PROMIXIN, POWDER FOR NEBULISER SOLUTION

Colistimethate Sodium Ph Eur

UK/H/0618/01/E01

Applicant: Profile Pharma Limited
LAY SUMMARY

On 21 March 2010, Austria, France, the Netherlands, Norway, Poland, Portugal and Sweden granted Profile Pharma Limited a Marketing Authorisation (licence) for the medicinal product Promixin 1 million International Units (IU), Powder for Nebuliser Solution (PL 19419/0001; UK/H0618/001/E01). This is a prescription-only medicine (POM) used to treat chest infections caused by Pseudomonas in people with cystic fibrosis (CF). Promixin is breathed into the lungs (inhaled) so that more of the antibiotic can work against the bacteria causing the infection.

Promixin 1 million International Units (IU), Powder for Nebuliser Solution, contains the active ingredient colistimethate sodium which is an antibiotic. It belongs to a group of antibiotics called polymyxins.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Promixin 1 million International Units (IU), Powder for Nebuliser Solution outweigh the risks; hence a Marketing Authorisation has been granted.
**TABLE OF CONTENTS**

<table>
<thead>
<tr>
<th>Module</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Module 1: Information about initial procedure</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Module 2: Summary of Product Characteristics</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>Module 3: Product Information Leaflet</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>Module 4: Labelling</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>Module 5: Scientific Discussion</td>
<td>14</td>
</tr>
<tr>
<td>5.1</td>
<td>1 Introduction</td>
<td>14</td>
</tr>
<tr>
<td>5.2</td>
<td>2 Quality aspects</td>
<td>17</td>
</tr>
<tr>
<td>5.3</td>
<td>3 Non-clinical aspects</td>
<td>19</td>
</tr>
<tr>
<td>5.4</td>
<td>4 Clinical aspects</td>
<td>19</td>
</tr>
<tr>
<td>5.5</td>
<td>5 Overall conclusions</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>Module 6: Steps taken after initial procedure</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Annex 1</td>
<td>29</td>
</tr>
</tbody>
</table>
**Module 1**

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Promixin 1 million International Units (IU), Powder for Nebuliser Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Bibliographic, Article 10(a)</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>COLISTIMETHATE SODIUM Ph Eur</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Powder for Nebuliser Solution</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>1,000,000 IU per vial</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Profile Pharma Limited, Chichester Business Park, City Fields Way, Tangmere, Chichester, West Sussex PO20 2FT</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Austria, France, The Netherlands, Norway, Poland, Portugal and Sweden</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/0618/001/E01</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 90 – 21st March 2010</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

NOTE: Please note that Sections 4.2, 4.3, 4.4, 4.5, 4.6, 5.1, 5.2, 5.3, 6.2, and 6.6 of the SmPC have changed due to subsequent variations which are detailed in Annex 1.

The UK Summary of Product Characteristics (SmPC) for Promixin 1 million International Units (IU), Powder for Nebuliser Solution (PL 19419/0001) approved during the Mutual Recognition Procedure (MRP) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Promixin 1 million International Units (IU), Powder for Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 1 million International Units (IU) which is approximately equivalent to 80 mg of colistimethate sodium.

3 PHARMACEUTICAL FORM
Powder for nebuliser solution. The powder is white to off-white.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Promixin is indicated for the treatment by nebulisation of colonisation and infections of the lung due to susceptible Pseudomonas aeruginosa in patients with cystic fibrosis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents

4.2 Posology and method of administration
Sputum cultures should be obtained to confirm colonisation with Pseudomonas aeruginosa sensitive to colistimethate sodium prior to initiating treatment with Promixin.

The following information provides guidance on recommended doses and the dose should be adjusted according to clinical response.

Recommended doses are:

Children >2 years and adults: 1-2 million IU two or three times daily

The dosage is determined by the severity and type of infection, and renal function of the patient.

The dose may be varied across this range depending on the condition being treated.

Initial colonisation with Pseudomonas aeruginosa sensitive to colistimethate sodium may be treated with a 3-week course of 2 million IU twice daily in conjunction with other parenteral or oral antibiotics.

For frequent, recurrent infections (Less than three positive cultures of Pseudomonas aeruginosa sensitive to colistimethate sodium in a six month period) the dose may be increased up to a maximum of 2 million IU three times daily for up to 3 months, in conjunction with other parenteral or oral antibiotics.

Chronic colonisation (Three or more positive cultures of Pseudomonas aeruginosa sensitive to colistimethate sodium in a six month period) may require long-term therapy with 1 to 2 million IU twice daily. Additional parenteral or oral antibiotics may need to be administered to treat acute exacerbations of pulmonary infection.

Nebulised Promixin should be administered after physiotherapy and other inhaled treatments, where used. Other inhaled therapies may include agents to reduce the viscoelasticity of sputum and bronchodilators (see Section 4.4).
Colistimethate sodium is renally excreted and is nephrotoxic if high serum concentrations are achieved. Whilst this is unlikely during inhalation therapy, serum concentration estimations are recommended especially in patients with renal impairment. Where there is renal impairment, excretion may be delayed and the daily dosage (magnitude of dose and dose interval) must be adjusted in relation to renal function to prevent accumulation of colistimethate sodium as indicated in the table.

### Suggested modification of dosage of Promixin for Patients with impaired renal function

<table>
<thead>
<tr>
<th>Degree of Renal Impairment</th>
<th>Normal (Creatinine (μmol/L))</th>
<th>Mild (Creatinine Clearance (% of normal))</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60 – 105</td>
<td>76 to 100</td>
<td>106 - 129</td>
<td>40 to 75</td>
</tr>
<tr>
<td>Unit dose (Million IU)</td>
<td>1.3 to 2</td>
<td>1 to 1.5</td>
<td>1</td>
<td>1 to 1.5</td>
</tr>
<tr>
<td>Frequency (Times per day)</td>
<td>3</td>
<td>2</td>
<td>1 or 2</td>
<td>Every 36 hours</td>
</tr>
<tr>
<td>Total Daily Dose (Million IU)</td>
<td>4 to 6</td>
<td>2 to 3</td>
<td>1 to 2</td>
<td>0.6 to 1</td>
</tr>
</tbody>
</table>

Promixin is administered by nebulisation using a suitable nebuliser. For instructions on reconstitution of the product before administration see section 6.6. Once reconstituted use immediately.

### 4.3 Contraindications

Promixin is contra-indicated in patients with known hypersensitivity to colistimethate sodium.

Colistimethate sodium is known to reduce the amount of acetylcholine released from the pre-synaptic neuromuscular junction and therefore should not be used in patients with myasthenia gravis.

### 4.4 Special warnings and precautions for use

Nebulisation of colistimethate sodium may induce coughing or bronchospasm. It is advisable to administer the first dose under medical supervision. Pre-dosing with a bronchodilator is recommended and should be routine, especially if this is part of the patient’s current therapeutic regimen. FEV₁ should be evaluated pre and post dosing. If there is evidence of colistimethate sodium induced bronchial hyperreactivity in a patient not receiving pre-treatment bronchodilators the test should be repeated on a separate occasion using a bronchodilator. Evidence of bronchial hyperreactivity in the presence of a bronchodilator may indicate an allergic response and Promixin should be discontinued. Bronchospasm that occurs should be treated as medically indicated.

Bronchial hyperreactivity in response to colistimethate sodium may develop with continued use over time and it is recommended that pre and post treatment FEV₁ s are evaluated at regular clinic visits.

Use with caution in renal impairment as colistimethate sodium is renally excreted.

Impairment of renal function has been reported, usually following use of higher than recommended intravenous or intramuscular doses in patients with normal renal function, or failure to reduce the intravenous or intramuscular dosage in patients with renal impairment or when used concomitantly with other nephrotoxic antibiotics. The effect is usually reversible on discontinuation of therapy.

High serum concentrations of colistimethate sodium after intravenous or intramuscular administration, may be associated with overdosage or failure to reduce the dosage in patients with renal impairment, and this may lead to neurotoxicity. Concomitant use with either non-depolarising muscle relaxants or antibiotics with similar neurotoxic effects can also lead to neurotoxicity. Dose reduction of colistimethate sodium may relieve symptoms. Neurotoxic effects that have been reported include: vertigo, transient facial paraesthesia, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis and apnoea. (see also section 4.5)
Use with extreme caution in patients with porphyria.

4.5 Interactions with other medicinal products and other forms of interaction
Due to the effects of colistimethate sodium on the release of acetylcholine, non-depolarising muscle relaxants should be used with extreme caution in patients receiving Promixin as their effects could be prolonged.

Concomitant use of inhaled colistimethate sodium with other medications that are nephrotoxic or neurotoxic (e.g. cephalothin sodium, aminoglycosides, non-depolarising muscle relaxants) including those which are administered by the i.v. or i.m. routes should only be undertaken with the greatest caution.

4.6 Pregnancy and lactation
Safety in human pregnancy has not been established. There is evidence that colistimethate sodium crosses the placenta and consequently there is potential for fetal toxicity if administered during pregnancy. Animal studies are insufficient with respect to effects on reproduction. Promixin should only be given during pregnancy if the benefits outweigh any potential risk.

Colistimethate sodium is excreted in breast milk, breast feeding is not recommended during therapy.

4.7 Effects on ability to drive and use machines
Neurotoxicity, characterised by dizziness, confusion or visual disturbances have been reported following parenteral administration of colistimethate sodium. If these effects occur patients should be warned against driving or operating machinery.

