Public Assessment Report

Decentralised Procedure

Colistimethate Sodium 1 Million International Units (I.U.)
Powder for solution for injection or infusion

(colistimethate sodium)

UK/H/4656/001/DC

UK licence numbers: PL 15011/0008

InfectoPharm Arzneimittel und Consilium GmbH
LAY SUMMARY

On 19 April 2012, the MHRA granted InfectoPharm a Marketing Authorisation (licence) for the medicinal product, Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion (PL 15011/0008). This is a prescription-only medicine (POM).

Colistimethate sodium is an antibiotic. It belongs to a group of antibiotics called polymyxins. Like all antibiotics, colistimethate sodium is only active against some bacteria, so it is only suitable for treating some types of infection. Colistimethate sodium is given by injection to treat some serious infections where other antibiotics are not suitable. These infections include some types of pneumonia and some bladder or kidney infections.

Based on the data submitted by InfectoPharm, Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion was considered to be a generic version of the reference product, Colomycin Injection 1 million International Units powder for solution for injection, infusion or inhalation (PL 00108/5006R, Forest Laboratories UK Limited).

No new or unexpected safety concerns arose from this application. It was judged that the benefits of Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion outweigh the risk; hence a Marketing Authorisation has been granted.
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# Module 1

## Information about Initial Procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td>Active Substances</td>
<td>Colistimethate sodium</td>
</tr>
<tr>
<td>Form</td>
<td>Powder for solution for injection or infusion</td>
</tr>
<tr>
<td>Strength</td>
<td>1 million International Units (I.U.)</td>
</tr>
<tr>
<td>MA Holder</td>
<td>InfectoPharm Arzneimittel und Consilium GmbH Von-Humboldt-Str. 1 D-64646 Heppenheim Germany</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>Concerned Member State (CMS)</td>
<td>Germany</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/4656/001/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 180 – 26 March 2012</td>
</tr>
</tbody>
</table>
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion (PL 15011/0008) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Colistimethate Sodium
1 Million International Units (I.U.)
Powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial contains 1 million I. U. colistimethate sodium.

3 PHARMACEUTICAL FORM
Powder for solution for injection or infusion
Creamy white lyophilised powder in a glass vial.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Colistimethate Sodium is indicated in the treatment of the following infections caused by susceptible aerobic Gram-negative bacteria (see section 5.1):
- Hospital acquired pneumonia (HAP)
- Complicated urinary tract infections

It is recommended that Colistimethate Sodium should be selected when antibacterial agents that are commonly used to treat these infections are not considered to be appropriate for the individual patient and/or the causative pathogen(s) (see sections 4.4 and 5.1).

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

4.2 Posology and method of administration
It is recommended that Colistimethate Sodium should be administered under the supervision of physicians with appropriate experience in its use.

Posology
The dose regimen of Colistimethate Sodium that is selected should take into account factors such as the susceptibility of the pathogen(s), the severity and type of infection, and the ideal body weight and renal function of the patient. The duration of treatment is usually at least 5 days.

Standard dose recommendations are as follows:

Up to 60kg: 50,000 I.U./kg (4mg/kg) bodyweight, to a maximum of 75,000 I. U./kg (6mg/kg), in 24 hours. The total daily dose should be administered as three equal doses at 8 hourly intervals.

Over 60kg: 1-2 million I. U. every 8 hours. The maximum standard dose is 6 million I. U. (480mg) in 24 hours.

Limited pharmacokinetic data from critically ill patients suggest that use of a loading dose and higher than standard doses may be appropriate (see section 5.2). For severe infections and in critically ill patients doses up to 9 million I. U. per day in divided doses have been reported in the literature. Clinical efficacy and safety data with these regimens are very limited and caution is advised (see sections 4.4 and 5.2).
**Paediatric population**
Dose recommendations are the same in adults and all paediatric subgroups.

**Renal impairment**
The suggested dose recommendations in the following table for patients with renal impairment are based on the standard total daily dose of 3-6 million I. U. per day. For patients with renal impairment in whom higher doses (e.g. up to 9 million I. U. per day) would be considered if their renal function was normal, corresponding proportional adjustments should be considered when calculating the dose. Caution is advised when administering Colistimethate Sodium to any patient with renal impairment due to the limited information available on safety and appropriate dose regimens (see section 4.4).

