PACKAGE LEAFLET

Package leaflet: Information for the user

Colistimethate sodium 1 million IU Powder for solution for injection/infusion
Colistimethate sodium 2 million IU Powder for solution for injection/infusion

Colistimethate sodium

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Colistimethate sodium is and what it is used for

This medicine contains the active substance colistimethate sodium. Colistimethate sodium is an antibiotic. It belongs to a group of antibiotics that are called polymyxins.

This medicine is given by injection to treat some types of serious infections caused by certain bacteria. It is used when other antibiotics are not suitable.

2. What you need to know before you are given Colistimethate sodium

Colistimethate sodium must not be given

- If you are allergic to colistimethate sodium, colistin or to other polymyxins**.**

Warnings and precautions
Talk to your doctor, pharmacist or nurse before receiving Colistimethate sodium if:
- if you have or have had kidney problems
- if you suffer from myasthenia gravis
- if you suffer from porphyria
- if you suffer from asthma

If you experience muscle spasm, fatigue or increased urine output at any time, tell your doctor immediately as these events may be related to a condition known as pseudo-Bartter syndrome.

Children
In premature and new-born babies, special care should be taken when using Colistimethate sodium as their kidneys are not yet fully developed.

Other medicines and Colistimethate sodium
Tell your doctor if you are taking, have recently taken or might take any other medicines.

If you are taking any of the following medicines, you may or may not be able to receive Colistimethate sodium. Sometimes the other medicines must be stopped (if only for a while) or you may need a lower dose of Colistimethate sodium or you may need to be monitored while you are undergoing treatment with this medicine. In some cases, the level of Colistimethate sodium in your blood may have to be measured from time to time to make sure that you are having the right dose.

- Medicines like antibiotics called aminoglycosides (which include gentamicin, tobramycin, amikacin and netilmicin) and cephalosporins which can affect how your kidneys function. Taking such medicines at the same time as Colistimethate sodium can increase the risk of damage to the kidneys (see section 4 of this leaflet).
- Medicines like antibiotics called aminoglycosides (which include gentamicin, tobramycin, amikacin and netilmicin) which can affect your nervous system. Taking such medicines at the same time as Colistimethate sodium can increase the risk of side effects in the ears and other parts of your nervous system (see section 4 of this leaflet).
- Medicines called muscle relaxants, often used during general anaesthesia. Colistimethate sodium can increase the effects of these medicines. If you have a general anaesthetic, let your anaesthetist know that you are having Colistimethate sodium.

If you suffer from myasthenia gravis (muscle weakness) and are also taking other antibiotics called macrolides (such as azithromycin, clarithromycin or erythromycin) or antibiotics called fluoroquinolones (such as ofloxacin, norfloxacin and ciprofloxacin), taking Colistimethate sodium further increases the risk of muscle weakness and breathing difficulties.

Having Colistimethate sodium as an infusion at the same time as receiving Colistimethate sodium as an inhalation can increase your risk of side effects.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
Small amounts of Colistimethate sodium pass into breast milk, hence, breastfeeding is not recommended. If you cannot stop breast-feeding while you take Colistimethate sodium, you should watch your baby carefully for any signs of illness and tell your doctor if you notice anything wrong.
Data on the possible impact of colistimethate sodium on human fertility are not available

Driving and using machines
When Colistimethate sodium is given into a vein there may be side effects such as dizziness, confusion or problems with vision. If these occur, you should not drive or operate machinery.

Colistimethate sodium contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium free’.

3. How to use Colistimethate sodium

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Depending on the reason (see section 1 of this leaflet), Colistimethate sodium may be given by fast injection (over 5 minutes into a special kind of tube in a vein) or slow injection (infusion over about 30 to 60 minutes) into a vein. Colistimethate sodium may occasionally be given by injection into the brain or the spine.

The usual daily dose in adults is 9 million units, divided into two or three doses. If you are quite unwell, you will be given a higher dose of 9 million units once at the start of treatment.
In some cases, your doctor may decide to give a higher daily dose of up to 12 million units.

The usual daily dose in children weighing up to 40 kg is 75,000 to 150,000 units per kg body weight, divided into three doses. Higher doses have occasionally been given in cystic fibrosis.

Children and adults with kidney problems, including those on dialysis, are usually given lower doses. Your doctor will monitor your kidney function regularly while you receive Colistimethate sodium.