4.8 Undesirable effects
The commonest undesirable effects following nebulisation of colistimethate sodium are coughing and bronchospasm (indicated by chest tightness which may be detected by a decrease in FEV₁) in approximately 10% of patients. (See also Section 4.4)

Adverse reactions are tabulated below by system organ class and frequency. Frequencies are defined as Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), not known (cannot be estimated from the available data)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Frequency</th>
<th>Reported adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
<td>Hypersensitivity reactions such as skin rash</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Very common</td>
<td>Cough, chest tightness, bronchoconstriction or bronchospasm</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Not known</td>
<td>Sore throat and sore mouth.</td>
</tr>
</tbody>
</table>

Should hypersensitivity reactions such as skin rash occur, treatment with colistimethate sodium should be withdrawn.

Cases of sore throat or sore mouth may be due to hypersensitivity or superinfection with Candida species.

4.9 Overdose
Overdosage may cause apnoea, muscle weakness, vertigo, transient facial paraesthesia, slurred speech, vaso-motor instability, visual disturbances, confusion, psychosis and renal insufficiency.

No antidote is available. Management of overdose is by means of supportive treatment and measures designed to increase clearance of colistimethate sodium such as inducing an osmotic diuresis with mannitol, peritoneal dialysis or prolonged haemodialysis.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other antibacterials, Polymyxins.
ATC code: J01XB01

General properties
Colistimethate sodium is a polymyxin antibiotic and is derived from Bacillus polymyxa var. colistinus. It is a polypeptide and is active against a number of aerobic, Gram-negative bacteria.

The polymyxin antibiotics are surface active agents and act by binding to and changing the permeability of the bacterial cell membrane causing bacterial cell death. Polymyxins are bactericidal against Gram-negative bacteria with a hydrophobic outer membrane.

Breakpoints
Susceptible (S) ≤ 4 mg/L  Resistant (R) ≥ 8 mg/L

Susceptibility
The table below lists bacterial species which are regarded as susceptible to colistimethate sodium. Bacterial resistance may vary according to region and information on resistant species in a specific area is desirable, particularly when treating severe infections. Only bacteria likely to be relevant to the clinical indication are listed.

<table>
<thead>
<tr>
<th>SUSCEPTIBLE BACTERIA</th>
<th>RESISTANT BACTERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter species</td>
<td>Brucella species</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Burkholderia cepacia and related species</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>Serratia species</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Proteus mirabilis</td>
</tr>
</tbody>
</table>

Resistance
Colistimethate sodium acquired resistance in mucoid Pseudomonas aeruginosa has been reported to be approximately 3%. Susceptibility testing should be performed on patients who are treated on a long term basis.

Cross resistance
Polymyxins including colistimethate sodium differ in their mechanism of action compared with other antibiotics and there is evidence to show that Gram-negative bacteria resistant to other antibiotics may be susceptible to colistimethate sodium. The resistance to polymyxins is not crossed with other antibiotic families.

5.2 Pharmacokinetic properties
Absorption
Gastrointestinal absorption is negligible hence the swallowing of colistimethate sodium deposited in the nasopharynx is unlikely to add to the systemic exposure. Absorption following lung administration appears to be variable and clinical work has shown that resultant serum concentrations may range from undetectable to rarely exceeding 4 mg/L (50,000 IU/L) compared to serum concentrations of 10–20 mg/L (approx. 125,000-250,000 IU/L) following intravenous use. Absorption following lung administration is influenced by the nebuliser system, aerosol droplet size and disease state of the lungs. A study in cystic fibrosis patients showed that colistimethate sodium was undetectable in the urine after 1 million IU were inhaled twice daily for 3 months. This is despite the fact that excretion is known to be primarily via the urine.

Distribution
Colistimethate sodium shows a low level of protein binding. Polymyxin antibiotics are known to persist in muscle tissue, liver, kidney, heart and brain.

Pharmacokinetics
Serum Concentrations and Pharmacokinetics in 5 patients receiving inhaled colistimethate sodium
Parameter & $160 \text{ mg (Approximately 2 million IU)}$ \\

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nebulised Colistimethate Sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0-4} (\text{h/mg/L})$</td>
<td>165.9 ± 76.5</td>
</tr>
<tr>
<td>$C_{\text{max}} (\text{mg/L})$</td>
<td>0.051 ± 0.0244</td>
</tr>
<tr>
<td>$T_{\text{max}} (\text{h})$</td>
<td>1.9 ± 1.2</td>
</tr>
<tr>
<td>$K_a (\text{h}^{-1})$</td>
<td>3.0 ± 1.8</td>
</tr>
<tr>
<td>$t_{\text{v}} (\text{h})$</td>
<td>10.4 ± 3.6</td>
</tr>
<tr>
<td>$\text{Cl/F}$</td>
<td>0.27 ± 0.15</td>
</tr>
</tbody>
</table>

Volume of distribution has been calculated to be 0.09 L/Kg in a single study in patients with CF.

**Biotransformation**
Colistimethate sodium undergoes conversion to its base *in-vivo*. Approximately 80% of the parenteral dose is recoverable unchanged in the urine. There is no biliary excretion.

**Elimination**
There is no information on the elimination of colistimethate sodium following nebulisation.

Following i.v. administration excretion is primarily renal with 40% of a parenteral dose recovered in the urine within 8 hours and around 80% in 24 hours. It follows that dose should be reduced in the renally impaired in order to prevent accumulation. Refer to Section 4.2.

The elimination half-life is approximately 1.5 hours following i.v. administration to healthy adults. This compares with an elimination half-life of 3.4 ± 1.4 hours when CF patients were given a single 30 minute i.v. infusion. Colistimethate sodium kinetics appear to be similar in all patient groups provided renal function is normal.

**5.3 Preclinical safety data**
Animal studies are insufficient with respect to effects on reproduction.

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.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**
None

**6.2 Incompatibilities**
The addition of other antibiotics to solutions of Promixin may lead to precipitation.

**6.3 Shelf life**
Unopened: 2 years

Once reconstituted: Use immediately

**6.4 Special precautions for storage**
No special precautions for storage

**6.5 Nature and contents of container**
The product is supplied in clear type I glass vials sealed with a siliconised chlorobutyl type I rubber stopper and protected by a 20 mm aluminium tear-off cap incorporating a red flip-up central plastic top. The product is supplied in packs of 30 vials. Each pack also contains a Promixin Disc® to enable use with the I-neb® AAD® system.
6.6 Instructions for use, handling and disposal
Promixin may be reconstituted with Water for Injections (WFI) to produce a clear colourless to pale yellow hypotonic solution or a 50:50 mixture of WFI and 0.9% saline to produce a clear colourless to pale yellow isotonic solution. When reconstituted, Promixin may be used with any conventional nebuliser suitable for delivery of antibiotic solutions.

Solutions should be used immediately after reconstitution (see section 4.2). Any unused solution remaining in the nebuliser must be discarded following treatment.

Promixin is supplied with a Promixin Disc, for use with the I-neb AAD System. For instructions on the use of Promixin with the I-neb AAD System, please refer to detailed instructions provided with the device.

Conventional nebulisers operate on a continuous flow basis and it is likely that some nebulised drug will be released into the local environment. When used with a conventional nebuliser, Promixin should be administered in a well-ventilated room, particularly in hospitals where several patients may be using nebulisers at the same time. Tubing or filters may be used to prevent waste aerosol from entering the environment.

7 MARKETING AUTHORISATION HOLDER
Profile Pharma Limited
Chichester Business Park
City Fields Way
Tangmere
Chichester
West Sussex
PO20 2FT
United Kingdom

8. MARKETING AUTHORISATION NUMBER
PL 19419/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20th February 2003/13th August 2008

10 DATE OF REVISION OF THE TEXT
09/01/2009
Module 3
Patient Information Leaflet

1. What Promixin is and what it is used for

Promixin contains colistimethate sodium, an antibiotic that fights infections caused by Pseudomonas aeruginosa. This is a very common bacterium that infects the lungs of nearly all patients with cystic fibrosis at some time during their lives. If the infection is not properly controlled it will continue to damage the lungs, causing further problems.

Promixin is used to treat chest infections caused by Pseudomonas in people with cystic fibrosis. Promixin is breathed into the lungs (inhaled) so that more of the antibiotic can work against the bacteria causing the infection.

2. Before you take Promixin

In certain circumstances your doctor may decide not to prescribe Promixin.

Do not use Promixin and tell your doctor if:
- you are pregnant or could get pregnant (please read the section 'Pregnancy and breast-feeding' below);
- you are breast-feeding (please read the section 'Pregnancy and breast-feeding' below);
- you are allergic (hypersensitive) to colistimethate sodium;
- you suffer from myasthenia gravis (a rare disease where your muscles are extremely weak and get tired very quickly);
- if any of these apply to you, see your doctor before you start taking Promixin.

Take special care with Promixin and tell your doctor if:
- you have or have had kidney problems;
- you suffer from porphyria (a rare metabolic disease that some people are born with);
- you suffer from asthma.

If any of these apply to you, tell your doctor.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines you bought without a prescription.

These medicines may interfere with the effect of Promixin:
- if you are taking antibiotics such as cephalosporin sodium, gentamicin, streptomycin and trimethoprim, please tell your doctor. Taking Promixin at the same time as these other antibiotics could increase your risk of kidney problems;
- Promixin could prolong the effects of muscle relaxing medicines, which may be used as part of a general anaesthetic. If you have an operation, if you need to have a general anaesthetic, tell the anaesthetist that you are taking Promixin.

