MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

Instruction for medical use of the pharmaceutical product

COLISTAT
powder for solution
for intravenous administration and inhalation
2 000 000 IU

Trade name Colistat.
The international non-proprietary name Colistin.
Pharmaceutical form Powder for solution for intravenous administration and inhalation.
Description White or almost white powder.
Content per 1 vial
Colistimethate sodium - 2 000 000 IU.
Pharmacotherapeutic group Antibacterials for systemic use, other antibacterials, polymyxins.
ATC code: J01XB01.
Pharmacological properties
Pharmacodynamics
Colistimethate sodium is a cyclic polypeptide antibiotic derived from *Bacillus polymyxa var. colistinus* and belongs to the polymyxin group. The active ingredient of Colistat is colistimethate sodium, which is a derivative of the methanesulfonic acid of colistin.
The medicinal product has a bactericidal action against Gram-negative bacteria, which is based on changes in the structure and impaired function of the cytoplasmic and outer membranes as a result of the polarization of the membrane structures.
The antibacterial activity of colistimethate sodium applies only to *aerobic Gram-negative bacteria* that have a hydrophobic outer membrane.
Polymyxins have a concentration-dependent bactericidal effect on susceptible bacteria. fAUC/ MIC is considered to be correlated with clinical efficacy.

EUCAST* Breakpoints	Susceptible	Resistant**
Acinetobacter	≤ 2 mg/L	> 2 mg/L
Enterobacteriaceae	≤ 2 mg/L	> 2 mg/L
Pseudomonas spp.	≤ 4 mg/L	> 4 mg/L

*EUCAST - European Committee on Antimicrobial Susceptibility Testing.
** Breakpoints apply to dosage of 2 000 000 – 3 000 000 IU 3 times a day. A loading dose 9 000 000 IU may be needed.
Mostly susceptible to colistimethate sodium are *Acinetobacter baumannii, Citrobacter spp., Escherichia coli, Haemophilus influenzae, Pseudomonas aeruginosa.*
The acquired resistance may vary geographically and with time for selected species
The acquired resistance is possible for *Stenotrophomonas maltophilia, Achromobacter xylosoxidans* (formerly *Alcaligenes xylosoxidans*). *Proteus spp., Providencia spp., Serratia spp., Burkholderia cepacia* and related species are resistant.
Cross resistance between colistimethate sodium and polymyxin B is expected. Since the mechanism of action of the polymyxins is different from that of other antibacterial agents, resistance to colistin and polymyxin B by the above mechanism would not be expected to result in resistance to other drug classes.
Pharmacokinetics
Absorption
Absorption from the gastrointestinal tract occurs in a small mount in the normal individual.
In case of inhalation use colistimethate sodium absorption has strong individual differences and depends on the aerosol particle size, nebuliser system and lung status of a patient. In case of inhalation use colistimethate sodium serum concentration may vary from 0 to potentially therapeutic concentrations of 4 mg/l and more. About 15 % of the administered dose of colistimethate sodium is retained in the lungs. Due to the low systemic bioavailability in case of inhalation use, the risk of colistimethate sodium reten-

tion in the body of patients with renal failure is low. However, the possibility of systemic absorption in case of inhalation method of use should be taken into account.

Distribution

Protein binding is slight. Colistimethate sodium accumulates in the liver, kidney, brain, heart and muscles. The medicinal product can penetrate through the placenta.

Penetration into the cerebrospinal fluid is minimal, but increases in the presence of meningeal inflammation.

Metabolism and excretion

In vivo colistimethate sodium is converted to the base (colistin). Colistimethate sodium is eliminated predominantly by the kidneys via glomerular filtration. In healthy subjects, 60% to 70% of Colistimethate sodium is excreted unchanged in the urine within 24 hours. The medicinal product is not displayed with the bile.

After i.v. administration the half-life of colistimethate sodium in healthy subjects is about 3 h. The elimination half-life of colistimethate sodium when used in cystic fibrosis patients is 3.4 + 1.4 h. In critically ill patients the elimination half-life increases to 9-18 h.

The routs of excretion of colistimethate sodium in case of inhalation administration have not been studied. Absorbed part of colistimethate sodium is allegedly excreted unchanged by the kidneys. Unabsorbed portion after inhalation is presumably excreted with the sputum. In patients with cystic fibrosis who received colistimethate sodium by inhalation at a dose of 1 000000 IU 2 times a day for 3 months, no medicinal product was detected in the urine.

Pharmacokinetics in special clinical situations

In renal failure the dose reduction of colistimethate sodium is required to prevent accumulation of medicinal product in the body.

Kinetics of colistimethate sodium is similar in children and adults, including the elderly, provided normal renal function.