Method of administration
Intravenous, intrathecal or intracerebroventricular use.
Colistimethate sodium is given to you by your doctor as an infusion into a vein over 30 – 60 minutes or by injection over a minimum of 5 minutes. Colistimethate sodium is given mainly in hospitals. If you are to treat yourself at home, your doctor or nurse will show you how to dissolve the powder and inject the right dose of solution.

Duration of treatment
Your doctor will decide how long your treatment should last depending of the severity of the infection. When treating bacterial infections it is important to complete the full course of treatment, so as to prevent worsening of the existing infection.

If you use more Colistimethate sodium than you should
If you think that you have given yourself too much Colistimethate sodium, you should contact your doctor or nurse immediately for advice or, if they are not available, contact or go to your nearest hospital accident and emergency department.

If too much Colistimethate sodium is accidentally given, the side effects can be serious and can include kidney problems, muscle weakness and difficulty (or even stopping) breathing.

If you miss a dose of Colistimethate sodium
If you are treating yourself and have missed any doses, you should give the missed dose as soon as you remember and then give the next dose 8 hours later if using Colistimethate sodium three times a day, or 12 hours later if using Colistimethate sodium twice a day. Carry on from there as instructed. Do not take a double dose to make up forgotten dose.
If you are being treated in hospital or at home by a doctor or nurse and think that you may have missed a dose or been given too much Colistimethate sodium, please ask your doctor or nurse about this.

If you stop using Colistimethate sodium
Do not stop your treatment early unless your doctor says you can. Your doctor will decide how long your treatment should last.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions
When Colistimethate sodium is given into a vein, an allergic reaction is possible.
Serious allergic reactions can happen even with the very first dose and can include rapid development of rashes, swelling of the face, tongue and neck, inability to breathe due to narrowing of the airways and loss of consciousness.

If you experience signs of an allergic reaction you should seek urgent medical attention.
Less severe allergic reactions include skin rashes that appear later during treatment.

You may experience, after intravenous administration, the following symptoms that may be related to a condition known as pseudo-Bartter syndrome (see section 2):

- muscle spasm
- increase in urine output
- fatigue

Side effects that affect the nervous system are more likely to occur when the dose of Colistimethate sodium is too high, in people who have poor kidneys or in those who are also taking muscle relaxants or other medicines with a similar effect on how the nerves work. The most serious of these possible side effects in the nervous system is inability to breathe because of paralysis of the chest muscles.

If you experience any difficulty breathing you should seek urgent medical attention.

Other possible side effects include numbness or tingling (especially around the face), dizziness or loss of balance, rapid changes in blood pressure or blood flow (including faintness and flushing), slurred speech, problems with vision, confusion and mental problems (including loss of sense of reality). There can be reactions at the site of the injection, such as irritation.

Kidney problems may also occur. These are especially likely in people who already have poor kidneys, or who are given Colistimethate sodium at the same time as other medicines that can cause side effects in the kidneys or who are given a dose that is too high. These problems will normally get better if treatment is stopped or the dose of Colistimethate sodium is reduced.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Colistimethate sodium

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial and carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Reconstituted / diluted solution:
Hydrolysis of colistimethate is significantly increased when reconstituted and diluted below its critical micelle concentration of about 80,000 IU per ml. Solutions below this concentration should be used immediately.

For solutions for bolus injection, the chemical and physical in-use stability of reconstituted solution in the original vial, with a concentration ≥80,000 IU/ml, has been demonstrated for:
- 1 MIU for 3 hours at 2-8°C when dissolved in 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or water for injection.
- 2 MIU for 3 hours at 2-8°C when dissolved in 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or water for injection.

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

Solutions for infusion, which have been diluted beyond the original vial volume and / or with a concentration < 80,000 IU/ml should be used immediately.

For solutions for intrathecal and intracerebroventricular administration, the reconstituted medicinal product should be used immediately.
Visually inspect the solution for particulate matter prior to administration. Only a clear and practically free from particles solution should be used.

Any remaining solution should be discarded.

Do not throw away any medicines via wastewater <or household waste>. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Colistimethate sodium contains
The active substance is colistimethate sodium.
Each vial contains 1 million IU colistimethate sodium.
Each vial contains 2 million IU colistimethate sodium.
There are no other ingredients.

What Colistimethate sodium looks like and contents of the pack
Colistimethate sodium powder for solution for injection/infusion, is supplied as a white to off white powder in single dose vials.