Pregnancy and breast-feeding

You must not take Promixin if you are pregnant or trying to get pregnant. Promixin may harm your unborn baby.

Do not breast-feed while you are taking this medicine.

Driving and using machines

Promixin may make you feel dizzy, confused or have problems with your sight, such as blurred vision. If this happens to you, do not drive or use any tools or machines.

Turn over
PAR Promixin 1 million International Units (IU), Powder for Nebuliser Solution

UK/H/0618/001/E01

3. How to take Promixin

Always take Promixin exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose for adults and children over the age of two years is 1-2 doses two or three times a day. Your doctor will work out the dose for you.

Tell your doctor if you have problems with your kidneys as you may need to take a lower dose of Promixin.

You should take your first dose of Promixin when you are with your doctor or nurse.

Take your Promixin after physiotherapy (if you have physiotherapy) and after taking any other nebulised medicines that you have been prescribed.

Promixin has to be breathed in from a nebuliser. Promixin can be taken using any nebuliser that can be used to deliver antibiotics to the lungs.

Promixin comes with a Promixin® Disc so that it can be used with the Inhala® AAD System. To find out how to use Promixin with Inhala, see the detailed instructions which come with the device. If you use a different nebuliser you should make sure the room is well ventilated.

How to prepare Promixin

Your doctor or nurse will show you how to use Promixin with your nebuliser.

Before Promixin can be taken it must be dissolved in sterile water or sterile saline (salt water). The following are general instructions on how to dissolve Promixin:

- Open the Promixin plastic pack.
- Carefully prise the torn seal from the top of the vial and remove completely.
- Take out the rubber bung carefully.
- Slowly add sterile water or sterile saline to the vial (the instructions with the nebuliser will tell you the correct volume of liquid to add to the Promixin vial).
- Roll the vial gently between your hands to dissolve the Promixin in the liquid. This will reduce foaming.
- Avoid shaking the vial too hard.
- Pour the solution into the nebuliser.
- Any unused solution should be disposed of (see section 5 "How to store Promixin" for instructions on how to dispose of Promixin). Once prepared Promixin should be used immediately.

If you take more Promixin than you should

If you realise that you have taken more Promixin than your doctor has recommended (or if someone else has taken some of your Promixin), contact your doctor straight away.

The symptoms of taking too much Promixin can include:

- tingling or numbness around the lips and face
- dizziness and spinning sensation (vertigo)
- slurred speech
- visual disturbance
- confusion
- mental disturbance
- flushing (redness of the face).

If you forget to take Promixin

Take the dose as soon as you remember, unless it is near the time for your next dose. You do not need to make up for the dose you have missed.

If you stop taking Promixin

Do not stop your treatment early unless your doctor says that you can. Your doctor will tell you how long your treatment will last.

4. Possible side effects

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

Promixin can sometimes cause allergic reactions like skin rash. If this happens you should stop taking Promixin and tell your doctor immediately.

Breathing in Promixin through a nebuliser can make some people notice tightness in their chest, feel wheezy, cough or become breathless. For this reason the first dose should be taken when you are with your doctor or nurse.

Your doctor may also advise you to take a medicine to help prevent any breathlessness. Your doctor may check your breathing at your clinic visits.

Promixin might also affect your kidneys, usually if the dose is high or you are taking other medications that may affect your kidneys.

Promixin may sometimes cause you to have a sore mouth or sore throat.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Promixin

Keep Promixin out of the reach of children.

Do not use Promixin after the expiry date which is stated on the vial or carton. The expiry date refers to the last day of that month.

Promixin does not require any special storage conditions.

Promixin contains no preservative. Once prepared, Promixin should be used immediately.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer require. These measures will help to protect the environment.

6. Further information

What Promixin contains

The active substance is colistimethate sodium (also known as colistin).

Each vial contains 1 million International Units (IU) of colistimethate sodium, which weighs about 0.05 milligrams (mg). There are no other ingredients.

What Promixin looks like and contents of the pack

Promixin is a powder for nebuliser solution, supplied as a sterile powder in a glass vial.

Promixin is supplied in packs containing 30 vials. Each pack contains a Promixin Disc to use with the Inhala® AAD System.

Marketing Authorisation Holder

Procle Pharma Ltd.
Chester Business Park,
City Road, Wirral, CK5 2FT, UK
Tel: +44 (0) 800 1300 856
Fax: +44 (0) 800 1300 855
Email: info@proxapharma.com

Manufacturer

Avalia Pharmaceuticals A/S
Danskaade 11
DK-2350 Copenhagen S
Denmark

Other formats:

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:
0000 11 2200 (UK only)

Please be ready to give the following information:

- Product name
- Promixin® 1 million IU powder for nebuliser solution unit dose
- Each vial contains 1 million International Units (IU) of colistimethate sodium
- Total pack contains 30 vials
- Reference number 16413/0001

This is a service provided by the Royal National Institute of Blind People.

11/11/2010 (Ireland)

This leaflet was last approved in XXX/XXX

FL300 issue 7
Module 4
Labelling

Carton

Vial Label
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Promixin, Powder for Nebuliser Solution in the treatment of colonisation and infections of the lung due to susceptible *Pseudomonas aeruginosa* in patients with cystic fibrosis, could be approved. A national Marketing Authorisation was granted on 20th February 2003.

This is a bibliographic, well established-use, application according to article 10a of Directive 2001/83/EC. Promixin is a generic version of Colomycin Injection 1 million International Units Powder for solution for injection, infusion or inhalation (PL 00108/5006R) marketed by Forest Laboratories Ltd formerly Pharmax UK Ltd registered in the UK since 1986.

A national marketing authorisation for Promixin, Powder for Nebuliser Solution was granted in the UK on 20th February 2003 to Profile Pharma Limited. The product went through a first wave Mutual Recognition Procedure (UK/H/0618/001/MR) involving Belgium, Germany, Denmark, Greece, Ireland, Italy, Luxembourg and Spain. The procedure was completed on 16 February 2004.

This product then went through a second wave Mutual Recognition Procedure (UK/H/0618/001/E01) involving Austria, France, The Netherlands, Norway, Poland, Portugal and Sweden. This procedure was completed on 21 March 2010.

Promixin powder for Nebuliser Solution contains the active substance colistimethate sodium which is the anionic inactive prodrug of colistin. Promixin is indicated for the treatment by nebulisation of lung infections where sensitivity testing suggests that they are caused by susceptible Gram-negative bacteria.

No new preclinical or clinical studies were conducted for this application, which is acceptable given that the application is for a generic version of product that has been licensed for over 10 years and that, the active constituent has a well-established use with an acceptable safety profile and recognised efficacy. Given that Promixin 1 million International Units, Powder for Nebuliser Solution has the same qualitative and quantitative composition as the reference product there is no requirement for a therapeutic equivalence study.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of
any adverse reaction suspected of occurring either in the Community or in a third country. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Promixin 1 million International Units (IU), Powder for Nebuliser Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>colistimethate sodium</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>ATC Code: J01XB01- Antibacterials for systemic use</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Powder for Nebuliser Solution, 1,000,000 IU per vial</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/0618/001/E01</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Austria, France, The Netherlands, Norway, Poland, Portugal and Sweden</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 19419/0001</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Profile Pharma Limited, Chichester Business Park, City Fields Way, Tangmere, Chichester, West Sussex PO20 2FT</td>
</tr>
</tbody>
</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

Drug substance
INN/Ph Eur name: Colistimethate sodium


Structural formula

```
N^4
RCO-Dbu-Thr-Dbu-Dbu-Dbu-DLeu-Leu-Dbu---Dbu-Thr
N^4R'  N^4R'  N^4R'  N^4R'  N^4R'
```

Dbu = L-2,4-diaminobutyric acid
R' = CH₂SO₃Na

Colistin A  -[CH₃]₄CHMeCH₂CH₃
Colistin B  -[CH₃]₄CHMe₂

Molecular formula: C₃₈H₁₀₇N₁₆O₂₄S₃Na₃
Molecular weight: 1585g/mol

General Properties
Characters: A white or almost white powder. Almost odourless.

Colistimethate sodium is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance colistimethate sodium are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

The active substance is stored in appropriate packaging. Satisfactory specifications have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph.Eur requirements and complies with Directive 2002/72/EC (as amended) and is suitable for contact with foodstuffs.
Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support the 5 years re-test period when stored at 25°C.

**Drug Product**

**Description and Composition of the Drug Product**

Promixin, 1 million International Units (IU) Powder for Nebuliser Solution is presented as a white to off-white powder. Each vial contains 1 million International Units (IU) which is approximately equivalent to 80mg of colistimethate sodium.

**Pharmaceutical development**

The objective of the development programme was to produce a powder for nebuliser solution that could be considered a generic medicinal product of Colomycin Injection 1 million International Units Powder for solution for injection, infusion or inhalation authorised to Forest UK Limited, formerly Pharmax UK Ltd since June 1986.

The finished product is a simple powder for nebulisation. The formulation is entirely controlled by the EDQM Certificate of Suitability. Consequently there is no formulation development.

**Manufacturing Process**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted. The validation data demonstrated consistency of the manufacturing process.

