MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

INSTRUCTION
for Medical Use of Medicinal Product

COLISTAT
powder for solution for intravenous administration
1 000 000 IU

Stamp: [APPROVED
by the MINISTRY OF HEALTH
OF THE REPUBLIC OF BELARUS
Order of the Ministry of Health
of the Republic of Belarus
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Trade name: Colistat.
International non-proprietary name: Colistin.
Pharmaceutical form: Powder for solution for intravenous administration.
Description: White or almost white powder.
One vial contains
Colistimethate sodium – 1 000 000 IU.
Pharmacotherapeutic group: Antibacterials for systemic use. Other antibacterials. Polymyxins.
ATC code: J01XB01.
Pharmacological properties
Pharmacodynamics
Colistin is a cyclic polypeptide antibiotic derived from *Bacillus polymyxa var. colistinus,* belonging to the polymyxin group. The active substance of Colistat is colistimethate sodium, which is a derivative of colistin methanesulfonic acid.
The medicinal product has bactericidal effect by damaging the cell membrane of bacteria due to the processes of polarization of membrane structures.
Colistimethate sodium is selective for *aerobic gram-negative bacteria* that have a hydrophobic outer membrane.
Polymyxin E has been reported to produce a concentration-dependent bactericidal effect on susceptible bacteria. fAUC/MIC (the minimum inhibitory concentration) is considered to be correlated with clinical efficacy.
Table 1. Breakpoints for the interpretation of MIC values (EUCAST*, v. 9.0, 01/01/2019)

Microorganisms	MIC Breakpoints	
	Susceptible (S)	Resistant (R)**
Acinetobacter	S ≤ 2 mg/l	R > 2 mg/l
Enterobacteriaceae	S ≤ 2 mg/l	R > 2 mg/l
Pseudomonas spp.	S ≤ 4 mg/l	R > 4 mg/l

*EUCAST – the European Committee on Antimicrobial Susceptibility Testing, http://www.eucast.org.

** Breakpoints apply to dosage of 2 000 000 – 3 000 000 IU x 3 times/day. A loading dose (9 000 000 IU) may be needed.

Commonly susceptible species: *Acinetobacter baumannii, Enterobacter aerogenes, Escherichia coli, Haemophilus influenzae, Klebsiella* spp., *Pseudomonas aeruginosa*.
The prevalence of acquired resistance may vary geographically and with time for selected species. Species for which acquired resistance may be a problem: *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans* (formerly *Alcaligenes xylosoxidans*). Inherently resistant gram-negative species: *Burkholderia cepacia* and related species, *Proteus* spp., *Providencia* spp., *Serratia* spp.
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

colistimethate sodium and polymyxin B by the above mechanism alone would not be expected to result in resistance to other drug classes.

Pharmacokinetics

Absorption

The information on the pharmacokinetics of colistimethate sodium and colistin is limited. There are indications that pharmacokinetics in critically ill patients differ from those in patients with less severe physiological derangement and from those in healthy volunteers.

After intravenous administration peak plasma levels were obtained in 10 minutes. Serum concentrations decreased with a half-life of 2 to 3 hours after intravenous or intramuscular administration in adults and children, including preterm neonates.

After infusion of colistimethate sodium the inactive pro-drug is converted to the active colistin. Peak plasma concentrations of colistin have been shown to occur with a delay of up to 7 hours after administration of colistimethate sodium in critically ill patients.

Absorption from the gastrointestinal tract does not occur to any appreciable extent in the normal individual.

Distribution

The volume of distribution of colistin in healthy subjects is low and corresponds approximately to extracellular fluid. The volume of distribution is relevantly enlarged in critically ill subjects. Protein binding is moderate and decreases at higher concentrations.

Both colistimethate sodium and colistin display linear pharmacokinetics in the clinically relevant dose range.

Colistimethate sodium accumulates in the liver, kidneys, brain, heart and muscles.

