MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

INSTRUCTION
for Medical Use of Medicinal Product

COLISTAT
powder for solution for inhalation
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
No. 829 dd. 10.08.2020]

Trade name: Colistat.
International non-proprietary name: Colistin.
Pharmaceutical form: Powder for solution for inhalation.
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 have 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 species: *Proteus* spp., *Providencia* spp., *Serratia* spp., *Burkholderia cepacia* and related species.
Bacterial resistance is due to the modification of phosphate groups of lipopolysaccharides, which are replaced by ethanolamine or aminoarabinose. Cross resistance between colistin (polymyxin E) 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 by the above mechanism alone would not be expected to result in resistance to other drug classes.

Pharmacokinetics

Absorption

When given by nebulisation, variable absorption has been reported that may depend on the aerosol particle size, nebuliser system and lung status. Studies in healthy volunteers and patients with various infections have reported serum levels from nil to potentially therapeutic concentrations of 4 mg/l or more. About 15% of the administered dose of colistimethate sodium is retained in the lungs.

In a study on healthy volunteers who received colistimethate sodium by inhalation, the C_{max} for polymyxin E1 (active fraction) was from 40.0 to 69.9 ng/ml and the AUC was from 350 to 668 ng/ml/h, depending on the sprayer, the volume of filling and the dose from 0.3 million IU to 2 million IU. The half-life was about 5.2 hours. Absolute bioavailability varied from 5 to 18%, depending on the sprayer.

AUC after an intravenous dose of 0.5 million IU was 3.352 ng/ml/h, and the C_{max} was 1.232 ng/ml.

Due to the low systemic bioavailability with inhalation, the risk of retention of colistimethate sodium in the body of patients with renal failure is low. Therefore, the possibility of systemic absorption should always be borne in mind when treating patients by inhalation.

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 very poor renal function (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.

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.

Ways of colistimethate sodium elimination after inhalation are not studied.

The absorbed part of colistimethate sodium is presumably excreted unchanged by the kidneys. The unabsorbed part after inhalation is presumably excreted in sputum. In patients with cystic fibrosis who received colistimethate sodium in the form of inhalation at a dose of 1 000 000 IU 2 times a day for 3 months, the medicinal product was not detected in the urine.

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 medicinal product *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 active substance 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

Management of adult and paediatric chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis.
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

Bronchospasm may occur on inhalation of antibiotics. This may be prevented or treated with appropriate use of β_2-agonists. If the use of β_2-agonists is not effective, treatment should be discontinued.
Colistimethate sodium should only be used in cases where commonly used antibiotics are ineffective or cannot be used.
In case of *an allergic reaction*, treatment with colistimethate sodium must be discontinued and appropriate measures implemented.

Renal impairment
Colistimethate sodium is excreted via the kidneys and is nephrotoxic at high serum levels. Although this is unlikely when using a solution for inhalation, however, neurotoxic reactions and renal function should be monitored, especially in patients with impaired renal function.
Renal impairment can occur, especially when high doses are given intravenously or intramuscularly in patients with normal renal function, or if the intravenous or intramuscular dose is not adjusted in a patient with renal insufficiency, or in the case of co-administration of other nephrotoxic antibacterials. These effects are usually reversible after treatment discontinuation.
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.
Colistat should not be used as inhalation monotherapy in the treatment of exacerbation of chronic infections caused by *Pseudomonas aeruginosa*.
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.
It is recommended to monitor the performance of forced expiratory volume 1-second (FEV_1) before and after inhalation of the medicinal product. If a patient shows signs of bronchial obstruction caused by the medicinal product, the test (FEV_1) should be repeated by adding a bronchodilator with subsequent use of Colistat-TF.
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.
In the treatment with colistimethate sodium, strains of resistant microorganisms may appear. Restoring the effectiveness of the medicinal product is possible after cancellation and/or modification of therapy.

Posology and method of administration

It is recommended that colistimethate sodium (CMS) should be administered by inhalation under the supervision of physicians with appropriate experience in its use. The course of treatment is determined individually and depends on the patient's clinical condition.
The dose is expressed in international units (IU) of 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.
Adults, adolescents and children ≥ 2 years
1 000 000 – 2 000 000 IU two to three times per day (max 6 000 000 IU/day).
Children < 2 years
500 000 – 1 000 000 IU twice daily (max 2 000 000 IU/day).
No dose adjustment is required for *elderly* patients, patients with *hepatic* or *renal impairment*; however, caution should be exercised when administering Colistat in patients with impaired renal function.
In small, uncontrolled clinical trials, doses of from 500 000 IU twice daily up to 2 000 000 IU three times daily have been found to be safe and effective in patients with cystic fibrosis.

Relevant clinical guidance on treatment regimens, including duration of treatment, periodicity and co-administration of other antibacterials should be adhered to.

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.

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

The contents of the vial is reconstituted with either water for injection to produce a hypotonic solution *for inhalation* or a 50:50 mixture of water for injection and 0.9% sodium chloride to produce an isotonic solution or 0.9% sodium chloride to produce a hypertonic solution. The reconstituted solution is clear, colorless.

The volume of reconstitution should be determined according to the instructions for use of nebulizer administration device, and is normally not more than 4 ml. The required amount of this solution is poured into a sprayer that attached to a device for supplying air/oxygen.

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 deep breaths as possible through the mouthpiece of the nebulizer. To facilitate the breath through the 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 solution for *inhalation* should be used immediately after preparation.

The unutilized medicinal product solution should be discarded.

Undesirable effects

The most common undesirable effects after inhalation of colistimethate sodium are cough and bronchospasm (in about 10% of patients).

The likelihood of undesirable effects may vary depending on age, renal function and the general condition of the patient.

Sore throat or mouth has been reported and may be due to *Candida* spp. infection or hypersensitivity.

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).
Infections and invasions: unknown - oral candidiasis.
Immune system disorders: unknown - hypersensitivity reactions such as skin rash. If this occurs treatment should be discontinued.
Respiratory, thoracic and mediastinum-related disorders: very common - reflex cough, bronchospasm.
General disorders and administration site conditions: unknown - pharyngodynia, oral pain.
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.
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 ingestion of medicinal product the development of toxicity is unlikely, since colistimethate sodium is absorbed from the gastrointestinal tract in small amount.

Interaction with other medicinal products

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.
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.
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 renal transporter substrates.
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.
Due to the effects of colistin on the release of acetylcholine, non-depolarising muscle relaxants should be used with caution in patients receiving Colistat as their effects could be prolonged.
Concomitant use of colistimethate sodium in the form of inhalation with inhalants anesthetics, muscle relaxants of central and peripheral action and aminoglycosides increases the risk of neuromuscular blockade.
Concomitant use of colistimethate sodium with other medicinal products of neurotoxic and/or nephrotoxic potential (e.g. cephalosporins, aminoglycosides, non-depolarizing muscle relaxants) including for intravenous or intramuscular administration, is recommended with extreme caution.

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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