**Finished Product Specification**

Finished product specifications are provided for both release and shelf-life, and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container-Closure System**

The finished product is licensed for marketing in Type I glass vials sealed with a siliconised chlorobutyl Type I rubber stopper and protected by a 20 mm aluminium tear-off cap incorporating a red flip-up central plastic top. The product is supplied in packs of 30 vials.

Each pack contains a Promixin Disc to enable use with the I-neb AAD Nebuliser System.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with Directive 2002/72/EC (as amended).

**Stability of the product**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of
2 years has been set, when the vial is unopened, which is satisfactory. Once reconstituted the product should be used immediately. There are no special storage conditions for this product.

**Bioequivalence Study**
The product is administered as a solution via a nebuliser therefore there are no bioequivalence issues.

**Quality Overall Summary**
A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that is contains.

**MAA Form**
The MAA form is pharmaceutically satisfactory.

**Conclusion**
The test product is pharmaceutically equivalent to the reference product, which has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to perform a bioequivalence study.

There are no objections to approval of Promixin, 1 million International Units (IU) Powder for Nebuliser Solution from a pharmaceutical point of view.

### III.2 PRE-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of colistimethate sodium are well-known. Therefore, no further studies are required and the applicant has provided none.

The pre-clinical overview was written by a suitably qualified person and is satisfactory. The *curriculum vitae* of the expert has been provided.

The SmPC is satisfactory from a pre-clinical viewpoint and is consistent with that for the reference product.

There are no objections to the approval of Promixin Powder for Nebuliser Solution from a pre-clinical point of view.

### III.3 CLINICAL ASPECTS

**Clinical Pharmacology**
*In vitro* bactericidal activity of colistimethate sodium is well documented in the literature.
3.1 Pharmacodynamics

Colistimethate sodium has been shown to be effective against many Gram-negative bacteria, including most strains of *P. aeruginosa*, *Shigella*, *Salmonella* spp, *Acinetobacter* spp, and *Klebsiella* spp. The minimum inhibitory concentration (MIC) of colistimethate sodium for sensitive organisms ranges from 1 to 4 mg/L.

Addition of colistimethate sodium at a concentration of 5mg/L increased the bactericidal effect of other antibiotics (cefazidime, meropenem, gentamycin, piperacillin and ciprofloxin).

The study by Diot et al (*Eur Respir J* 1997, 10, 1995) showed that nebulisation did not affect the antibiotic properties of colistimethate sodium.

3.2 Pharmacokinetics

Colistimethate sodium is predominately renally excreted. In patients with creatinine clearance below 20 mL/min, colistimethate sodium blood concentrations are inversely proportional to the degree of renal impairment. Reduced dosage is therefore recommended in patients with renal insufficiency, and peritoneal dialysis is recommended in the event of serious toxicity or overdosage. Colistimethate sodium is sequestered into sputum, even following intravenous administration.

There are limited published data on the pharmacokinetics of colistimethate sodium following the inhaled use. The systemic exposure following inhalation is considerably less than after I.V. dosing. The maximum concentration following inhaled therapy is 0.2% of the maximum concentration following intravenous infusion and the half life is prolonged by a factor of approximately 3.

Reed MD et al.
*The pharmacokinetics of colistin in patients with cystic fibrosis (CF).*

The pharmacokinetics of colistimethate sodium have been evaluated in CF patients receiving intravenous (IV) injections of colistimethate sodium. At a dose of 5-7 mg/kg/day IV, administered in three equally divided doses as a 30 minute IV infusion, the pharmacokinetic parameters were determined after first dose and at steady-state (Table 1).

**Table 1. Pharmacokinetics of colistimethate sodium in patients with CF**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Colistimethate Sodium Pharmacokinetics Parameter Estimates</th>
<th>First Dose (n=30)</th>
<th>Steady State (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>21.4</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{min}}_{8, \text{h}}$ (mg/L)</td>
<td>2.8</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>$t_{\text{1/2}}$ (h)</td>
<td>3.4</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>MRT (h)</td>
<td>4.4</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>VD$_{\text{ss}}$ (L/kg)</td>
<td>0.09</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Cl (mL/min/kg)</td>
<td>0.35</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Clr (mL/min/kg)</td>
<td>0.24</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Clr:Cl</td>
<td>0.62</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ Maximum plasma CMS concentration; $C_{\text{min}}_{8\, \text{h}}$ 8-hour CMS trough concentration; $t_{\text{1/2}}$ elimination half life; MRT mean residence time; VD$_{\text{ss}}$ steady state volume of distribution; Cl body clearance; Clr renal clearance
No differences in colistimethate sodium disposition characteristics between first dose and steady state evaluations were observed. Overall, 62.5% of the dose was excreted unchanged in the urine during the first 8 hours. The most of renal excretion occurred in the first 4 hours after dosing.

The study also investigated the concentration of colistimethate sodium in sputum in 8 patients. The baseline sputum concentration averaged 88.6 mg/g. Overall sputum colistimethate sodium concentrations were highly variable but significantly exceeded the serum concentration at each time-point sampled.

3.3 Bioavailability / Bioequivalence
No bioavailability/bioequivalence data have been submitted.
Colistimethate sodium is presented as sterile powder for solution (for injection or inhalation) with no excipients. Given that Promixin 1 million International Units, Powder for Nebuliser Solution has the same qualitative and quantitative composition as the reference product the there is no requirement for clinical studies.

4. Efficacy
No new efficacy data have been submitted.

Colistimethate sodium has been used in Europe as an injectable antibiotic since 1960s and for the inhaled use since 1970s.
The MAH has reviewed published literature relating to the efficacy of inhaled colistimethate sodium.
It is not known whether any of the submitted studies have been performed to GCP standards.

Jensen T et al.
Colistin inhalation therapy in cystic fibrosis patients with chronic Pseudomonas aeruginosa lung infection.
Forty CF patients, aged 7-35 years, with chronic bronchopulmonary P. aeruginosa infection were entered into the double-blind, randomised, placebo controlled study. Patients were treated with inhaled colistin (1 Million Units) or placebo (saline) twice daily for 90 days (before entering the study a two week course of parenteral anti-pseudomonas treatment was given to all patients: tobramycin in combination with a β-lactam antibiotic).
Aerosols were formed using a nebulising chamber at a flow rate of compressed air of 10 L/min generating particles from 0.5 to 5.0 μm.
Parameters studied were: clinical score, pulmonary function tests, and sputum samples at Days 1, 14 and 90.

Twenty-nine patients completed the study (18 in the colistin group and 11 in the placebo group). Two patients were withdrawn from the colistin group, one required elective surgery and the other developed a severe asthma attack. Nine patients dropped out of the placebo group (4 - treatment failure, 4 - no benefit from treatment and 1 - cough after inhalation).
The forced vital capacity decreased during the treatment period in both groups, but the mean fall after 90 days was significantly less in the colistin group than with placebo (Table 2.)
Table 2. Mean lung function tests

<table>
<thead>
<tr>
<th></th>
<th>Treatment Day</th>
<th>Colistin N = 18 % of normal mean ± S.D.</th>
<th>Placebo N = 11 % of normal mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced</td>
<td>0</td>
<td>86 ± 26</td>
<td>89 ± 31</td>
</tr>
<tr>
<td>Vital</td>
<td>30</td>
<td>78 ± 20</td>
<td>79 ± 25</td>
</tr>
<tr>
<td>Capacity</td>
<td>60</td>
<td>76 ± 23</td>
<td>77 ± 27</td>
</tr>
<tr>
<td>(FVC)</td>
<td>90</td>
<td>79 ± 25</td>
<td>71 ± 28</td>
</tr>
<tr>
<td>Change, day 0-day 90</td>
<td></td>
<td>7 ± 8</td>
<td>18 ± 14 a</td>
</tr>
<tr>
<td>Forced</td>
<td>0</td>
<td>71 ± 25</td>
<td>79 ± 29</td>
</tr>
<tr>
<td>Expiratory</td>
<td>30</td>
<td>67 ± 24</td>
<td>68 ± 24</td>
</tr>
<tr>
<td>Volume</td>
<td>60</td>
<td>63 ± 24</td>
<td>62 ± 25</td>
</tr>
<tr>
<td>In the first</td>
<td>90</td>
<td>60 ± 24</td>
<td>62 ± 29</td>
</tr>
<tr>
<td>Second Change, day 0-day 90</td>
<td></td>
<td>11 ± 6</td>
<td>17 ± 11</td>
</tr>
</tbody>
</table>

a p<0.05 when comparing colistin to placebo

The decrease in mean forced expiratory volume (FEV1) was less pronounced in the colistin group, but was not significantly different from the placebo group. In 20 patients with more advanced infection the reduction in FEV1 was significantly less in the colistin group than with placebo.

*P. aeruginosa* was not eradicated from the sputum of any patient and the MIC of colistin against *P. aeruginosa* did not change during the study period. No super-infection with colistin-resistant micro-organisms was observed.

Day A.J. et al.
Evaluation of inhaled colomycin in children with cystic fibrosis.
Poster R(c)3
10th International Cystic Fibrosis Congress, 1988, Sydney

It was a double-blind, crossover study comparing inhaled colomycin, 1 Million units twice daily, with saline, in 14 children, aged 5-16, with CF and colonised with Pseudomonas aeruginosa. Each treatment period lasted 6 months.
Both FVC and FEV1 decreased significantly during saline treatment, but were maintained during colomycin treatment. After 6 months of treatment with colomycin, FVC (mean 74% of predicted normal) was significantly greater than after saline (mean 67.5%).