Details regarding the use of the medicinal product in infants are restricted. In this group of patients it is necessary to consider the possibility of higher maximum concentrations in blood plasma and a longer half-life, as well as control the level of active substance in the serum.

Indications for use

Medicinal product is indicated in the treatment of the infections caused by susceptible bacteria.

Parenteral administration

Treatment of some serious infections caused by Gramnegative bacteria, including those of the lower respiratory tract and urinary tract, when more commonly used systemic antibacterial agents may be contraindicated or may be ineffective because of bacterial resistance.

Inhalation

Treatment of pulmonary infections caused by *Pseudomonas aeruginosa* in patients with cystic fibrosis.

Contraindications

Hypersensitivity to colistimethate sodium or to polymyxin B.

Precautions

Use during pregnancy and lactation

Clinical safety of colistimethate sodium during pregnancy has not been established. Colistimethate sodium is able to penetrate the placenta and can cause fetal toxicity. The medicinal product should not be used during pregnancy except in cases where the potential benefit of its use justify the potential risk to the fetus.

In each case, the medicinal product should be used under the direct supervision of a doctor!

Colistimethate sodium is able to penetrate into breast milk, so in case of need to use colistimethate sodium during lactation the termination of breastfeeding should be considered.

Effects on ability to drive and use machines

During parenteral treatment with colistimethate sodium neurotoxicity may occur with the possibility of dizziness, confusion or visual disturbance. If such reactions appear the patient should refrain from driving and operating other machines during the period of use of the medicinal product.

Cautions

Colistimethate sodium should be used with caution in patients with porphyria.

In case of excess of the recommended dose of colistimethate sodium for parenteral use nephrotoxic effects can occur.
Colistimethate sodium should be prescribed with caution in patients with impaired renal function. It is recommended to evaluate renal function of such patients at the start of treatment and monitor it during treatment and control the occurrence of side effects on the nervous system (facial paraesthesia, muscle weakness, vertigo, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis and apnoea). Monitoring should be performed for perioral paraesthesia and paraesthesia in the extremities, which are signs of overdose.
It is also necessary to control the concentration of colistimethate sodium in serum.
Colistimethate sodium should be prescribed with caution to infants < 1 year of age as renal function is not fully mature in this age group.
In case of an allergic reaction, treatment with colistimethate sodium must be discontinued and appropriate measures implemented.
Intravenous colistimethate sodium does not cross the blood brain barrier to a clinically relevant extent.
Antibiotic-associated colitis and pseudomembranous colitis are reported with all anti-bacterial agents and may occur with colistimethate sodium. They may range from mild to life-threatening in severity. In case of diarrhoea during the use of colistimethate sodium the therapy should be discontinued and the specific treatment for *Clostridium difficile* should be prescribed. Medicinal products that inhibit peristalsis should not be given.
Do not use Colistat as inhalation monotherapy in the treatment of exacerbation of chronic infections caused by *Pseudomonas aeruginosa*. Inhalation of colistimethate sodium may cause bronchospasm, which can be prevented or arrested by appropriate β_2-agonists. Therefore, the first dose of Colistat should be introduced under the supervision of experienced medical personnel, wherein inhalation of Colistat, must be preceded by the use of bronchodilators if patient's treatment includes it. If the use of β_2-agonists is not effective, treatment should be discontinued.
It is recommended to monitor the performance of forced expiratory volume in one second (FEV_1) before and after inhalation of the medicinal product. If a patient shows signs of bronchial obstruction caused by the medicinl product, at the next time of Colistat administration the sample (FEV_1) should be repeated, adding bronchodilator.
Inhalation of colistimethate sodium may enhance the cough, so in the case of use in hemoptysis the risk-benefit ratio should be carefully evaluated.
It is necessary to make an interval between inhalation of dornase alpha and inhalation of Colistat.
Therapy by colistimethate sodium may cause appearance of resistant strains of microorganisms. The recovery of the medicinal product efficiency is possible after cancellation and/or modification of the therapy.

Dosage and administration

Colistat is applied parenterally and by inhalation.
Parenteral administration
The dosage regimen and treatment duration are set depending on the type and severity of the infection, the sensitivity of the pathogen, the patient's condition and age, body weight and condition of the patient's renal function.
The optimal dosing regimen of Colistat is based on calculation of loading and maintenance doses. In patients who are critically ill, maximum loading and maintenance doses of 9 000 000 IU should be administered, in exceptional cases the doses may be up to 12 000 000 IU.
The introduction of the first maintenance dose should be done in 24 hours.
Calculation of the loading dose is the same for all categories of patients, regardless of kidney failure.
For adults and adolescents maintenance dose is 9 million IU/day divided in 2-3 doses.
For patients with *renal impairment* (creatinine clearance < 50 ml/min) dose reductions are recommended.
The recommended frequency of administration is 2 times daily.