For 1 million IU: Clear type I glass vials closed with type I bromobutyl rubber stoppers 20 mm and sealed with 20 mm white pull-off caps and aluminum discs.
For 2 million IU: Clear type I glass vials closed with type I bromobutyl rubber stoppers 20 mm and sealed with 20 mm orange pull-off caps and aluminum discs.

Pack sizes: 1, 10 and 30 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Noridem Enterprises Ltd.
Evagorou & Makariou,
Mitsi Building 3, Office 115,
Nicosia 1065, Cyprus

Manufacturer
DEMO S.A. PHARMACEUTICAL INDUSTRY
21st Km National Road Athens–Lamia,
14568 Krioneri, Attiki, Greece
T: +30 210 8161802, **F:** +30 2108161587

This medicine is authorised in the Member States of the European Economic Area under the following names:

Germany	Colistimethat-Natrium Noridem 1 Million I.E. Pulver zur Herstellung einer Injektions-/Infusionslösung Colistimethat-Natrium Noridem 2 Millionen I.E. Pulver zur Herstellung einer Injektions-/Infusionslösung
Ireland	Colistimethate sodium 1 million IU Powder for solution for injection/infusion Colistimethate sodium 2 million IU Powder for solution for injection/infusion
Czech Republic	Colistimethate Noridem Colistimethate Noridem

Greece	KOLELANG 1 MIU Κόνις για ενέσιμο διάλυμα/ διάλυμα προς έγχυση KOLELANG 2 MIU Κόνις για ενέσιμο διάλυμα/ διάλυμα προς έγχυση
Austria	Colistimethat-Natrium DEMO 1 Mio. I.E. Pulver zur Herstellung einer Injektions-/Infusionslösung Colistimethat-Natrium DEMO 2 Mio. I.E. Pulver zur Herstellung einer Injektions-/Infusionslösung
Italy	Colistimetato sodico Noridem Ltd Colistimetato sodico Noridem Ltd
Poland	Colistimethatum natricum Noridem Colistimethatum natricum Noridem
Slovakia	Colistimethate Noridem 1 MIU prášok na injekčný/infúzny roztok Colistimethate Noridem 2 MIU prášok na injekčný/infúzny roztok

This leaflet was last revised in 04/05/2023.

The following information is intended for healthcare professionals only:

Preparation and handling

Instructions for preparation of the solution for injection / infusion

For bolus injection:
Reconstitute the contents of the vial with not more than 10 ml water for injection or sodium chloride 9 mg/ml (0.9 %) solution for injection.

For infusion:
The contents of the reconstituted vial may be diluted, usually with 50 ml sodium chloride 9 mg/ml (0.9 %) solution for injection.

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

After reconstitution, the solution is clear and colorless or not more intensively colored than Y6 solution free from visible particles.

Solutions are for single use only and any remaining solution should be discarded.

The medicinal product is to be visually inspected prior to use (also after dilution). Only clear solutions practically free from particles should be used.

Incompatibilities

Mixed infusions and injections solutions involving colistimethate sodium.

Posology and method of administration

Posology
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:

Adults and adolescents
Maintenance dose 9 million IU/day in 2-3 divided doses

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

Elderly
No dose adjustments in older patients with normal renal function are considered necessary.

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 creatinine clearance < 50 ml/min:
Twice daily dosing is recommended.

Creatinine clearance (ml/min)	**Daily dose**
< 50-30	5.5 - 7.5 million IU
< 30-10	4.5 - 5.5 million IU
< 10	3.5 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 million IU/day (2.2-2.3 million IU/day).
HD days: 3 million 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.

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 intracerebroventricular administration
Based on limited data, the following dose is recommended in adults:

Intracerebroventricular route
125,000 IU/day

Intrathecally administered doses should not exceed those recommended for intracerebroventricular use.

No specific dosing recommendation can be made in children for intrathecal and intracerebroventricular routes of administration.

Method of administration

Intravenous, intrathecal or intracerebroventricular use.

Colistimethate sodium is administered intravenously 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 million units in 10 ml given over a minimum of 5 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.

Dose conversion table:
In the EU, the dose of colistimethate sodium (CMS) must be prescribed and administered only as 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 active substance = 12,500 IU/mg

Overdose

Signs

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 BUN and creatinine.

Treatment

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.