edema and fever.

Cardio-vascular system and blood disorders (bleeding, hemostasis): heart rhythm disturbance, leukytosis, leucopenia, eosinophilia (5%), thrombocytopenia.

Other: electrolyte imbalance, including hypokalaemia; myalgia, rough breathing (as a result of respiratory muscles hypotonia); soreness, infiltration, development of sterile abscesses or increased bleeding sickness in the administration site.

Overdose

Symptoms: renal impairment up to complete tubule necrosis (increased risk in geriatric patients, when associated with initial renal dysfunction, hypohydration).

Damage of auditory and vestibular portions of VIII pair of cerebral nerves is more frequently observed in patients with renal insufficiency or hypohydration as well as upon treatment with drugs producing ototoxic action. These patient frequently experience dizziness and tinnitus.

Quick intravenous injection can lead to neuromuscular blockage or respiratory paralysis.

By development of toxic action of Capreocin hypokalaemia, hypocalcemia, hypomagnemia and electrolyte imbalance can be observed resembling Bartter syndrome.

Treatment in case of overdose is provided with account of possibility of overdose of several drugs and their interaction. As a rule, prescribed are activated carbon, gastric lavage and symptomatic treatment: support of breathing and blood circulation, hydration, ensuring urea outflow at the level of 3-5 ml/kg/h (with normal renal function).

To arrest neuromuscular blockage including respiratory depression anticholinesterase drugs and calcium drugs are administered. Hemodialysis is performed (especially in patients with severe renal impairment): water and electrolyte imbalance and creatinine clearance monitoring is required.

Drug interactions

Capreocin is incompatible with drugs producing ototoxic (aminoglycosides, polymyxins, furosemide, etacrynic acid) and nephrotoxic (aminoglycosides, polymyxins, methoxyflurane) action and causing neuromuscular blockage (aminoglycosides, polymyxins, ethyl oxide and galogenized hydrocarbons for inhalation anesthesia, citrated blood additives). Myorelaxant effect is weakened by neostigmine.

Storage conditions and shelf life.

Store at the temperature not above 25°C protected from moisture and light.

Keep out of the reach of children.

Shelf life is 3 years. Do not use at the end of shelf life specified on a package.

Prescribing information.

Prescription only.

Package

500 mg, 750 mg or 1000 mg in a 10 ml bottle.

1 or 5 bottles in a package.

24 or 36 bottles in a cardboard box (a package for hospitals)

Manufacturer

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