Creatinine clearance (ml/min)	Daily dose
< 50-30	5 500 000 – 7 500 000 IU
< 30-10	4 500 000 – 5 500 000 IU
< 10	3 500 000 IU

Colistin appears to be dialyzable through conventional haemodialysis and continuous venovenous haemo(dia)filtration (CVVHF, CVVHDF).
For patients on haemodialysis the following dosing regimen is recommended.
No-haemodialysis days: 2 250 000 IU daily (2 200 000 – 2 300 000 IU/daily).
Haemodialysis days: 3 000 000 IU daily. The medicinal product should be administered after haemodialysis session. The daily dose should be divided into two doses.
Dosing regimen in patients on CVVHF/ CVVHDF is as in patients with normal renal function. Three times daily dosing is recommended.
Colistimethate sodium in patients with *hepatic impairment* should be given with caution. Dose correction in *elderly patients* with normal renal function is not required.
Renal maturity should be taken into consideration when selecting the dose in *children*. The dosage should be established on the basis of ideal body weight. For children with body weight ≤ 40 kg the doses of 75 000 – 150 000 IU/kg daily are recommended, divided into 3 doses. For children with a body weight >40 kg, use of the dosing recommendation for adults should be considered.
In exceptional cases the use of doses >150 000 IU/kg/day in children with cystic fibrosis is possible. The use of high doses of colistimethate sodium in critically ill children, in children with impaired renal function and in infants < 1 year should be with great caution under careful supervision of physician.
Colistat should be given as a slow intravenous infusion during 30-60 minutes. Patients with a totally implantable venous access device (TIVAD) in place may tolerate a bolus injection of Colistat (of up to 2 000 000 IU in 10ml of solvent) given over a minimum of 5 minutes.
Inhalation
For local treatment of lower respiratory tract infections the medicinal product is used by inhalation. The course of treatment is determined individually and depends on the clinical condition of the patient. Colistimethate sodium should be administered by inhalation under careful supervision of physician.
Adults, children >2 years Colistat should be given in doses 1 000 000 IU - 2 000 000 IU 2-3 times daily (up to 6 000 000 IU daily).
Children <2 years Colistat should be given in doses 500 000 IU – 1 000 000 IU 2 times daily (up to 2 000 000 IU daily).
Dose corrections in *elderly patients, in patients with impaired hepatic function, in patients with impaired renal function* are not required, however caution is advised in patients with renal impairment.

Terms of preparation and administration of the solution

The medicinal product does not contain preservatives, therefore when preparing solutions standard aseptic techniques must be observed.
Parenteral administration
Colistat should be administered as an intravenous *bolus injection* during 5 minutes or as an intravenous *infusion* during 30-60 minutes.
To prepare a solution for intravenous *bolus injection* the Colistat vial content is dissolved in 10 ml of water for injection or 0.9 % sodium chloride solution. The solvent should be injected into the vial slowly, gently shaking the vial until a clear solution, avoiding the appearance of foam.
For intravenous *infusion* the solution for intravenous bolus injection is quantitatively transferred into vial or container with water for injection or 0.9% sodium chloride and diluted to 50 - 200 ml and gently swirled.
The solution for intravenous infusion should be used immediately after preparation!
The unutilized solution of the medicinal product must be discarded!
To prevent the administration of the dose less than required, the medicinal product should be completely dissolved. The prepared solution should be carefully removed from the vial.

Inhalation
To prepare the *solution for inhalation* the contents of the vial is pre-dissolved in 3 ml of 0.9 % sodium chloride solution or water for injection. The required amount of this solution is poured into a sprayer that attached to a device for supplying air / oxygen, and used in accordance with the instructions for use of the device.
To use antibiotics as an aerosol spray nebulizers (ultrasonic or jet type) are recommended which, when used with an appropriate compressor, create respirable particles of diameter not more than 5 microns (for the most efficient absorption by lungs). When the nebulizer and compressor are used, the instructions of the device manufacturer should be followed.
The patient should perform the procedure of inhalation of the medicinal product sitting or standing vertically, in a normal, calm state, producing as much as possible deep breaths through the mouthpiece of the nebulizer. To facilitate the breath through your mouth, the nose clip could be used.
After each use, the mouthpiece should be washed and disinfected, following the manufacturer's instructions.
Patients treated with bronchodilators should use inhalation of Colistat immediately after their application and after physiotherapy on the chest.
The reconstituted solutions for *i.v. bolus injection* and *inhalation* in the vials of the manufacturer retain physical and chemical stability during 24 hours in the dark place at the temperature 2-8 °C (refrigerator). From a microbiological point of view, the medicinal product should be used immediately, otherwise the in-use storage times and conditions are the responsibility of user.
The unutilized medicinal product solution must be disposed.

