SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Colistat 2 000 000 IU powder for solution for intravenous administration and inhalation

2. Qualitative and quantitative composition
Each vial contains 2 000 000 IU of colistimethate sodium.

3. Pharmaceutical form
Powder for solution for intravenous administration and inhalation.
White or almost white powder.

4. Clinical particulars
4.1 Therapeutic indications
Colistat *by intravenous administration* 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 (see sections 4.2, 4.4, 4.8 and 5.1).
Colistat *by inhalation* is also indicated for the management of adult and paediatric chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (see section 5.1).
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Posology
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.
The following dose recommendations are made based on limited population-pharmacokinetic data in critically ill patients (see section 4.4).
Systemic treatment
Adults and adolescents
Recommended maintenance dose is 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.
Special populations
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.
Haemodialysis
- 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.

CVVHF/ CVVHDF
As 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.
Intrathecal and intraventricular administration
Based on limited data, the following dose is recommended in adults:
Intraventricular route
125 000 IU/day
Intrathecally administered doses should not exceed those recommended for intraventricular use.
No specific dosing recommendation can be made in children for intrathecal and intraventricular routes of administration.
Aerosol inhalation
It is recommended that colistimethate sodium (CMS) should be administered under the supervision of physicians with appropriate experience in its use.
The dosage can be adjusted depending on the severity of the condition and clinical response.
Recommended dose range:
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).
Relevant clinical guidance on treatment regimens, including duration of treatment, periodicity and co-administration of other antibacterial agents should be adhered to.
Elderly
Dose adjustment is not considered necessary.
Renal impairment
Dose adjustment is not considered necessary; however caution is advised in patients with renal impairment (see sections 4.4 and 5.2).
Hepatic impairment

Dose adjustment is not considered necessary.

Method of administration

Parenteral use

Colistat is administered intravenously as a bolus injection given over a minimum of 5 minutes or as a slow infusion over 30-60 minutes.

Patients with a totally implantable venous access device (TIVAD) in place may tolerate a bolus injection of up to 2 000 000 IU in 10 ml given over a minimum of 5 minutes (see section 6.6).

Colistimethate sodium undergoes hydrolysis to the active substance colistin in aqueous solution. The medicinal product does not contain preservatives, therefore, reconstitution of the required dose must be performed using strict aseptic technique (see section 6.6).

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	**≈ 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 drug substance = 12 500 IU/mg

Inhalation use

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.

4.3 Contraindications

Hypersensitivity to colistimethate sodium, colistin or to polymyxin B.

4.4 Special warnings and precautions for use

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 col-

istin 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 for special populations (patients with renal impairment and the paediatric population). Colistimethate sodium 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.
Impairment of renal function
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 (see section 4.2). Patients who are hypovolemic or those receiving other potentially nephrotoxic drugs are at increased risk of nephrotoxicity from colistin (see sections 4.5 and 4.8).
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, which may be associated with overdosage or failure to reduce the dosage in patients with renal impairment, have been reported to lead to neurotoxic effects. Concomitant administration with non-depolarizing muscle relaxants or antibiotics with similar neurotoxic effects also causes neurotoxicity. Dose reduction of colistimethate sodium may improve symptoms. Neurotoxic adverse effects include vertigo, facial paraesthesia, 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 (see section 4.9).
Colistimethate sodium should be used with extreme caution in patients with porphyria.
Colistimethate sodium is known to reduce the presynaptic release of acetyl-choline 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. It is important to consider this diagnosis in patients who develop diarrhoea during or after the use of colistimethate sodium (see section 4.8). Discontinuation of therapy and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.
Intravenous colistimethate sodium does not cross the blood brain barrier to a clinically relevant extent. The use of intrathecal or intraventricular administration of colistimethate sodium in the treatment of meningitis was not systematically investigated in clinical trials and is supported by case reports only. Data supporting the posology are very limited. The most commonly observed adverse effect of CMS administration was aseptic meningitis (see section 4.8).
Colistat should not be used as inhalation monotherapy in the treatment of exacerbation of chronic infections caused by *Pseudomonas aeruginosa*. Bronchospasm may occur on inhalation of antibiotics. This may be prevented or treated with appropriate use of beta$_2$-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 beta$_2$-agonists is not effective, treatment should be discontinued.
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.
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 drug is possible after cancellation and/or modification of therapy.
Sodium
Colistat contains less than 1 mmol sodium (23 mg) per vial that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction
Concomitant use of intravenous colistimethate sodium with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with great caution.
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 drugs known to inhibit or induce drug metabolizing enzymes or drugs 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 (see section 4.4).
Neuromuscular blocking medicinal products 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.
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 (see section 4.4).
Concomitant use of colistimethate sodium with other medicinal products of neurotoxic and/or nephrotoxic potential should be avoided. These include the aminoglycoside antibiotics such as gentamicin, amikacin, netilmicin and tobramycin. There may be an increased risk of nephrotoxicity if given concomitantly with cephalosporin antibiotics.