**Table: Suggested modification of dosage of Colistimethate Sodium for adults with impaired renal function**

<table>
<thead>
<tr>
<th>Degree of Renal Impairment</th>
<th>Normal (%)</th>
<th>Mild (%)</th>
<th>Moderate (%)</th>
<th>Severe (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance</td>
<td>76 to 100</td>
<td>40 to 75</td>
<td>25 to 40</td>
<td>Less than 25</td>
</tr>
</tbody>
</table>

**Dose**

<table>
<thead>
<tr>
<th>Unit dose (million I.U.)</th>
<th>1.3 to 2</th>
<th>1 to 1.5</th>
<th>1</th>
<th>1 to 1.5</th>
</tr>
</thead>
<tbody>
<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 I.U.)</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>

**Hepatic impairment**
It is not known whether the dose of Colistimethate Sodium requires adjustment in patients with hepatic impairment and therefore caution is advised.

**Method of Administration**
Administration is by intravenous infusion. Each dose of Colistimethate Sodium can be diluted with 50ml and administered by intravenous infusion over a period of 30 minutes. Patients fitted with a totally implantable venous access device (TIVAD) may tolerate an injection of up to 2 million I. U. in 10ml given over a minimum of 5 minutes.

For instructions on dilution of the product before administration, see section 6.6.

**4.3 Contraindications**
Hypersensitivity to colistimethate sodium (also known as colistin) or to other polymyxins.

**4.4 Special warnings and precautions for use**
Use with extreme caution in patients with porphyria.

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, unless in life-threatening situations.

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

Nephrotoxicity or neurotoxicity may occur especially if the recommended dose is exceeded (see also section 4.5). There are limited safety data when colistimethate sodium is used in doses exceeding 6 million I. U. per day.

Monitoring of renal function should be performed before initiating treatment with Colistimethate Sodium. Monitoring of serum creatinine must continue at regular intervals (at least daily) during therapy. Particular caution should be exercised when administering doses greater than 6 million I. U.
per day. The dose of Colistimethate Sodium may have to be reduced if serum creatinine concentrations rise or exceed the upper limit of normal (see section 4.2).

There is evidence that it is the total cumulative dose (not the daily dose) of colistimethate sodium that may be associated with risk of nephrotoxicity.

Do not use concomitantly with other medications with nephrotoxic or neurotoxic effects except with the greatest caution (see also section 4.5).

_Clostridium difficile_ associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of _C. difficile_. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of colistimethate sodium. Discontinuation of therapy with colistimethate sodium and the administration of specific treatment for _C. difficile_ should be considered. Medicinal products that inhibit peristalsis should not be given.

This medicinal product contains less than 1mmol sodium (23mg) per vial, i.e. essentially ‘sodium-free’.

### 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 Colistimethate Sodium as their effects could be prolonged (see also section 4.4).

Concomitant use of colistimethate sodium with other medicinal products of neurotoxic and/or nephrotoxic potential should only be undertaken with greatest caution. These include the aminoglycoside antibiotics such as gentamicin, amikacin, netilmicin and tobramycin as well as cephalotin sodium and non-depolarising muscle relaxants.

The potential of colistimethate sodium to affect the pharmacokinetics of other medicinal products has not been evaluated. Caution is recommended if colistimethate sodium is combined with medicinal products with a narrow therapeutic index.

### 4.6 Fertility, Pregnancy and lactation

**Fertility**

Data on the possible impact of colistimethate sodium on human fertility are not available. Animal studies do not indicate effects with respect to fertility (see Section 5.3).

**Pregnancy**

There are no adequate data from the use of colistimethate sodium in pregnant women. However, single dose studies in human pregnancy show that colistimethate crosses the placental barrier and there may be a risk of foetal toxicity if repeated doses are given to pregnant patients. Animal studies are insufficient with respect to the effect of colistimethate sodium on reproduction and development (see Section 5.3).

