SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Colixin 1.000.000 I.U. Powder for solution for injection or for nebuliser solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial for injectable contains 1 million of International Units of Colistimethate sodium (corresponding approximately to 80 mg of colistimethate sodium).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or for nebuliser solution.
White or almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Colixin is indicated in adults and children including neonates for the treatment of serious infections due to selected aerobic Gram-negative pathogens with limited treatment options (see sections 4.2, 4.4, 4.8 and 5.1).

Colixin is indicated for the management in adult and paediatric of 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

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.

It is recommended that colistimethate sodium (CMS) should be administered under the supervision of physicians with appropriate experience in its use.

<u>Posology</u>

The following dose recommendations are made based on limited population-pharmacokinetic data in critically ill patients (see section 4.4):

Intravenous administration

Adults and adolescents
Maintenance dose 9 MIU/day in 2-3 divided doses.

In patients who are critically ill, a loading dose of 9 MIU 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 MIU 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.

The following dose adjustments are suggested as guidance.

Dose reductions are recommended for patients with xreatinine clearance < 50 ml/min:
Twice daily dosing is recommended.

Creatinine clearance (ml/min)	**Daily dose**
< 50-30	5.5-7.5 MIU
<30-10	4.5-5.5 MIU
<10	3.5 MIU

MIU = million IU

Haemodialysis and continuous haemo(dia)filtration
Colistin appears to be dialyzable through conventional haemodialysis and continuous venovenous 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: 2.25 MIU/day (2.2 – 2.3 MIU/day).
HD days: 3 MIU/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.

Older people
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 ≤ 40 kg
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.

Administration via inhalation

Adults, adolescents and children ≥ 2 years
1-2 MIU two to three times per day (max 6 MIU/day)

Children < 2 years
0.5-1 MIU twice daily (max 2 MIU/day)

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

Older people
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

Intravenous use
Colixin is administered intravenously as a slow infusion over 30 – 60 minutes.

Colistimethate sodium undergoes hydrolysis to the active substance colistin in aqueous solution. For dose preparation, particularly where combination of multiple vials is needed, reconstitution of the required dose must be performed using strict aseptic technique (see section 6.6).

Inhalation use

For special precautions for disposal and handling of reconstituted solutions, see section 6.6.

If other treatments are being taken, they should be taken in the order recommended by the physician.

Dose conversion table:
In the EU, 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 dose is expressed in the US, and other parts of the world, as milligrams of colistin base activity (mg CBA).

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	**≈ 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

4.3 Contraindications

Colixin is contraindicated in patients with hypersensitivity to colistimethate sodium and 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 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 emergency 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 MIU/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.

Renal function monitoring should be performed at the start of treatment and regularly during treatment in all patients. The dose of colistimetahte sodium should be adjusted according to creatinine clearance (see section 4.2). Patients who are hypovolaemic 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.

In case of an allergic reaction, treatment with colistimethate sodium must be discontinued and appropriate measures implemented.

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 such as 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 (see section 4.9).

Colistimetahte sodium is known to reduce the presynaptic release of acetyl-choline at the neuro-muscular 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 colistimetahte sodium. Impaired renal function increases the possibility of apnoea and neuromuscular blockade following administration of colistimetahte sodium.

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

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 and 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 colistimetahte 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 adminsitration was aseptic meningitis (see section 4.8).

The inhalation of colistimethate sodium may induce cough or bronchospasm. The occurrence of bronchospasm may be prevented or treated with the use of beta$_2$-agonists.

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 equal unknown. 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.

The potential for drug-drug interactions should be borne in mind when Colixin is co-administered with drugs known to inhibit or induce drug metabolising 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).

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).

4.6 Fertility, pregnancy and lactation

Pregnancy:
The safety in pregnancy has not been yet established. There are no adequate studies on the use of colistimethate sodium in human pregnancy. 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 women.

Colistimethate sodium should not be used in pregnancy unless the potential benefits outweighs the potential risks for the foetus.

Breast-feeding:
Colistimethate sodium is excreted in breast milk, therefore, should not be administered to breastfeeding women unless clearly needed.

Fertility:
Animal studies are insufficient regarding the colistimethate sodium effect over reproduction and development (see section 5.3). There are no data available in humans about the effect of colistimethate sodium in fertility.