The medicinal product can cross the placenta.

Biotransformation and elimination

It is estimated that approximately 30% of colistimethate sodium is converted to colistin in healthy subjects, its clearance is dependent on creatinine clearance and as renal function decreases, a greater portion of colistimethate sodium is converted to colistin. In patients with severe renal impairment (creatinine clearance < 30 ml/min), the extent of conversion could be as high as 60% to 70%.

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 elimination of the active colistin is incompletely characterised. Colistin undergoes extensive renal tubular reabsorption and may either be cleared non-renally or undergo renal metabolism with the potential for renal accumulation. Colistin clearance is decreased in renal impairment, possibly due to increased conversion of colistimethate sodium.

Average urine levels ranged from about 270 μg/ml after 2 hours to about 15 μg/ml 8 hours after intravenous administration and from 200 μg/ml to about 25 μg/ml during a similar period after intramuscular administration.

After intravenous administration half-life of colistin in healthy subjects and those with cystic fibrosis is reported to be around 3 h and 4 h, respectively, with a total clearance of around 3 l/h. In critically ill patients, half-life has been reported to be prolonged to around 9-18 h.

Pharmacokinetics in special populations

In patients with *renal impairment* dose adjustment is required to prevent the accumulation of colistimethate sodium in the organism.

Clinical studies of colistimethate sodium did not include a sufficient number of *elderly patients* (65 years and older) to determine the features of pharmacokinetic parameters. Clinical experience has not revealed differences in elderly and young patients. In general, the dose selection for an elderly patient should be careful, usually starting at the lower end of the dosage range, reflecting the greater frequency of decreased liver, kidney, or heart function and associated illnesses or other drug therapy. This medicinal product is known to be significantly excreted by the kidneys, and the risk of toxic reactions to it may be greater in patients with *impaired renal function*. Since

elderly patients are likely to have reduced renal function, care should be taken when selecting the dose, and monitoring of renal function may be useful.
The data on the use of colistin *in infants* are limited. It is necessary to consider the possibility of higher maximum plasma concentrations and a longer half-life, as well as to control the plasma level of colistin in this group of patients.

Preclinical safety data

Data on potential genotoxicity are limited and carcinogenicity data for colistimethate sodium are lacking. Colistimethate sodium has been shown to induce chromosomal aberrations in human lymphocytes *in vitro*. This effect may be related to a reduction in mitotic index, which was also observed. Reproductive toxicity studies in rats and mice do not indicate teratogenic properties. However, colistimethate sodium given intramuscularly during organogenesis to rabbits at 4.15 and 9.3 mg/kg resulted in talipes varus in 2.6 and 2.9% of fetuses respectively. These doses are 0.5 and 1.2 times the maximum daily human dose. In addition, increased resorption occurred at 9.3 mg/kg.
There are no other preclinical safety data of relevance to the prescriber which are additional to safety data derived from patient exposure.

Therapeutic indications

Colistat is indicated in adults and children including neonates for the treatment of serious infections due to selected aerobic Gram-negative pathogens in patients with limited treatment options.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Contraindications

Hypersensitivity to colistimethate sodium, colistin or to polymyxin B.

Special warnings and precautions for use

Use during pregnancy and lactation

There are no adequate data from the use of colistimethate sodium in pregnant women. Single dose studies in human pregnancy show that colistimethate sodium crosses the placental barrier and there may be a risk of foetal toxicity if repeated doses are given to pregnant patients. Animal studies are insufficient with respect to the effect of colistimethate sodium on reproduction and development. However, it has been demonstrated that colistimethate sodium crosses the placenta and therefore, at a therapeutic dose for pregnant women, there is a risk of fetal toxicity. Colistimethate sodium should be used in pregnancy only if the benefit to the mother outweighs the potential risk to the fetus. *In each case, Colistat should be used under medical supervision!*
Colistimethate sodium is excreted in breast milk, therefore, if it is necessary to use colistimethate sodium during lactation, discontinuation of breastfeeding should be considered.