Frederiksen B et al.

The study was carried out at the Danish CF Centre in Copenhagen and compared 48 patients, treated according to the 3-step protocol (colistin inhalations and oral ciprofloxacin at the time of initial colonisation with *P. aeruginosa*), to 43 historic controls.
The study was carried out over 44 months and included 218 patient-years. Only 16% of the treated patients developed a chronic infection after 3.5 years compared with 72% of the control patients. The treatment prevented or delayed chronic *P. aeruginosa* infection in 78% of the patients for 3.5 years. In addition, the treatment maintained or increased pulmonary
function (FVC and FEV₁ % predicted) compared with the control group, in which pulmonary function declined. Some of the treated patients eventually developed a chronic infection, and despite of it, had significantly better pulmonary function at the onset of chronic infection compared with control patients. When the different steps in the intensive three-step-protocol were analysed, there was a trend suggesting that three months of high-dose treatment with colistin inhalation and oral ciprofloxacin produced the best results in terms of postponement or prevention of chronic *P. aeruginosa* infection.

*Mukhopadhyay S. et al.*


The paper reviewed the results of relevant randomised controlled trials. The therapeutic end points compared were:

- the number of pulmonary exacerbations requiring treatment with systemic antibiotics
- the measurable alteration in respiratory tract pseudomonal load
- alteration in lung function on spirometric assessment
- development of resistance in respiratory tract *Pseudomonas* strains to the nebulised antipseudomonal used in each trial
- renal and auditory impairment.

Five studies were chosen for meta-analysis.

Meta-analysis showed benefit for nebulised anti-pseudomonal antibiotic therapy with no demonstrable adverse effect other than a possible increase in *in vitro* antibiotic resistance of *P. aeruginosa* of the respiratory tract.

**Medical Assessor’s comments:**

*Very few controlled clinical trials were conducted with inhaled colistimethate sodium. The reviewed papers indicated that colistimethate sodium was used effectively in the treatment of variety of respiratory infections. In particular, colistimethate sodium given as inhalation was successful on preventing or delaying chronic *P. aeruginosa* colonisation in CF patients.*

### 4.1 Resistance

**Pitt T.L., Sparrow M.:**

*Survey of antimicrobial resistance of *Pseudomonas aeruginosa* isolates from cystic fibrosis patients. 24th European Cystic Fibrosis Consensus Conference, Vienna, 2001.*

A total of 282 patient isolates from 15 hospitals, collected over a four month period, were tested for susceptibility to ceftazidime, piperacillin, ciprofloxacin, colomycin, gentamicin and tobramycin by agar dilution. British Society of Antimicrobial Chemotherapy MIC breakpoints for the agents were used, and isolates were classified as susceptible, intermediate susceptible or resistant.

The resistance rate for ceftazidime was 32%, piperacillin 24%, ciprofloxacin 16%, colomycin 5%, gentamicin 47% and tobramycin 24%. Resistance to all six antimicrobials was rare (0.9%), but 27% of isolates exhibited resistance to three or more agents and only 31% could be classified as intermediate or fully susceptible to all agents. Pulsed-field gel electrophoresis of DNA digests of selected isolates from three centres showed that most patients harboured unique strains and that multi-resistance was not associated with clusters of the same strain in a centre.
Susceptibility to colomycin was maintained despite its widespread use in the CF community.

5. Safety
No new safety data have been submitted for Promixin. The MAH has provided a review of published papers on the safety of colistimethate sodium given by inhalation and injection.

Inhalation use

Cunningham S. et al.
Bronchoconstriction following nebulised colistin in cystic fibrosis.

Fifty eight children (> 5 years) received standard dose of colistin made up to a total of 4 ml volume with 0.9% saline (< 7 years: 0.5 MU, ≥ 7 years 1 MU). Spirometry was performed immediately before and immediately after nebulisation, and at 15 minutes post-nebulisation. Children with bronchoconstriction at 15 minutes had further spirometry performed at 30 minutes.

Of the children included in the study, 55 were regular colistin users (41 for over 2 years), and three were using colistin for the first time. The mean age of the children was 12.0 ± 3.1 years (range 5.1-17.4 years). The mean FEV1 before colistin was 59.3% ± 18.3%.

Colistin was associated with a significant fall in FEV1 in the group as a whole at 0 minutes (mean decrease of 5.9% ± 9.6%, p< 0.001) and 15 minutes (mean decrease 3.3% ± 10.2%, p<0.004) post-nebulisation. Twenty children (34%) had more than a 10% reduction in FEV1 (17.8% ± 5.9%), with a maximum fall of 37.5%. Five children (9%) continued to have an FEV1 at 10% below baseline at 30 minutes. In the group as a whole there was also a significant reduction in MEF25% and oxygen saturation at 0 (p<0.003 and p<0.001 respectively) and 15 minutes (p<0.001 and p=0.023 respectively). No significant difference was found for changes in spirometry post-nebulisation between those patients experiencing chest discomfort in association with nebulisation (n=9) or those with current symptoms of respiratory tract infection (n=10).

Dodd ME et al.
Effect of tonicity of nebulised colistin on chest tightness and pulmonary function in adults with cystic fibrosis.

It was a randomised double-blind study to evaluate chest tightness and changes in lung function in response to the inhalation of nebulised colistin.

Twenty-seven adult patients with cystic fibrosis, who were chronically colonised with P. aeruginosa, and with an FEV1 of 54% predicted (range 24-98) were included in the study. Patients inhaled a nebulised solution of hypertonic, isotonic, and hypotonic colistin over three consecutive days. Measurements of chest tightness, using a visual analogue scale and FEV1 were recorded before and 0, 15, 30, 60 and 90 minutes following inhalation. All solutions caused a significant fall in FEV1 % and an increase in chest tightness. The mean (±SE) time to the maximum fall in FEV1 % predicted was significantly different between the solutions: hypertonic 7.8 (±2.1) minutes, isotonic 19.2 (±5.5) minutes and hypotonic 34.2 (±5.9) minutes, with a mean difference (95% CI) between hypotonic and hypertonic solutions of 28.04 (14.6 to 41.5) minutes (p<0.001), between isotonic and hypertonic solutions of 12.0 (-0.1 to 24.1) minutes (p<0.05), and between hypotonic and isotonic solutions of 15.6 (1.8 to
29.4) minutes (p<0.05). Positive correlations existed for the maximum fall in FEV1 % predicted between the hypertonic and isotonic solutions (r=0.62, p<0.001) and between the hypotonic and isotonic solutions (r=0.64, p<0.001). All solutions of colistin caused symptoms of chest tightness and reduction in pulmonary function.

**Intravenous use**

*Bosso J.A. et al.*  
**Toxicity of colistin in cystic fibrosis patients**  

Nineteen patients were monitored during 21 courses of colistin therapy (dosage ranged from 3-8 mg/kg/day in three divided doses). One case of renal toxicity occurred, in a patient with a history of renal intolerance to colistin. Six cases of neurotoxicity were characterised by perioral paraesthesia, ataxia or both. These effects were usually transient.

*Conway S.P. et al.*  
**Safety and tolerability of bolus intravenous colistin in acute respiratory exacerbations in adults with cystic fibrosis**  

Twelve patients with chronic *P. aeruginosa* infection were enrolled into an open label study. On Day 1 patients received 2 MU colistin (160 mg) tid by IV infusion over 30 minutes. On days 2, 3 and 4 the same dose of colistin was administered by bolus injection over five minutes from a hand-held syringe after reconstitution in 20, 15 and 10 ml saline. If this dose was tolerated, it was continued over the remaining days of the study, if not, treatment reverted to the previously tolerated concentration. No serious adverse events occurred during the course of the trial. There was no evidence of bronchoconstriction associated with the administration of the increased concentration of colistin. There were no clinically significant changes in renal function.

*Ledson MJ et al.*  
**Four years’ experience on intravenous colomycin in an adult cystic fibrosis unit.**  

This paper reviewed the original publications, which reported significant renal and neurotoxic side effects and concluded that this concern resulted from inappropriate patient selection and the use of higher than recommended doses.

**Medical Assessor’s comment:**

*The most significant and serious adverse effects of treatment by injection are renal toxicity and neurotoxicity. Following inhaled colistimethate sodium therapy the commonest side effect reported is chest tightness and several studies have demonstrated a fall in FEV1.*

6. **Clinical Expert Report**

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified physician. The *curriculum vitae* of the expert has been provided.
7. **Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPCs and PILs are medically acceptable, and consistent with those for the reference products. The labelling is medically acceptable and in-line with current requirements.

8. **MAA form**
The MAA form is medically satisfactory.

9. **Conclusion**
This application has been submitted as a so called “bibliographic application”; the Applicant has submitted no new data. The pharmacodynamics and pharmacokinetics of colistimethate sodium are documented in the literature and it is considered that no further work is required. In respect of clinical efficacy the Applicant presents a literature review and highlights three placebo-controlled studies. Efficacy of colistimethate sodium was demonstrated in the treatment of a variety of respiratory infections; in particular in the prevention or delaying chronic P. aeruginosa colonisation in CF patients.

Colistimethate sodium has been used in Europe as an injectable antibiotic since 1960s and for the inhaled use since 1970s. The most significant and serious adverse effects of treatment by injection are renal toxicity and neurotoxicity. The commonest reported side effect following inhaled colistimethate sodium therapy is chest tightness and several studies have demonstrated a fall in FEV\textsubscript{1}.