4.7 Effects on ability to drive and use machines

Neurotoxicity may occur during the treatment with colistimethate sodium, namely, dizziness, confusion and visual disturbances, therefore, patients should be warned for the fact that the occurrence of these symptoms may limit the ability for the execution of tasks such as drive and use of machines.

4.8 Undesirable effects

a. Summary of the safety profile
Systemic treatment:
When administered by intravenous use, neurotoxicity and nephrotoxicity are the most severe undesirable effects of Colixin, and occur mainly with the use of higher doses than recommended or in patients with impairment of renal function.

In cystic fibrosis patients neurological events have been reported in up to 27% of the patients.

In cystic fibrosis patients treated within the recommended dosage limits, nephrotoxicity appears to be rare (less than 1%). In seriously ill hospitalised non cystic fibrosis patients, signs of nephrotoxicity have been reported in approximately 20% of the patients.

Nebulisation treatment (aerosol inhalation)
Bronchoconstriction is the most serious undesirable effect reported in adults and children with cystic fibrosis treated with Colixin by nebulisation.

b. Summary of adverse effects
The undesirable effects are reported in the approximate frequencies:

Systemic treatment:
Psychiatric disorders
Rare (≥1/10,000 to <1/1,000): mental confusion, psychotic episodes.

Nervous system disorders
Very common (≥1/10): neurological events (with cystic fibrosis)
Rare (≥1/10,000 to <1/1,000): slurred speech
Not known (cannot be estimated from the available data): transient sensory disturbances, such as facial paraesthesia and vertigo

Eye disorders
Rare (≥1/10,000 to <1/1,000): blurred vison

Vascular disorders
Rare (≥1/10,000 to <1/1,000): vasomotor instability

Respiratory, thoracic and mediastinal disorders
Not known (cannot be estimated from the available data): apnoea.

Skin and subcutaneous tissue disorders
Not known (cannot be estimated from the available data): hypersensitivity reactions including skin rash

Renal and urinary disorders
Very common (≥1/10): nephrotoxicity (non cystic fibrosis)
Uncommon (≥1/1,000 to <1/100): nephrotoxicity (cystic fibrosis)
Not known (cannot be estimated from the available data): decrease urine output, increased concentrations of urea and creatinine, proteinuria, hematuria, urinary detection of cylinders, acute tubular necrosis.

General disorders and administration site conditions
Not known (cannot be estimated from the available data): local irritation at the site of the injection

Nebulisation treatment (aerosol inhalation):
The frequency of the following adverse effects are unknown (cannot be estimated from the available data):

Nebulisation may induce coughing or bronchospasm.

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

c. Description of selected adverse effects

The neurological adverse effects generally appear in the first 4 days of therapy and disappear when the drug is discontinued. When these effects occur, colistimethate sodium therapy does not necessarily have to be discontinued, but the patient should be closely monitored. Dose reduction may relieve some of the neurologic symptoms. Patients receiving Colixin may present neuromuscular blockage, which can result in respiratory arrest and apnoea, especially in patients with neuromuscular disease, such as *myasthenia gravis*, or with the concomitant use, of curariform agents or other drugs with similar neurological effects.

Adverse effects on renal function have been reported, usually following the administration of higher doses than the recommended doses in patients with normal renal function, in patients with renal impairment were dose reduction was not successful or during the concomitant use of other nephrotoxic drugs. The effects are usually reversible with the discontinuation of the therapy; however, additional increase of the serum creatinine concentration of can be seen one to two weeks after the suspension of the drug.

Bronchospasm occurred almost immediately, after the beginning of Colixin administration by nebulisation, which may last 30 minutes (see section 4.4).

Hypersensitivity reactions including skin rash have been reported. If these occur, treatment should be withdrawn.

d. Paediatric population
The available information suggest that the safety profile of the treatment of paediatric patients with Colixin is no different form the observed in the treatment of adult patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

The 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 urea and creatinine.

There is no specific antidote. Support treatment and measures to increase the elimination of colistimethate sodium, such as induction of osmotic diuresis with mannitol, prolonged haemodialysis or peritoneal dialysis may be useful.

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 polymycin group. Polymyxins work by damaging the cell membrane and 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 (polymycin 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.