Colistimethate sodium should be used in pregnancy only if the benefit to the mother outweighs the potential risk to the foetus.

**Breast-feeding**

Colistimethate is secreted in human milk; hence, breast-feeding is not recommended during therapy.

### 4.7 Effects on ability to drive and use machines

During parenteral treatment with colistimethate sodium neurotoxicity may occur with the possibility of dizziness, confusion or visual disturbance. Patients should be warned not to drive or operate machinery if these effects occur.

### 4.8 Undesirable effects

The most commonly reported adverse reaction is renal function impairment, and more rarely renal failure, usually following use of higher than recommended doses in patients with normal renal
function, or failure to reduce the dosage in patients with renal impairment or when used concomitantly with other nephrotoxic antibiotics.

The effect is usually reversible on discontinuation of therapy, but rarely intervention (renal replacement therapy) may be required.

High serum concentrations of colistimethate sodium, which may be associated with overdosage or failure to reduce the dosage in patients with renal impairment, have been reported to lead to neurotoxic effects such as facial paraesthesia, muscle weakness, vertigo, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis and apnoea. 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.

Hypersensitivity reactions such as skin rash and angioedema have been known to occur. In the event such reactions occur, treatment with colistimethate sodium should be withdrawn.

Adverse reactions are tabulated below by system organ class and frequency. Frequencies are defined as

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Reported adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common:</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Common:</td>
<td>≥ 1/100 to &lt;1/10</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>≥ 1/1,000 to &lt;1/100</td>
</tr>
<tr>
<td>Rare:</td>
<td>≥ 1/10,000 to &lt;1/100</td>
</tr>
<tr>
<td>Very rare:</td>
<td>&lt; 1/10,000</td>
</tr>
<tr>
<td>Not known:</td>
<td>frequency cannot be estimated from the available data</td>
</tr>
</tbody>
</table>

<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 and angioedema</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Neurotoxicity such as facial, mouth and peri-oral paraesthesia, headache, and muscle weakness</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very common</td>
<td>Pruritus</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very common</td>
<td>Renal impairment demonstrated by increased blood creatinine and/or urea and/or decreased creatinine renal clearance</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Renal failure</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Not known</td>
<td>Injection site reaction</td>
</tr>
</tbody>
</table>

4.9 **Overdose**

Overdose can result in neuromuscular blockade that can lead to muscular weakness, apnoea and possible respiratory arrest. Vertigo, transient facial paraesthesia, slurred speech, vasomotor instability, visual disturbances, confusion, and psychosis have been reported.
Overdose can also cause acute renal failure characterised by decreased urine output and increased serum concentrations of BUN and creatinine.

There is no specific antidote available.

Manage by supportive treatment and measures to increase the rate of elimination of colistimethate sodium e.g. mannitol diuresis, prolonged haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: OTHER ANTIBACTERIALS, Polymyxins
ATC Code: J01X B01.

Mode of action
Colistimethate sodium (also known as colistin) is a cyclic polypeptide antibiotic derived from Bacillus polymyxa var. colistinus and belongs to the polymyxin group. The polymyxin antibiotics are cationic, surface active agents and act by binding to and damaging the cell membrane. The resulting physiological effects are lethal to the bacterium. Polymyxins are selective for Gram-negative bacteria that have a hydrophobic outer membrane.

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

Mechanisms of resistance
Acquired resistance to colistimethate sodium in Pseudomonas aeruginosa appears to be related to alterations in the bacterial outer membrane. In-vitro studies with Salmonella and E. coli have shown that resistance may occur due to modification of the cell wall lipopolysaccharide phosphate groups. Modification is achieved by substitution of the phosphate groups with ethanolamine or aminoorabinoose. Proteus mirabilis, Burkholderia cepacia and other naturally resistant Gram-negative bacteria, show complete substitution of their lipopolysaccharide groups.

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.

There is no co-resistance between polymyxins and other groups of antibiotics.