Sufficient clinical information has been submitted to support this application. The product literature is approved. The grant of a Marketing Authorisation was recommended on medical grounds.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT
QUALITY
The important quality characteristics of Promixin 1 million International Units (IU), Powder for Nebuliser Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL
No new pre-clinical data were submitted and none are required for an application of this type.

EFFICACY
No new data are submitted and none are required for this type of application.

The published literature supports the efficacy of this product in the proposed indication of colonisation and infections of the lung due to susceptible *Pseudomonas aeruginosa* in patients with cystic fibrosis. The safety and efficacy of colistimethate sodium is well-known. The presented evidence for well-established use of the active substance is sufficient.

The literature review identifies no new safety issues or concerns. The safety profile of colistimethate sodium is well-known.

PRODUCT LITERATURE
The SmPC, label and PIL are acceptable, and consistent with those for the reference product.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

Mock-ups of the labeling have been provided. The approved labeling artwork complies with statutory requirements. In line with current legislation, the name of the product appears on the outer packaging in Braille.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. Colistimethate sodium is an active substance of well-known safety and efficacy. It has been used for a number for decades in the EEA. Extensive clinical experience with colistimethate sodium is considered to have demonstrated the therapeutic value of the active substance. The benefit:risk ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

The following table lists non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the last MRP. The table includes updates that have been incorporated into the text of this Public Assessment Report (PAR) or added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>23/04/2010</td>
<td>Type II</td>
<td>To harmonise sections 4.2 (Posology and method of administration), 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.6 (Pregnancy and lactation), 5.1 (Pharmacodynamic properties), 5.2 (Pharmacokinetic properties), 5.3 (Preclinical safety data), 6.2 (Incompatibilities) and 6.6 (Instructions for use, handling and disposal) of the SPC with the outcome of the repeat-wave Mutual Recognition Procedure which was completed on 22 March 2010 (UK/H/618/01/E01), with consequential changes made to the PIL and labelling.</td>
<td>Approved 11 November 2010</td>
</tr>
<tr>
<td>29/09/2010</td>
<td>Type II</td>
<td>To include comparative nebuliser data in section 4.2 (Posology and administration) of the SPC following the completion of a study to generate comparative information on the performance of Promixin with several commonly used nebulisers.</td>
<td>Approved 15 June 2011</td>
</tr>
</tbody>
</table>
Annex 1

Reference: PL 19419/0001; UK/H/0618/001/II/017

Product: Promixin 1 million International Units (IU), Powder for Nebuliser Solution

MAH: Profile Pharma Limited

Active Ingredient: Colistimethate sodium

Reason:
To harmonise sections 4.2 (Posology and method of administration), 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.6 (Pregnancy and lactation), 5.1 (Pharmacodynamic properties), 5.2 (Pharmacokinetic properties), 5.3 (Preclinical safety data), 6.2 (Incompatibilities) and 6.6 (Instructions for use, handling and disposal) of the SmPC with the outcome of the repeat-wave Mutual Recognition Procedure which was completed on 22 March 2010 (UK/H/618/01/E01), with consequential changes made to the PIL and labelling.

Conclusion:
This variation was approved on 11 November 2010. Satisfactory, updated SmPC fragments, PIL and label were submitted in support of this variation application.
Summary of Product Characteristics-updated

The fragments updated in view of the above stated variation are reproduced below:

4.2 Posology and method of administration
Sputum cultures should be obtained to confirm colonisation with \textit{Pseudomonas aeruginosa} sensitive to colistimethate sodium prior to initiating treatment with Promixin.

The following information provides guidance on recommended doses and the dose should be adjusted according to clinical response.

Recommended doses are:
Children $>2$ years and adults: 1-2 million IU two or three times daily
Children $<2$ years: The safety and efficacy of Promixin has not been demonstrated in patients less than 2 years of age.

The dosage is determined by the severity and type of infection. The dose may be varied across this range depending on the condition being treated.

\textbf{Initial colonisation} with \textit{Pseudomonas aeruginosa} sensitive to colistimethate sodium may be treated with a 3-week course of 2 million IU twice daily in conjunction with other parenteral or oral antibiotics.

\textbf{For frequent, recurrent infections} (Less than three positive cultures of \textit{Pseudomonas aeruginosa} sensitive to colistimethate sodium in a six month period) the dose may be increased up to a maximum of 2 million IU three times daily for up to 3 months, in conjunction with other parenteral or oral antibiotics.

\textbf{Chronic colonisation} (Three or more positive cultures of \textit{Pseudomonas aeruginosa} sensitive to colistimethate sodium in a six month period) may require long-term therapy with 1 to 2 million IU twice daily. Additional parenteral or oral antibiotics may need to be administered to treat acute exacerbations of pulmonary infection. Nebulised Promixin should be administered after physiotherapy and other inhaled treatments, where used. Other inhaled therapies may include agents to reduce the viscoelasticity of sputum and bronchodilators (see Section 4.4).

\textbf{Mode of administration}
Promixin for nebulisation is intended for administration by nebulisation using a suitable nebuliser. For special precautions for disposal and handling of reconstituted solutions, see Section 6.6

4.3 Contraindications
Promixin is contraindicated in patients with known hypersensitivity to colistimethate sodium or other polymyxins.
Colistimethate sodium is known to reduce the amount of acetylcholine released from the pre-synaptic neuromuscular junction and therefore should not be used in patients with myasthenia gravis.

4.4 Special warnings and precautions for use
\textbf{Bronchospasm}
Nebulisation of colistimethate sodium may induce coughing or bronchospasm. It is advisable to administer the first dose under medical supervision. Pre-dosing with a bronchodilator is recommended and should be routine, especially if this is part of the patient’s current therapeutic regimen. FEV$_1$ should be evaluated pre and post dosing. If there is evidence of colistimethate sodium induced bronchial hyperreactivity in a patient not receiving pre-treatment bronchodilators the test should be repeated on a separate occasion using a bronchodilator. Evidence of bronchial hyperreactivity in the presence of a bronchodilator may indicate an allergic response and Promixin should be discontinued. Bronchospasm that occurs should be treated as medically indicated.
Bronchial hyperreactivity in response to colistimethate sodium may develop with continued use over time and it is recommended that pre and post treatment FEV$_1$s are evaluated at regular clinic visits.
Renal impairment
Colistimethate sodium is renally excreted and is nephrotoxic if high serum concentrations are achieved. Whilst this is unlikely during inhalation therapy, serum concentration estimations are recommended especially in patients with renal impairment.

Nephrotoxicity
Impairment of renal function has been reported, usually following use of higher than recommended intravenous or intramuscular doses in patients with normal renal function, or failure to reduce the intravenous or intramuscular dosage in patients with renal impairment or when used concomitantly with other nephrotoxic antibiotics. The effect is usually reversible on discontinuation of therapy.

Neurotoxicity
High serum concentrations of colistimethate sodium after intravenous or intramuscular administration, may be associated with overdosage or failure to reduce the dosage in patients with renal impairment, and this may lead to neurotoxicity. Concomitant use with either non-depolarising muscle relaxants or antibiotics with similar neurotoxic effects can also lead to neurotoxicity. Dose reduction of colistimethate sodium may relieve symptoms. Neurotoxic effects that have been reported include: vertigo, transient facial paraesthesia, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis and apnoea (see also Section 4.5)

Porphyria
Use with extreme caution in patients with porphyria.

Microbial Resistance
Colistimethate sodium acquired resistance in mucoid Pseudomonas aeruginosa during clinical use has been reported. Susceptibility testing should be performed on patients who are treated on a long term basis (see Section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction
Due to the effects of colistimethate sodium on the release of acetylcholine, non-depolarising muscle relaxants should be used with extreme caution in patients receiving Promixin as their effects could be prolonged (see Section 4.4). Concomitant use of inhaled colistimethate sodium with other medications that are nephrotoxic or neurotoxic (e.g. cephalothin sodium, aminoglycosides, non-depolarising muscle relaxants) including those which are administered by the i.v. or i.m. routes should only be undertaken with the greatest caution (see Section 4.4).

4.6 Pregnancy and lactation
Safety in human pregnancy has not been established. Animal studies do not indicate a teratogenic potential. However there is evidence that colistimethate sodium crosses the placenta and consequently there is potential for foetal toxicity if administered during pregnancy. Promixin should only be given during pregnancy if the benefits outweigh any potential risk. Colistimethate sodium is excreted in breast milk; breast feeding is not recommended during therapy.

4.7 Effects on ability to drive and use machines
Neurotoxicity, characterised by dizziness, confusion or visual disturbances have been reported following parenteral administration of colistimethate sodium. If these effects occur patients should be warned against driving or operating machinery.

4.8 Undesirable effects
The commonest undesirable effects following nebulisation of colistimethate sodium are coughing and bronchospasm (indicated by chest tightness which may be detected by a decrease in FEV₁) in approximately 10% of patients. (See also Section 4.4)
Adverse reactions are tabulated below by system organ class and frequency. Frequencies are defined as Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), not known (cannot be estimated from the available data)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Frequency</th>
<th>Reported adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
<td>Hypersensitivity reactions such as skin rash</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Very common</td>
<td>Cough, chest tightness, bronchoconstriction or bronchospasm</td>
</tr>
<tr>
<td>General disorders and</td>
<td>Not known</td>
<td>Sore throat and sore mouth.</td>
</tr>
</tbody>
</table>
Should hypersensitivity reactions such as skin rash occur treatment with colistimethate sodium should be withdrawn. Cases of sore throat or sore mouth may be due to hypersensitivity or superinfection with Candida species.