EUCAST Breakpoints

	Susceptible (S)	Resistant (R)[(a)]
Acinetobacter	S≤2	R>2 mg/L
Enterobacteriaceae	S≤2	R>2 mg/L
Pseudomonas spp	S≤4	R>4 mg/L

[(a)] *Breakpoints apply to dosage of 2-3 MIU x 3. A loading dose (9 MUI) 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

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 health 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.

Distribution
The volume of distribution of colistin in health 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 health 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/ml), 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 eliminação 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 3 L/h. In critically ill patients, half-life has been reported to be prolonged to around 9-18h.

5.3 Preclinical safety data

Animal studies are insufficient regarding the colistimethate sodium effect over reproduction.

Colistimethate sodium has shown *in vitro* to be an inductor of chromosomic aberrations in human lymphocytes. This effect may be related with a reduction of the 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 doses of 4.15 and 9.3 mg/kg resulted in talipes varus in 2.6 and 2.9% of the foetuses respectively. These doses are 0.5 and 1.2 times the maximum daily human dose. In addition, increased resorption occured at 9.3 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

The mixture of infusions, injections and nebuliser solutions involving colistimethate sodium should be avoided.

6.3 Shelf life

3 years.

After reconstitution:
The hydrolysis of Colistimethate sodium increases significantly when reconstituted and diluted below the critical micelle concentration which is approximately 80.000 IU per ml.

In solutions for bolus injection of for nebulisation with a concentration ≥ 80.000 IU/ml, it was demonstrated that the physical and chemical stability of the reconstituted solution is maintained for 24 hours at 2 – 8ºC.

From a microbiological point of view, unless the method of opening/reconstitution/dilution prevent the risk of microbial contamination, the solution of colistimethate sodium should be used immediately. If not used immediately, the conditions and in-use storage times are the responsibility of the user.

The solutions for infusion, which have been diluted with a volume superior of the original vial and/or with a dilution concentration < 80.000 IU/ml should be used immediately.

For solutions for intrathecal and intraventricular administration, the reconstituted product should be used immediately.

6.4 Special precautions of storage

Store below 25ºC. Keep the vials in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

Colourless glass vials for injectable, type I, 10 ml, with rubber stopper and “flip-off top” aluminium cap.

Colixin is presented in packs of 10 and 30 vials for injectable.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Systemic administration

For bolus injection

Reconstitute the content of the vial with no more than 10 ml of water for injection or 0.9% sodium chloride.

For infusion
The content of the reconstituted vial is usually diluted with 50 ml 0.9% sodium chloride.

The normal adult dose of 2.000.000 IU should be dissolved in 10-50 ml of 0.9% sodium chloride or in water for injections to form a clear solution.

The solution is for single use only and any remaining solution should be discarded.

The compatible infusion solutions are 0.9% sodium chloride, 5% dextrose, 5% fructose, Ringer's solution and 10% dextrose in sodium chloride.

For intrathecal and intraventricular use
The volume administered should not exceed 1 ml (reconstituted solution of 125.000 IU/ml). Reconstitute the content of one vial of 1.000.000 IU with 8 ml of 0.9% sodium chloride.

For inhalation by nebulization
Reconstitute the content of the vial with water for injections to produce a hypotonic solution or a 50:50 mixture of water for injections and 0.9% sodium chloride to produce a isotonic solution, or with 0.9% sodium chloride to produce a hypertonic solution.

The volume of reconstitution should be according with the instructions for use of the nebuliser administration device, and normally is not more than 4 ml.

During the reconstitution stir gently to avoid foaming.

The required amount of powder is dissolved preferably in 2-4 ml of 0.9% sodium chloride and poured into the nebuliser. Alternatively, water for injections may be used.

The solution will be slightly hazy and may foam if shaken. Usually jet or ultrasonic nebulisers are preferred for antibiotic delivery. These should produce the majority of their output in the respirable particle diameter range of 0.5-5.0 microns when used with a suitable compressor. The instructions from the manufacturers should be followed for the maintenance and care of the nebuliser and compressor.

The output from the nebuliser may be vented to the open air or a filter may be fitted. Nebulisation should take place in a well ventilated room.

The solution is for single use only and any remaining solution must be discarded.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.