EUCAST Breakpoints

<table>
<thead>
<tr>
<th>Species</th>
<th>Susceptible (S)</th>
<th>Resistant (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter</td>
<td>≤2mg/l</td>
<td>&gt;2mg/l</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>≤2mg/l</td>
<td>&gt;2mg/l</td>
</tr>
<tr>
<td>Pseudomonas spp</td>
<td>≤4mg/l</td>
<td>&gt;4mg/l</td>
</tr>
</tbody>
</table>

*Breakpoints apply to dosage of 2-3 million I.U. x 3. A loading dose (9 million I.U.) may be needed.

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Acinetobacter species
Klebsiella species
Pseudomonas aeruginosa

Species for which acquired resistance may be a problem
Stenotrophomonas maltophilia
Achromobacter xylosoxidans
5.2 Pharmacokinetic properties

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

Distribution
After administration to cystic fibrosis (CF) patients of 7.5 mg/kg/day in divided doses given as 30 minute intravenous infusions to steady state the $C_{\text{max}}$ was determined to be 23 (±6) mg/l and $C_{\text{min}}$ at 8 hr was 4.5 (±4) mg/l. In another study in CF patients given 2 million units every 8 hours for 12 days the $C_{\text{max}}$ was 12.9 mg/l (5.7 – 29.6 mg/l) and the $C_{\text{min}}$ was 2.76 mg/l (1.0 – 6.2 mg/l). In healthy volunteers given a bolus injection of 150 mg (approximately 2 million units) peak serum levels of 18 mg/l were observed 10 minutes after injection.

Protein binding is low. Polymyxins persist in the liver, kidney, brain, heart and muscle.

The volume of distribution of colistin following administration of colistimethate sodium in healthy volunteers and in patients with cystic fibrosis has been reported to be 12.4 L and 20.4 L respectively. In comparison the volume of distribution for colistin following administration of colistimethate sodium has been shown to be between 90.6 L and 139.9 L in critically ill patients. The increase in the volume of distribution in critically ill patients, may lead to a delay in reaching effective plasma concentrations. Therefore the use of an initial loading dose of up to 9 million I. U. has been suggested, especially in critically ill patients.

In critically ill patients given colistimethate sodium 2 million I. U. and 3 million I. U. three times a day intravenously, peak colistin plasma concentrations of 2.21 and 2.93 mg/l, respectively, were observed.

Biotransformation
Colistimethate sodium is partly converted to the base colistin in-vivo.

Elimination
The main route of elimination of unchanged colistimethate sodium after parenteral administration is by renal excretion with around 60% of a parenteral dose recovered in the urine within 8 hours. Because colistimethate is largely excreted in the urine, dosage reduction is required in renal impairment to prevent accumulation. Refer to the table in Section 4.2. The free base colistin is excreted by the non-renal route.

After intravenous administration to healthy adults the elimination half-life of colistimethate sodium is around 1.5 hrs. In a study in CF patients given a single intravenous infusion over 30 minutes the elimination half-life was 3.4 ± 1.4 hrs.

The half-life of colistin following administration of colistimethate sodium in healthy volunteers and in patients with cystic fibrosis has been reported to be 3 hours and 4.2 hours respectively. The half-life of colistin following administration of colistimethate sodium has been reported to increase when administered to critically ill patients compared to healthy volunteers and mean half-life is estimated to range from approximately 5.9 hours to 7.4 hours following intravenous administration to critically ill patients.

In patients with renal impairment, colistimethate sodium excretion is reduced and a higher proportion may be converted to colistin, leading to increased plasma colistin concentrations.

Colistimethate pharmacokinetics appear to be similar in children and adults, including the elderly, provided renal function is normal. Limited data are available on use in neonates that suggest that pharmacokinetics are similar to children and adults but the possibility of higher peak serum levels and prolonged half-life in these patients should be considered.
5.3 Preclinical safety data

Data on potential genotoxicity are limited and carcinogenicity data for colistimethate sodium are lacking. Colistimethate sodium has been shown to induce chromosomal aberrations in human lymphocytes in vitro. This effect may be related to a reduction in mitotic index, which was also observed.