4.6 Fertility, pregnancy and lactation
Pregnancy
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 (see section 5.3). Colistimethate sodium should be used in pregnancy only if the benefit to the mother outweighs the potential risk to the foetus.
Lactation
Colistimethate sodium is secreted in breast milk. If use of sodium colistimethate during lactation is necessary, it should be considered to stop breastfeeding.

4.7 Effects on ability to drive and use machines
Colistimethate sodium may affect the ability to drive and use machines. During parenteral treatment with colistimethate sodium neurotoxicity may occur with the possibility of dizziness, confusion or visual disturbance. Patients should be warned not to drive or operate machinery if these effects occur.

4.8 Undesirable effects
Systemic treatment
The likelihood of adverse events may be related to the age, renal function and condition of the patient.
In cystic fibrosis patients neurological events have been reported in up to 27% of patients. These are generally mild and resolve during or shortly after treatment.
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. Effects may include apnoea, transient sensory disturbances (such as facial paraesthesia and vertigo) and, rarely, vasomotor instability, slurred speech, visual disturbances, confusion or psychosis.
Adverse effects on renal function have 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 drugs. 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.
Hypersensitivity reactions including skin rash and drug fever have been reported. If these occur treatment should be withdrawn.
Local irritation at the site of injection may occur.
Inhalation treatment
Inhalation may induce coughing or bronchospasm.
Sore throat or mouth has been reported and may be due to *Candida albicans* infection or hypersensitivity. Skin rash may also indicate hypersensitivity, if this occurs treatment should be withdrawn.

Reporting of suspected adverse reactions
It is important to report suspected adverse reactions after drug 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 drug product. Adverse reaction reports provide more information on the safety of a drug product.

4.9 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 (BUN) and creatinine.
There is no specific antidote. Manage by supportive treatment and 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.
Overdose is unlikely by the inhaled route but has been recognized after systemic use.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use. Other antibacterials. Polymyxins.
ATC code: J01XB01.
Mechanism of action
Colistin is a cyclic polypeptide antibacterial agent belonging to the polymyxin group. Polymyxins work by damaging the cell membrane and the resulting physiological effects are lethal to the bacterium. Polymyxins are selective for aerobic Gram-negative bacteria that have a hydrophobic outer membrane.
Resistance
Resistant bacteria are characterised by modification of the phosphate groups of lipopolysaccharide, which become substituted with ethanolamine or aminoarabinose. Naturally resistant Gram-negative bacteria, such as *Proteus mirabilis* and *Burkholderia cepacia*, show complete substitution of their lipid phosphate 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.
PK/PD relationship
Polymyxins have been reported to have a concentration-dependent bactericidal effect on susceptible bacteria. fAUC/ MIC is considered to be correlated with clinical efficacy.