Effects on ability to drive and use machines

Colistimethate sodium may affect the ability to drive and use machinery. 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 be warned not to drive or use machines.

Special warnings

Consideration should be given to co-administering intravenous colistimethate sodium with another antibacterial agent whenever this is possible, taking into account the remaining susceptibilities of the pathogen(s) under treatment. As the development of resistance to intravenous colistin has been reported in particular when it is used as a monotherapy, co-administration with other antibacterial should also be considered in order to prevent the emergence of resistance.
There are limited clinical data on the efficacy and safety of intravenous colistimethate sodium. The recommended doses in all subpopulations are equally based on limited data (clinical and pharmacokinetic/pharmacodynamics data). In particular there are limited safety data for the use of high doses (> 6 000 000 IU/day) and the use of a loading dose, and the use for special populations (patients with renal impairment and the paediatric population). Colistat should only be used when other, more commonly prescribed antibiotics are not effective or not appropriate.
In case of *an allergic reaction*, treatment with colistimethate sodium must be discontinued and appropriate measures implemented.

Renal impairment
Renal function monitoring should be performed at the start of treatment and regularly during treatment in all patients. The dose of colistimethate sodium should be adjusted according to creatinine clearance. Patients who are hypovolemic or those receiving other potentially nephrotoxic medicinal products are at increased risk of nephrotoxicity from colistin.
Nephrotoxicity has been reported to be associated with cumulative dose and treatment duration in some studies. The benefit of prolonged treatment duration should be balanced against the potentially increased risk of renal toxicity.
Caution is advised when administering colistimethate sodium to infants <1 year of age as renal function is not fully mature in this age group. Further, the effect of immature renal and metabolic function on the conversion of colistimethate sodium to colistin is not known.
Neurotoxicity
High serum concentrations of colistimethate sodium after intravenous or intramuscular administration can be caused by overdose or failure to reduce the dosage in patients with impaired renal function and lead to neurotoxicity.
Concomitant administration of non-depolarizing muscle relaxants or antibiotics with similar neurotoxic effects also causes neurotoxicity. Reducing the dose of colistimethate sodium may improve symptoms. Described neurotoxic side effects include dizziness, temporary facial paresthesia, speech impairment, vasomotor instability, visual impairment, confusion, psychosis, and apnoea. Monitoring should be performed for perioral paraesthesia and paraesthesia in the extremities, which are signs of overdose.
Colistimethate sodium should be used with extreme caution in patients with porphyria.
Colistimethate sodium is known to reduce the presynaptic release of acetylcholine at the neuromuscular junction and should be used in patients with myasthenia gravis with the greatest caution and only if clearly needed.
Respiratory arrest has been reported following intramuscular administration of colistimethate sodium. Impaired renal function increases the possibility of apnoea and neuromuscular blockade following administration of colistimethate sodium.
Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti-bacterial agents and may occur with colistimethate sodium. They may range from mild to life-threatening in severity. In patients who develop diarrhoea during or after the use of colistimethate sodium discontinuation of therapy and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Posology and method of administration
The dose to be administered and the treatment duration should take into account the severity of the infection as well as the clinical response. Therapeutic guidelines should be adhered to.
The dose is expressed in international units (IU) of colistimethate sodium (CMS). A conversion table from CMS in IU to mg of CMS as well as to mg of colistin base activity (CBA) is included at the end of this section.
Posology
The following dose recommendations are made based on limited population-pharmacokinetic data in critically ill patients:
Adults and adolescents
Maintenance dose 9 000 000 IU/day in 2-3 divided doses.
In patients who are critically ill, a loading dose of 9 000 000 IU should be administered.
The most appropriate time interval to the first maintenance dose has not been established.
Modelling suggests that loading and maintenance doses of up to 12 000 000 IU may be required in patients with good renal function in some cases. Clinical experience with such doses is however extremely limited, and safety has not been established.
The loading dose applies to patients with normal and impaired renal functions including those on renal replacement therapy.
Renal impairment

Dose adjustments in renal impairment are necessary, but pharmacokinetic data available for patients with impaired renal function is very limited.
Dose reductions are recommended for patients with creatinine clearance < 50 ml/min. Twice daily dosing is recommended.