Reproductive toxicity studies in rats and mice do not indicate teratogenic properties. However, colistimethate sodium given intramuscularly during organogenesis to rabbits at 4.15 and 9.3 mg/kg resulted in talipes varus in 2.6 and 2.9% of foetuses respectively. These doses are 0.5 and 1.2 times the maximum daily human dose. In addition, increased reabsorption occurred at 9.3 mg/kg.

No effects were seen on mouse or rat fertility at intravenous doses up to 25 mg/kg/day.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

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

6.3 Shelf life

2 years

From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in-house storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours in the refrigerator (2 to 8°C).

6.4 Special precautions for storage

Do not store above 25°C.
Store the vial in the outer carton in order to protect from light.
Do not freeze.
Reconstituted solution may be kept for up to 24 hours stored in a refrigerator.

6.5 Nature and contents of container

10 ml Type III glass vial with a rubber stopper and an aluminium cap. Each carton contains 1 or 10 vials.

6.6 Special precautions for disposal

For dilution use 0.9 % sodium chloride intravenous infusion or water for injections.
The reconstituted product is a clear solution.

The outer surface of the primary container is non-sterile. For single use only. Any unused solution should be disposed of in accordance with local requirements.

Does not contain preservatives.

7 MARKETING AUTHORISATION HOLDER

**InfecoPharm Arzneimittel und Consilium GmbH**
Von-Humboldt-Str. 1
D-64646 Heppenheim
Germany

Phone +49 (0) 62 52/95 70 00
Fax +49 (0) 62 52/95 88 44
E-mail: kontakt@infecopharm.com
8 MARKETING AUTHORISATION NUMBER(S)
   PL 15011/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   19/04/2012

10 DATE OF REVISION OF THE TEXT
    19/04/2012
Module 3

Patient Information Leaflet – text version

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities, as appropriate.

PACKAGE LEAFLET: INFORMATION FOR THE PATIENT
COLISTIMETHATE SODIUM, 1 MILLION I.U., POWDER FOR SOLUTION FOR INJECTION OR INFUSION
1 million international units/vial

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

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

What is in this leaflet:
1. What Colistimethate Sodium is and what it is used for
2. What you need to know before you are given Colistimethate Sodium
3. How Colistimethate Sodium is given
4. Possible side effects
5. How to store Colistimethate Sodium
6. Contents of the pack and other information

1. WHAT COLISTIMETHATE SODIUM IS AND WHAT IT IS USED FOR

Colistimethate Sodium is an antibiotic. It belongs to a group of antibiotics called polymyxins. Like all antibiotics, Colistimethate Sodium is only active against some bacteria, so it is only suitable for treating some types of infection.

Colistimethate Sodium is given by injection to treat some serious infections where other antibiotics are not suitable. These infections include some types of pneumonia and some bladder or kidney infections.

2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN COLISTIMETHATE SODIUM

Colistimethate Sodium is not suitable for everyone. Some people must not have this injection.

Do not have the injection:
- if you are allergic to Colistimethate Sodium (also known as colistimethate) or to other antibiotics with similar structure called polymyxins

If you are unsure about anything, ask your doctor before you have the injection.

Take special care with Colistimethate Sodium and tell your doctor if:
- you have or have had kidney problems;
- you suffer from myasthenia gravis (a rare disease where your muscles are extremely weak and get tired very quickly);
- you suffer from porphyria (a rare metabolic disease that some people are born with).

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

Other medicines and Colistimethate Sodium
You must tell your doctor if you are taking any of the following medicines:
- Other antibiotics called aminoglycosides (such as gentamicin, tobramycin, amikacin, or netilmicin) as well as cephalosporin sodium. Having Colistimethate Sodium at the same time as one of these antibiotics can increase the risk of damage to the kidneys or cause side effects in the ears and parts of the nervous system.
- Muscle relaxant medicines often used during general anaesthesia. Colistimethate Sodium can increase the effects of these drugs. If you need to have a general anaesthetic, make sure that the anaesthetist knows that you are having Colistimethate Sodium.

Make sure the doctor knows about any other medicines that you are taking, including medicines that you obtained without a prescription.

**Pregnancy and breast-feeding**
- Colistimethate Sodium is not known to harm the unborn child but, like all medicines, it will only be given to a pregnant woman if it is really needed.
- Small amounts of Colistimethate Sodium enter the milk. Hence, breast-feeding is not recommended during therapy with Colistimethate Sodium.