Microorganism	**Susceptible**	**Resistant**[a]
Acinetobacter	≤2 mg/L	>2 mg/L
Enterobacteriaceae	≤2 mg/L	>2 mg/L
Pseudomonas spp.	≤4 mg/L	>4 mg/L

[a] Breakpoints apply to dosage of 2 000 000-3 000 000 IU x 3. A loading dose (9 000 000 IU) may be needed.

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent, in at least some types of infections, is questionable.
Commonly susceptible species
Acinetobacter baumannii
Haemophilus influenzae
Klebsiella spp.
Pseudomonas aeruginosa
Species for which acquired resistance may be a problem
Stenotrophomonas maltophilia
*Achromobacter xylosoxidans (*formerly *Alcaligenes xylosoxidans)*
Inherently resistant organisms
Burkholderia cepacia and related species
Proteus spp.
Providencia spp.
Serratia spp.

5.2 Pharmacokinetic properties

Absorption

The information on the pharmacokinetics of colistimethate sodium (CMS) 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. The following data are based on studies using HPLC to determine CMS/colistin plasma concentrations.

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

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 4mg/l or more. 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 (ECF). The volume of distribution is relevantly enlarged in critically ill subjects. Protein binding is moderate and decreases at higher concentrations. In the absence of meningeal inflammation, penetration into the cerebrospinal fluid (CSF) is minimal, but increases in the presence of meningeal inflammation.

Both CMS and colistin display linear PK in the clinically relevant dose range.

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 CMS 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%. CMS is eliminated predominantly by the kidneys via glomerular filtration. In healthy subjects, 60% to 70% of CMS 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 CMS.

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

5.3 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 foetuses respectively. These doses are 0.5 and 1.2 times the maximum daily human dose. In addition, increased reabsorption occurred at 9.3 mg/kg.

There are no other preclinical safety data of relevance to the prescriber that are additional to safety data derived from patient exposure and already included in other sections of the SPC.

6. Pharmaceutical particulars

6.1 List of excipients

None.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

The solution for intravenous infusion should be used immediately after preparation.

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 a 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.

6.4 Special precautions for storage

Keep protected from moisture and light at a temperature not exceeding 25 °C.

Keep out of the reach of children.

For storage conditions of the reconstituted/diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

2 000 000 IU in 10 ml vials for injection. Vials are corked up by rubber stoppers and plugged up by aluminum caps with plastic covers. The plastic cover can have an inscription "FLIP OFF" or have no inscription.

The medicinal product is supplied in packs of 5 vials.

6.6 Special precautions for disposal and other handling

The medicinal product does not contain preservatives, therefore when preparing solutions standard aseptic techniques must be observed.

Parenteral use

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.

The reconstituted solution is a clear, colorless solution.

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 diluted solution is a clear, colorless solution.

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.

When the intrathecal and intraventricular routes of administration are used, the volume administered should not exceed 1 ml (reconstituted concentration 125 000 IU/ml).

Inhalation use

To prepare hypotonic *solution for inhalation* the contents of the vial is pre-dissolved in water for injection, for isotonic solution – in a mixture of 50:50 water for injection and 0.9% sodium chloride solution, for hypertonic solution – in 0.9% sodium chloride solution. The volume of the reconstituted solution is determined by the instructions for use of the nebulizer and usually does not exceed 4 ml. The required amount of this solution is poured into a sprayer that attached to a

device for supplying air/oxygen.
Nebulisation should take place in a well ventilated room.
The unutilized solution of the medicinal product must be discarded!
For storage conditions of the reconstituted/diluted medicinal product, see section 6.3.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder
TriplePharm JLLC, Minskaya str., 2B, 223141, Logoysk, Republic of Belarus.
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8. Marketing authorisation number(s)

9. Date of first authorisation/renewal of the authorisation
Date of first authorisation: 07/05/2017
Date of latest renewal:

10. Date of revision of the text
01/2022