4.9 Overdose
Overdosage may cause apnoea, muscle weakness, vertigo, transient facial paraesthesia, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis and renal insufficiency.

No antidote is available. Management of overdose is by means of supportive treatment and measures designed to increase clearance of colistimethate sodium such as inducing an osmotic diuresis with mannitol, peritoneal dialysis or prolonged haemodialysis.

5. Pharmacological properties
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other antibacterials, Polymyxins.
ATC code: J01XB01

General properties

Mode of action
Colistimethate sodium is a polymyxin antibiotic, with a polypeptide structure and is derived from Bacillus polymyxa var. colistinus. The polymyxin antibiotics are surface active agents and act by binding to and changing the permeability of the bacterial cell membrane causing bacterial cell death. Polymyxins are bactericidal against Gram-negative bacteria with a hydrophobic outer membrane.

PK/PD relationship
Polymyxins have a concentration-dependent bactericidal effect on susceptible bacteria.

Mechanisms of resistance
Resistance develops due to modifications of lipopolysaccharide (LPS) or other components in the bacterial cell membrane.

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 species
Haemophilus influenzae
Klebsiella species
Pseudomonas aeruginosa
Stenotrophomonas maltophilia
Alcaligenes xylosoxidans

Inherently resistant organisms
Burkholderia cepacia and related species

Resistance
Colistimethate sodium acquired resistance in mucoid Pseudomonas aeruginosa has been reported to be approximately 3% (see Section 4.4).

Cross resistance
Polymyxins including colistimethate sodium differ in their mechanism of action compared with other antibiotics and there is evidence to show that Gram-negative bacteria resistant to other antibiotics may be susceptible to colistimethate sodium. The resistance to polymyxins is not crossed with other antibiotic families.
5.2 Pharmacokinetic properties

Absorption
Gastrointestinal absorption is negligible hence the swallowing of colistimethate sodium deposited in the nasopharynx is unlikely to add to the systemic exposure.
Absorption following lung administration is influenced by the nebuliser system, aerosol droplet size and disease state of the lungs.

Pharmacokinetics
A study in healthy volunteers, who inhaled colistimethate sodium, demonstrated the Cmax of polymyxin E1 (the active moiety) varied between 40.0 and 69.9 ng/mL and the AUC varied between 350 and 668 ng/mL/h depending on the nebuliser and the fill volume and concentration, which varied the dose from 0.3 million IU to 2 million IU. The half-life was approximately 5.2 hours. The absolute bioavailability was calculated to vary between 5% and 18% depending on the nebuliser. The AUC following an intravenous dose of 0.5 million IU was 3,352 ng/ml/h and the Cmax was 1,232 ng/mL.

Biotransformation
Colistimethate sodium undergoes conversion to its base in vivo.

Elimination
There is no information on the elimination of colistimethate sodium following nebulisation. Following i.v. administration excretion is primarily renal with 62% of a parenteral dose recovered in the urine within 8 hours and around 80% in 24 hours.

5.3 Preclinical safety data
Animal studies with colistimethate do not indicate adverse effects on fertility or embryo-foetal development. Peri-postnatal studies have not been conducted. Data on potential genotoxicity and carcinogenicity for colistimethate sodium are lacking. Colistin has been shown to induce chromosomal aberrations in human lymphocytes in vitro, an effect that might be related to a reduction in mitotic index, which was also observed. Colistin was not mutagenic in a set of other tests.

6.2 Incompatibilities
The addition of other antibiotics to solutions of Promixin may lead to precipitation. This medicinal product should not be mixed with other medicinal products except those mentioned in section 6.6.

6.6 Instructions for use, handling and disposal
Promixin may be reconstituted with Water for Injections (WFI) to produce a clear colourless to pale yellow hypotonic solution or a 50:50 mixture of WFI and 0.9% saline to produce a clear colourless to pale yellow isotonic solution. When reconstituted, Promixin may be used with any conventional nebuliser suitable for delivery of antibiotic solutions. Solutions should be used immediately after reconstitution. Any unused solution remaining in the nebuliser must be discarded following treatment. Promixin is supplied with a Promixin Disc, for use with the I-neb AAD System. For instructions on the use of Promixin with the I-neb AAD System, please refer to detailed instructions provided with the device. Conventional nebulisers operate on a continuous flow basis and it is likely that some nebulised drug will be released into the local environment. When used with a conventional nebuliser, Promixin should be administered in a well-ventilated room, particularly in hospitals where several patients may be using nebulisers at the same time. Tubing or filters may be used to prevent waste aerosol from entering the environment.
The approved label and leaflet approved this variation are as follows:

1. What Promixin is and what it is used for

Promixin contains colistimethate sodium, an antibiotic that fights infections caused by Pseudomonas aeruginosa. This is a very common bacterium that infects the lungs of nearly all patients with cystic fibrosis at some time during their lives. If the infection is not properly controlled it will continue to damage the lungs, causing further problems.

Promixin is used to treat chest infections caused by Pseudomonas in people with cystic fibrosis. Promixin is breathed into the lungs (inhaled) so that more of the antibiotic can work against the bacteria causing the infection.

2. Before you take Promixin

In certain circumstances your doctor may decide not to prescribe Promixin.

Do not use Promixin and tell your doctor if:

- you are pregnant or could get pregnant (please read the section 'Pregnancy and breast-feeding' below);
- you are breast-feeding (please read the section 'Pregnancy and breast-feeding' below);
- you are allergic (hypersensitive) to colistimethate sodium or other polymyxins;
- you suffer from myasthenia gravis (a rare disease where your muscles are extremely weak and get tired very quickly).

If any of these apply to you, see your doctor before you start taking Promixin.

Take special care with Promixin and tell your doctor if:

- you have or have had kidney problems;
- you suffer from porphyria (a rare metabolic disease that some people are born with);
- you suffer from asthma. If any of these apply to you, tell your doctor.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicine, including medicines you bought without a prescription.

These medicines may interfere with the effect of Promixin.

- if you are taking antibiotics such as cefuroxim sodium, gentamicin, amikacin, netilmicin and tobramycin, please tell your doctor. Taking Promixin at the same time as these other antibiotics could increase your risk of kidney problems.

- Promixin could prolong the effects of muscle relaxing medicines, which may be used as part of a general anaesthetic if you have an operation. If you need to have a general anaesthetic, tell the anaesthetist that you are taking Promixin.

Pregnancy and breastfeeding

You must not take Promixin if you are pregnant or trying to get pregnant. Promixin may harm your unborn baby.

Do not breast-feed while you are taking this medicine. Promixin can pass into breast milk.

Driving and using machines

Promixin may make you feel dizzy, confused or have problems with your sight, such as blurred vision. If this happens to you, do not drive or use any tools or machines.
PAR Promixin 1 million International Units (IU), Powder for Nebuliser Solution

3. How to take Promixin

Always take Promixin exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose for adults and children over the age of two years is 1-2 doses two or three times a day. Your doctor will work out the best dose for you.

Tell your doctor if you have any problems with your kidneys so you may need to take a lower dose of Promixin.

You should take your first dose of Promixin before you go to bed at night.

Take your Promixin after physiotherapy and after taking any other nebulised medicines that you have been prescribed.

Promixin has to be breathed in from a nebuliser. Promixin can be taken using any nebuliser system that can be used to deliver antibiotics to the lungs. Promixin comes with a Promixin Disc so that it can be used with the 1-neb AAD System. To find out how to use Promixin with 1-neb, see the detailed instructions which come with the 1-neb.

If you use a different nebuliser you should make sure the room is well ventilated.

How to prepare Promixin

Your doctor or nurse will show you how to use Promixin with your nebuliser.

Before Promixin can be taken it must be dissolved in sterile water or a half and half mixture of sterile water and sterile saline (salt water).

The following are general instructions on how to dissolve Promixin:

- Flip open the Promixin plastic cap.
- Carefully rip the foil seal from the top of the vial and remove it completely.
- Take out the rubber bung carefully.
- Slowly add sterile water or sterile water and sterile saline to the vial. (The instructions with the nebuliser will tell you the correct volume of liquid to add to the Promixin vial).
- Roll the vial gently between both hands to dissolve the Promixin in the liquid. This will reduce foaming.
- Avoid shaking the vial too hard.
- Pour the solution into the nebuliser.
- Any unused solution should be disposed of (see section 5 'How to store Promixin' for instructions on how to dispose of Promixin. Once prepared Promixin should be used immediately.

If you take more Promixin than you should

If you realise that you have taken more Promixin than your doctor has recommended or if someone else has taken some of your Promixin, contact your doctor straight away.

The symptoms of taking too much Promixin can include:

- Tingeing or numbness around the lips and face
- Dizziness and spinning sensation (vertigo)
- Slurred speech
- Visual disturbance
- Confusion
- Mental disturbance
- Flushing (reddening of the face)

If you forget to take Promixin

Take the dose as soon as you remember, unless it is near the time for your next dose. You do not need to make up for the dose you have missed.

If you stop taking Promixin

Do not stop your treatment early unless your doctor says that you can. Your doctor will tell you how long your treatment will last.

4. Possible side effects

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

Promixin can sometimes cause allergic reactions such as skin rash. If this happens you should stop taking Promixin and tell your doctor immediately.