**Driving and using machines**
Some people have reported side effects such as dizziness, confusion or problems with vision. If you are affected do not drive or operate machinery.

**Colistimethate Sodium contains sodium**
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium-free'.

3. **HOW COLISTIMEHATE SODIUM IS GIVEN**

The Colistimethate Sodium powder is made up into a solution and will be given to you either as an injection or infusion (drip) into a vein. Your doctor will decide how Colistimethate Sodium should be given and how long your treatment should last. This will usually be at least 5 days. When treating bacterial infections it is important to complete the full course of treatment.

The doctor will calculate the dose depending on the infection you have and how severe it is. It will also depend on your age, weight and how well your kidneys work.

**The usual dose for adults and children weighing more than 60 kg is between 1 and 2 million units three times a day.** The maximum standard dose is 6 million units in 24 hours. In special circumstances doses up to 9 million units per day may be recommended.

**The usual daily dose for adults and children weighing up to 60 kg is 50,000 to 75,000 units/kg in 24 hours.** The total daily dose should be divided into three doses given at approximately 8-hour intervals.

People who have moderate or severe kidney problems will probably be given a lower dose.

**If you are given too much Colistimethate Sodium**

As a doctor or nurse will be giving you Colistimethate Sodium, it is unlikely that you will receive an incorrect dose. Tell your doctor or nurse if you have any concerns about the amount of medication that you are given.
The symptoms of having too much Colistimethate Sodium can include:
- dizziness and spinning sensation (vertigo)
- slurred speech
- visual disturbance
- confusion
- mental disturbance
- tingling or numbness of the face
- kidney problems
- muscle weakness
- feeling as though you cannot breathe

If you were not given Colistimethate Sodium when expected
If you think that you may have missed a dose, please speak to your doctor or nurse.

Stopping Colistimethate Sodium
Your doctor will decide how long you should be given Colistimethate Sodium. It is important that your treatment is completed as advised by your doctor or your symptoms may get worse.

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

4. POSSIBLE SIDE EFFECTS

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

Tell the doctor or nurse immediately if you notice any of the following symptoms:
- Wheezing or breathing difficulties which can lead to collapse, a rash, itching or hives on the skin, or sudden swelling of the face, throat or lips. These can be signs of a severe allergic reaction.

Colistimethate Sodium can also affect your kidneys, especially if the dose is high or you are taking other medicines that may affect your kidneys.

Very common side effects (affecting more than 1 person in 10)
- blood tests may show changes in the way the kidneys are working
- headache
- tingling or numbness around the mouth, lips and face
- itching
- muscle weakness

Rare side effects (affecting less than 1 person in 1 000)
- kidney failure

Other side effects can include:
- dizziness
- difficulty in controlling movements
- soreness at the site of injection

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet.

5. HOW TO STORE COLISTIMETHATE SODIUM

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the outer carton and the vials after “Exp.”. The expiry date refers to the last day of that month.
Do not freeze.
Store below 25°C.
Keep the vial(s) in the outer carton, in order to protect from light.
Reconstituted/diluted solution should be used immediately, or within 24 hours when stored in the refrigerator (2 to 8°C).
For single use only. Discard any unused solution.
Do not use this medicine if you notice any discoloration or cloudiness of the solution.
Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Colistimethate Sodium contains:
- The active substance is colistimethate sodium.
There are no other ingredients.

What Colistimethate Sodium looks like and contents of the pack
Colistimethate Sodium is a creamy white powder for solution for injection or infusion in single dose 10ml glass vials. Each carton contains 1 or 10 vials. Each vial contains the active ingredient, colistimethate (also called Colistin) as an amount of powder equivalent to one million international units.

Marketing Authorisation Holder
InfectoPharm Arzneimittel und Consultum GmbH
Von-Humboldt-Str. 1
D-64646 Heppenheim
Germany

Manufacturer
Alfa Wassermann S.p.A., Via Enrico Fermi, 1, 65020 Altano, Italy.