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

Haemodialysis and continuous haemo(dia)filtration
Colistin appears to be dialyzable through conventional haemodialysis and continuous veno-venous haemo(dia)filtration (CVVHF, CVVHDF). There are extremely limited data from population PK studies from very small numbers of patients on renal replacement therapy. Firm dose recommendations cannot be made.
The following regimes could be considered.
No-HD days: 2 250 000 IU/day (2 200 000 - 2 300 000 IU/day).
HD days: 3 000 000 IU/day on haemodialysis days, to be given after the HD session. Twice daily dosing is recommended.
In patients receiving CVVHF/ CVVHDF the dosage regimen corresponds to the dosage regimen in patients with normal renal function. Three times daily dosing is recommended.
Hepatic impairment
There are no data in patients with hepatic impairment. Caution is advised when administering colistimethate sodium in these patients.
Elderly
No dose adjustments in older patients with normal renal function are considered necessary.
Paediatric population
The data supporting the dose regimen in paediatric patients are very limited. Renal maturity should be taken into consideration when selecting the dose. The dose should be based on lean body weight.
Children ≤ 40kg
75 000-150 000 IU/kg/day divided into 3 doses.
For children with a body weight above 40 kg, use of the dosing recommendation for adults should be considered.
The use of doses >150 000 IU/kg/day has been reported in children with cystic fibrosis.
There are no data regarding the use or magnitude of a loading dose in critically ill children.
No dose recommendations have been established in children *with impaired renal function.*
Method of administration
Colistat is administered *intravenously* as a slow infusion over 30-60 minutes.
Colistimethate sodium undergoes hydrolysis to the active substance colistin in aqueous solution.
Dose conversion table
The dose of colistimethate sodium (CMS) must be prescribed and administered only as International Units (IU). The product label states the number of IU per vial.
Confusion and medication errors have occurred because of the different expressions of dose in terms of potency.
The following conversion table is prepared for information and the values must be considered nominal and approximate only.
CMS conversion table

Potency		≈ mass of CMS (mg)*
IU CMS	≈ mg CBA	
12 500	0.4	1

Potency		≈ mass of CMS (mg)*
IU CMS	**≈ mg CBA**	
150 000	5	12
1 000 000	34	80
4 500 000	150	360
9 000 000	300	720

* Nominal potency of the active substance = 12 500 IU/mg

Preparation and administration of solution

The medicinal product does not contain preservatives, therefore when preparing solutions standard aseptic techniques must be observed. During injecting the solvent into the vial, swirl gently avoiding frothing, until a clear solution.

Colistat should be administered as an intravenous *bolus injection* during 5 minutes or as a slow intravenous *infusion* over 30-60 minutes.

To prepare a solution for intravenous *bolus injection* the content of the vial is dissolved in 10 ml of water for injection or 0.9% sodium chloride solution. The reconstituted solution is clear, colorless.

For intravenous *infusion* the solution for intravenous bolus injection is quantitatively transferred into vial or container with 0.9% sodium chloride and diluted to 50-200 ml and gently swirled. The diluted solution is clear, colorless.

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.

Freshly prepared solutions for *intravenous bolus injection* and *inhalation* in the manufacturer's vials remain their physical and chemical stability for 24 hours protected from light at a temperature 2-8 °C (refrigerator). From a microbiological point of view, the medicinal product should be applied immediately; otherwise the responsibility for the time and storage conditions during use lies with the consumer.

Any remaining solution should be discarded.