Undesirable effects

Parenteral administration
The likelihood of adverse events may be related to the age, renal function and condition of the patient.
CNS disorders: neurotoxicity (may be associated with overdose, poorly selected dose in patients with renal insufficiency, and concomitant use of neuromuscular blocking agents or other medicinal products with similar neurological effects, dose reduction may help to reduce these symptoms); apnoea, transient sensory disturbances (face paresthesia, dizziness); vasomotor instability, slurred speech, blurred vision, confusion or psychosis. In cystic fibrosis patients moderate neurological reactions may occur which disappear during the treatment or after its termination.
Urinary system disorders: reduced glomerular filtration rate, increased urination, decreased serum creatinine, increased gas production usually occurs after use of doses higher than recommended in patients with normal renal function or in connection with insufficient reduced dose of the medicinal product in patients with renal failure or due to concomitant use of other nephrotoxic medicinal products. These side effects are usually reversible and disappear after cessation of therapy. In cystic fibrosis patients receiving the recommended dose of the medicinal product nephrotoxicity reactions are rare. Signs of nephrotoxicity may occur in critically ill hospitalized patients without diagnosed cystic fibrosis.
Hypersensitivity reactions: skin rash, tremors. If any such reactions appear the use of colistimethate sodium must be stopped.
Local reactions: rash at the site of injection.
Inhalation
The respiratory system disorders: cough reflex, bronchospasm, apnoea, increased sputum generation, airways mucositis, pharyngitis.
Infections: oral candidiasis.
Hypersensitivity reactions: rash, itching, angi-neuropathic edema. If any such reactions appear the use of colistimethate sodium must be stopped.
Gastrointestinal tract disorders: nausea, burning tongue, unpleasant taste.

Overdose

Overdose can result in neuromuscular blockade that can lead to muscular weakness, apnoea and possible respiratory arrest. Overdose can also cause acute renal failure characterised by decreased urine output and increase of concentration of nitrogen in urea and creatinine in the blood plasma.
There is no specific antidote, manage by supportive treatment. Measures to increase the rate of elimination of colistin e.g. mannitol diuresis, prolonged haemodialysis or peritoneal dialysis may be tried, but effectiveness is unknown.

When inhaled colistimethate sodium intake into the systemic circulation, and hence the risk of intoxication are negligible. Data on the development of these reactions are absent.
In case of accidental drug intake the development of toxicity is unlikely, since colistimethate sodium is absorbed from the gastrointestinal tract in small amount.

Interaction with other medicinal products

Concomitant use of colistimethate sodium with other medicinal products of neurotoxic and/or nephrotoxic potential, for example, aminoglycosides (gentamicin, amikacin, netilmicin and tobramycin) is prohibited. There may be an increased risk of nephrotoxicity if given concomitantly with cephalosporins.
Caution should be taken with concomitant use of colistimethate sodium in different formulations since the information about summative toxicity is limited.
The potential for drug-drug interactions should be borne in mind when colistimethte sodium is co-administered with medicinal products known to inhibit or induce drug metabolising enzymes or medicinal products known to be substrates for renal carrier mechanisms.
Due to the effects of colistin on the release of acetylcholine, non-depolarising muscle relaxants should be used with caution in patients receiving colistimethate sodium since the effects of muscle relaxants could be prolonged.
Co-treatment with colistimethate sodium and macrolides such as azithromycin and clarithromycin, or fluoroquinolones such as norfloxacin and ciprofloxacin should be undertaken with caution in patients with myasthenia gravis.
Neuromuscular blocking medicinal products and ether should be used with extreme caution in patients receiving colistimethate sodium.
Concomitant use of colistimethate sodium via inhalation with inhaled anesthetics, muscle relaxants of central and peripheral actions and aminoglycosides, the risk of the blockade of neuromuscular transmission is increased.
Data about colistimethate sodium interaction with other medicinal products *in vivo*, as well as about its excretion from the organism are limited. Colistimethate sodium or colistin did not induce the activity of any P 450 (CYP) enzyme tested (CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4/5) in *in vitro* studies in human hepatocytes.

Storage conditions and shelf life

Store protected from moisture and light at a temperature not exceeding 25 °C.
Keep out of the reach of children.
Shelf life is 2 years. Do not use beyond the expiration date printed on the package.
The reconstituted solutions for *i.v. bolus injection* and *inhalation* in the vials of the manufacturer retain physical and chemical stability during 24 hours in the dark place at the temperature 2-8 °C (refrigerator).
From a microbiological point of view, the medicinal product should be used immediately, otherwise the in-use storage times and conditions are the responsibility of user.

Prescription status

The medicinal product is sold by prescription.

Package

2 000 000 IU in a vial 10 ml.
5 vials with an instruction for medical use in a pack or 36 vials with an instruction for medical use in a box (packing for hospitals).

Information about manufacturer

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