This medicinal product is authorised in the Member States of the EEA under the following names:

Germany: Colistin Infectopharma 1 Mio I.E., Pulver zur Herstellung einer Injektions- oder Infusionslösung
United Kingdom: Colistimethate Sodium 1 Million I.U., Powder for solution for injection or infusion

This leaflet was last revised in March 2012
If you find this leaflet difficult to read or understand, please speak to the doctor or nurse or contact the marketing authorisation holder at the above address.

<--------------------------->

The following information is intended for medical or healthcare professionals only:

COLISTIMETHATE SODIUM, 1 MILLION I.U., POWDER FOR SOLUTION FOR INJECTION OR INFUSION
Please read this information carefully before using Colistimethate Sodium. Further information is contained in the Summary of Product Characteristics.

PRESENTATION

Colistimethate Sodium is a creamy white lyophilised powder in a 10ml glass vial. Each vial contains 1 Million I.U. (International Units) of colistimethate sodium.

DOSAGE AND METHOD OF ADMINISTRATION

To be given by IV bolus or IV infusion.

Dilution/flush solution: 0.9% sodium chloride or water for injections. Reconstituted Colistimethate Sodium is a clear solution.

Administration rate:
IV infusion: 50ml over 30 minutes.
IV bolus (up to 2 million units) through a TIVAD: 10ml over a minimum 5 minutes.

Dosage (adjustment required in renal impairment):
Adults and children:
- over 60 kg: 1-2 million units three times daily. Maximum standard dose: 5 million units in 24 hours. For severe infections and critically ill patients doses up to 9 million units per day in divided doses may be appropriate.
- up to 60 kg: 50,000 units/kg/day, to a maximum of 75,000 units/kg/day. The total daily dose should be divided into three doses given at approximately 8-hour intervals.

For dosing in patients with renal impairment, see SmPC.

Stability of the reconstituted solution: Up to 24 hours in a refrigerator (2-8°C).

Incompatibilities with commonly used mixtures: Do not mix reconstituted solution with other medicinal products.

Special handling information: For single use only. Discard any remaining solution. The outer surface of the primary container is non-sterile.

CONTRAINDICATIONS

- patients with known hypersensitivity to colistimethate sodium or other polymyxins

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Colistimethate Sodium may interact with aminoglycoside antibiotics, cephalotin sodium, and curariform muscle relaxants.

PHARMACEUTICAL INFORMATION

Excipients: There are no other excipients.
Shelf-life: 2 years

STORAGE PRECAUTIONS

Do not store above 25°C. Store the vial in the outer carton in order to protect from light.
Do not freeze. From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in-house storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours in the refrigerator (2 to 8°C).

**Nature of Container**

10ml Type III glass vials with rubber stoppers and aluminium crimp seals. Each carton contains 1 or 10 vials.
Module 4

Labelling – text version

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities, as appropriate.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Colistimethate Sodium
1 Million I.U.
Powder for solution for injection or infusion

2. METHOD OF ADMINISTRATION

For intravenous use.
See leaflet for details of reconstitution.

3. EXPIRY DATE

Exp.

4. BATCH NUMBER

Batch No.

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each vial contains 1 million I.U. colistimethate sodium.

6. OTHER

PL 15011/0008
INFECTOPHARM
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

#### CARTON

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistimethate Sodium</td>
</tr>
<tr>
<td>1 million I.U.</td>
</tr>
<tr>
<td>Powder for solution for injection or infusion</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each vial contains 1 million I.U. (International Units) colistimethate sodium.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
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<tbody>
<tr>
<td>Contains sodium (less than 23 mg per vial).</td>
</tr>
<tr>
<td>See leaflet for further information.</td>
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</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder for solution for injection or infusion</td>
</tr>
<tr>
<td>10 vials.</td>
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<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>For intravenous use.</td>
</tr>
<tr>
<td>Sterile and non-pyrogenic. Use only as directed by a medical practitioner.</td>
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<tr>
<td>For further information see the enclosed leaflet.</td>
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</table>

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<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
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<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
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<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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<tr>
<td>For single use only. Discard any unused solution. Do not use unless the container is undamaged.</td>
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<tr>
<th>8. EXPIRY DATE</th>
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<tbody>
<tr>
<td>Exp.</td>
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<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
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<tr>
<td>Store below 25°C. Store vial in outer carton to protect from light. Do not freeze.</td>
</tr>
<tr>
<td>The reconstituted product should be used immediately or within 24 hours if stored in the refrigerator (2-8°C).</td>
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Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted InfectoPharm a Marketing Authorisation for the medicinal product, Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion (PL 15011/0008, UK/H/4656/001/DC) on 19 April 2012. The product is a prescription-only medicine.