Undesirable effects

The likelihood of adverse events may be related to the age, renal function and condition of the patient.

All adverse reactions are listed under system organ class and frequency: very common (≥1/10), common (from ≥1/100 to <1/10), uncommon (from ≥1/1000 to <1/100), rare (from ≥1/10000 to <1/1000), very rare (<1/10000) and unknown (difficult to establish according to the information available).

Immune system disorders: unknown - skin rash, anaphylactic reactions, drug fever. If these occur treatment should be withdrawn.

Nervous system disorders: very common - neurotoxicity (may be associated with overdose, failure to reduce the dose in patients with renal insufficiency and concomitant use of either neuromuscular blocking drugs or other drugs with similar neurological effects; reducing the dose may alleviate symptoms); rare - vasomotor instability, slurred speech, visual disturbances, confusion or psychosis; unknown - respiratory arrest, transient disturbances of sensitivity (facial paresthesia, dizziness), drowsiness, ataxia. In patients with cystic fibrosis, moderate neurological reactions may be observed (in 27% of patients), which disappear on their own during the course of treatment or after its termination.

Gastrointestinal disorders: unknown - gastrointestinal disturbance.

Skin and subcutaneous tissue disorders: very common - general pruritus, urticaria.

Renal and urinary disorders: very common - impaired renal function; rare - renal disorder. Impaired renal function has been reported, usually following use of higher than recommended doses in patients with normal renal function, or failure to reduce the dosage in patients with renal impairment or during

concomitant use of other nephrotoxic medicinal products. The effects are usually reversible on discontinuation of therapy. In cystic fibrosis patients treated within the recommended dosage limits, nephrotoxicity appears to be rare (less than 1%). In seriously ill hospitalised non-CF patients, signs of nephrotoxicity have been reported in approximately 20% of patients.
General disorders and administration site conditions: unknown - irritation at the injection site.
Reporting of adverse reactions
It is important to report suspected adverse reactions after medicinal product registration in order to ensure continuous monitoring of the benefit-to-risk ratio. Healthcare providers are encouraged to report any suspected adverse drug reactions through national ADR systems.
If any adverse reactions occur, patients are advised to consult a doctor or report adverse reactions to the Adverse Drug Reactions Information Database. This recommendation applies to any possible adverse reactions, including those not listed in the instructions for medical use, including reports of ineffectiveness of the medicinal product. Adverse reaction reports provide more information on the safety of a medicinal product.

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 increased serum concentrations of blood urea nitrogen and creatinine.
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.

Interaction with other medicinal products

Colistat should not be used concomitantly with drugs of neurotoxic and/or nephrotoxic action, such as aminoglycosides (gentamicin, amikacin, netilmicin and tobramycin). There may be an increased risk of nephrotoxicity if given concomitantly with cephalosporin antibiotics.
Caution should be taken with concomitant use with other formulations of colistimethate sodium as there is little experience and there is a possibility of summative toxicity.
The potential for drug-drug interactions should be borne in mind when Colistat is co-administered with medicinal products known to inhibit or induce drug metabolizing 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 as their effects 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 should be used with extreme caution in patients receiving colistimethate sodium.
No *in vivo* interaction studies have been performed. The mechanism of conversion of colistimethate sodium to the active substance, colistin, is not characterised. The mechanism of colistin clearance, including renal handling, is equally unknown. Colistimethate sodium or colistin did not induce the activity of any P450 (CYP) enzyme tested (CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4/5) in *in vitro* studies in human hepatocytes.

Storage conditions and shelf life

Keep 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.

Prescription status

Prescription only medicinal product.

Package

1 000 000 IU in 10 ml injection vial. Vials are corked with rubber stoppers and plugged up by aluminum caps with plastic covers with inscription "FLIP OFF" or without inscription.

5 vials with an instruction for medical use in a pack or 36 vials with instructions for medical use in a box (hospital packing).

Information about manufacturer

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