Breathing in Promixin through a nebuliser can make some people notice tightness in their chest, feel wheezy, cough or become breathless. For this reason the first dose should be taken when you are with your doctor or nurse. Your doctor may also advise you to take a medicine to help prevent any breathlessness. Your doctor may check your breathing at your clinic visits.

Promixin might also affect your kidneys, usually if the dose is high or you are taking other medicines that may affect your kidneys.

Promixin may sometimes cause you to have a sore mouth or sore throat.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Promixin

Keep Promixin out of the reach of children and pets.

Do not use Promixin after the expiry date which is stated on the vial or carton. The expiry date refers to the last day of that month.

Promixin does not require any special storage conditions.

Promixin contains no preservatives. Once prepared, Promixin should be used immediately.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer require. These measures will help to protect the environment.

6. Further information

What Promixin contains

The active substance is colistimethate sodium (also known as colistin). Each vial contains 1 million International Units (IU) of colistimethate sodium, which weighs about 98 milligrammes. There are no other ingredients.

What Promixin looks like and contents of the pack

Promixin is supplied in packs containing 30 vials. Each pack contains a Promixin® Disc for use with the 1-neb AAD System.

Marketing Authorisation Holder

Profil Pharma Ltd.
Chesham Business Park,
City Fields Way, Taplere,
Chesham, Buckinghamshire,
HP5 2EE, UK.
Tel: +44 (0) 800 1300 855
Fax: +44 (0) 800 1300 856
Email: info@profilpharma.com

Manufacturer

Astellas Pharmaceuticals ApS
Dalslandsade 11
DK-2300 Copenhagen S
Denmark

Other formats:

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge: 0800 156 5000 (UK Only).

Please be ready to give the following information:

Product name:
Promixin 1 million unit powder for nebuliser solution with added diluent.

Reference number:
12461/00001

This is a service provided by the National Health Service
PA 114/12/1 (Ireland)

This leaflet was last approved in 2018.

PL368 Issue 9

35
Reference: PL 19419/0001; UK/H/0618/001/II/019

Product: Promixin 1 million International Units (IU), Powder for Nebuliser Solution

MAH: Profile Pharma Limited

Active Ingredient: Colistimethate sodium

Reason:
To include comparative nebuliser data in section 4.2 (Posology and administration) of the SmPC following the completion of a study to generate comparative information on the performance of Promixin with several commonly used nebulisers.

Introduction
In the repeat use procedure UK/H/0618/001/E01, the MAH agreed to generate additional comparative data for the output of colistimethate from different nebulisers as requested by the Concerned Member States (FR).

Evaluation

The MAH conducted in vitro studies in 3 different types of nebulisers (I neb, SideStream and Pari LC plus) whilst nebulising colistimethate sodium solutions.

I-neb
Study PT85ST478.1Ra investigated the particle size characteristics of 3 I-neb chambers, using 0.3 and 0.5ml chamber sizes. Study PT85ST474.1Rb investigated the output performance of 3 I-neb chambers (0.3 and 0.5ml) into a CEN breathing pattern. (1 MIU reconstituted in 1ml of 0.45% (w/v) saline were used in all cases.)

<table>
<thead>
<tr>
<th>ID</th>
<th>MMD (μm)</th>
<th>% &lt;5μm</th>
<th>Mean</th>
<th>Stdev</th>
<th>RSD %</th>
<th>Mean</th>
<th>Stdev</th>
<th>RSD %</th>
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</thead>
<tbody>
<tr>
<td>Ineb 0.3ml Chamber</td>
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<td>9.30</td>
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<td>Ineb 0.5ml Chamber</td>
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<td>0.27</td>
<td>5.59</td>
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<td>53.01</td>
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<table>
<thead>
<tr>
<th>ID</th>
<th>Mean Treatment Time (seconds)</th>
<th>Output to Filter (IU)</th>
<th>Mean</th>
<th>Stdev</th>
<th>RSD %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ineb 0.3 ml Chamber</td>
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<td>332997</td>
<td>8443</td>
<td></td>
<td>2.536</td>
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<tr>
<td>Ineb 0.5 ml Chamber</td>
<td>509</td>
<td>579140</td>
<td>26657</td>
<td></td>
<td>4.603</td>
</tr>
</tbody>
</table>
SideStream
Study PT85ST476.1Rb investigated the particle size characteristics and the output to filter of 3 SideStream nebulisers driven by a Portaneb compressor. (1 MIU reconstituted in 3ml of 0.45% (w/v) saline.

<table>
<thead>
<tr>
<th>ID</th>
<th>Output to Filter (IU)</th>
<th>Treatment Time (seconds)</th>
<th>MMD (µm)</th>
<th>% &lt;5µm</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Stdev</td>
<td>RSD %</td>
<td>Mean</td>
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<td>SideStream</td>
<td>238840</td>
<td>16017</td>
<td>6.706</td>
<td>318</td>
</tr>
</tbody>
</table>

Pari LC Plus
Study PT85ST480.1Ra investigated the particle size characteristics of 3 Pari LC Plus nebulisers driven by a Turbo Boy S compressor. Study PT85ST479.1Ra investigated the output performance of 3 Pari LC Plus nebulisers driven by a Turbo Boy S compressor into a CEN breathing pattern. (1 MIU reconstituted in 3 ml of 0.45% (w/v) saline and 1 MIU reconstituted in 3ml of 0.9% (w/v) saline.

<table>
<thead>
<tr>
<th>ID</th>
<th>MMD (µm)</th>
<th>% &lt;5µm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Stdev</td>
</tr>
<tr>
<td>Pari LC Plus (0.45% Saline)</td>
<td>4.78</td>
<td>0.16</td>
</tr>
<tr>
<td>Pari LC Plus (0.9% Saline)</td>
<td>4.62</td>
<td>0.25</td>
</tr>
</tbody>
</table>

For the I-neb, the table proposed for section 4.2 includes the data from the 0.3 ml chamber using 0.45% (w/v) saline. For the Pari LC plus/ Turbo Boy S combination and Sidestream/Portaneb combination, the table also includes the data generated when using 0.45% (w/v) saline. Data for 0.9% (w/v) saline were not generated for I-neb and SideStream nebulisers.
Summary of Product Characteristics-updated

The fragment updated in view of the above stated variation is reproduced below:

4.2 Posology and method of administration

Sputum cultures should be obtained to confirm colonisation with *Pseudomonas aeruginosa* sensitive to colistimethate sodium prior to initiating treatment with Promixin.

The following information provides guidance on recommended doses and the dose should be adjusted according to clinical response.

Recommended doses are:
Children >2 years and adults: 1-2 million IU two or three times daily
Children < 2 years: The safety and efficacy of Promixin has not been demonstrated in patients less than 2 years of age.

The dosage is determined by the severity and type of infection.

The dose may be varied across this range depending on the condition being treated.

**Initial colonisation** with *Pseudomonas aeruginosa* sensitive to colistimethate sodium may be treated with a 3-week course of 2 million IU twice daily in conjunction with other parenteral or oral antibiotics.

**For frequent, recurrent infections** (Less than three positive cultures of *Pseudomonas aeruginosa* sensitive to colistimethate sodium in a six month period) the dose may be increased up to a maximum of 2 million IU three times daily for up to 3 months, in conjunction with other parenteral or oral antibiotics.

**Chronic colonisation** (Three or more positive cultures of *Pseudomonas aeruginosa* sensitive to colistimethate sodium in a six month period) may require long-term therapy with 1 to 2 million IU twice daily. Additional parenteral or oral antibiotics may need to be administered to treat acute exacerbations of pulmonary infection. Nebulised Promixin should be administered after physiotherapy and other inhaled treatments, where used. Other inhaled therapies may include agents to reduce the viscoelasticity of sputum and bronchodilators (see Section 4.4).

**Mode of administration**
Promixin for nebulisation is intended for administration by nebulisation using a suitable nebuliser.

Drug delivery characteristics from *in vitro* studies with different nebuliser systems are detailed below;
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nebuliser system</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Respironics I-neb AAD</td>
</tr>
<tr>
<td></td>
<td>With 0.3 mL (grey) medication chamber</td>
</tr>
<tr>
<td>(a) Droplet Size Distribution (µm)</td>
<td>Median Particle Size: $d_{50}$</td>
</tr>
<tr>
<td>(b) Total Drug Delivered from Nebuliser mouthpiece (Million IU)</td>
<td>0.333</td>
</tr>
<tr>
<td>(c) Fine Particle Fraction (% &lt; 5 µm)</td>
<td>59.55</td>
</tr>
<tr>
<td>(d) Total Drug Delivered to patient (Million IU &lt; 5 µm)</td>
<td>0.198</td>
</tr>
<tr>
<td>(e) Delivery Time (seconds)</td>
<td>3 minutes, 36 seconds</td>
</tr>
<tr>
<td>(f) Drug Delivery Rate to patient (Million IU/minute)</td>
<td>0.055</td>
</tr>
</tbody>
</table>

- Measured using 1 million IU of Promixin using 1mL (I-neb AAD) and 3mL (Pari LC plus and Sidestream) of a 50:50 mixture of WFI and 0.9% saline to the recommended volume for each nebuliser system.
- TurboBoy S operated at 1.2 bar pressure, 4.5 L/min flow rate. Portaneb operated at: 0.8 bar pressure, 6 L/min flow rate.
- (d) is calculated from (b) / 100 x (c)
- (f) = (d) / (e)

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