This is a generic application for Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The application refers to the UK product, Colomycin Injection 1 million International Units powder for solution for injection, infusion or inhalation (PL 00108/5006R), authorised to Forest Laboratories UK Limited as a product licence of right on 04 June 1986. The reference product has been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

With the UK as the Reference Member State (RMS) in this Decentralised Procedure, InfectoPharm applied for a Marketing Authorisation for Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion in Germany.

Colistimethate sodium is indicated in the treatment of the following infections caused by susceptible aerobic Gram-negative bacteria (see SmPC section 5.1):

- Hospital acquired pneumonia (HAP)
- Complicated urinary tract infections

It is recommended that colistimethate sodium should be selected when antibacterial agents that are commonly used to treat these infections are not considered to be appropriate for the individual patient and/or the causative pathogen(s) (see SmPC sections 4.4 and 5.1). Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Colistimethate sodium (also known as colistin) is a cyclic polypeptide antibiotic derived from Bacillus polymyxa var. colistinus and belongs to the polymyxin group. The polymyxin antibiotics are cationic, surface active agents and act by binding to and damaging the cell membrane. The resulting physiological effects are lethal to the bacterium. Polymyxins are selective for Gram-negative bacteria that have a hydrophobic outer membrane.

The medicinal product is presented as a sterile, creamy white lyophilised powder for solution for injection or infusion. The solution is prepared by dissolving the powder in an appropriate infusion solution, as detailed in Section 6.6 of the SmPC. The reconstituted product is a clear solution. This medicine is not for self-administration; it will be administered to the patient by a qualified healthcare professional.

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that the application cross-refers to a product that has been licensed for over
10 years. Bioequivalence studies are not necessary to support this application for a parenteral product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. 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 Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) 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 MAH 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, routine pharmacovigilance activities are proposed and 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.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion</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>Other antibacterials, polymyxins (J01XB01)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Powder for solution for injection or infusion 1 million International Units (I.U.)</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/4656/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>DE</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 15011/0008</td>
</tr>
</tbody>
</table>
| Name and address of the authorisation holder     | InfectoPharm Arzneimittel und Consilium GmbH  
Von-Humboldt-Str. 1  
D-64646 Heppenheim  
Germany                                                                 |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Colistimethate sodium

Nomenclature:
INN: Colistimethate sodium
CAS No: 8068-28-8
Physical form: A white or almost white, hygroscopic powder
Solubility: Very soluble in water, slightly soluble in ethanol, practically insoluble in acetone

The active substance, colistimethate sodium, is the subject of a European Pharmacopeia (Ph. Eur) monograph.

All aspects of the manufacture and control of colistimethate sodium are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of colistimethate sodium for inclusion in this medicinal product.
MEDICINAL PRODUCT

Description and Composition

Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion is presented as a sterile, creamy white lyophilised powder for solution for injection or infusion, supplied in a 10 ml glass vial. Each vial contains 1 million I. U. colistimethate sodium. The solution is prepared by dissolving the powder in an appropriate infusion solution, as detailed in Section 6.6 of the SmPC. The medicinal product contains no excipients.

Pharmaceutical development

In view of the simplicity of the formulation, and as this is a well-known pharmaceutical product, no pharmaceutical development studies were necessary. The aim was to obtain a stable, sterile, generic medicinal product, pharmaceutically equivalent to the reference product, Colomycin Injection 1 million International Units powder for solution for injection, infusion or inhalation (Forest Laboratories UK Limited).

Manufacture

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 were conducted and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process.

Finished product specification

Finished product specifications are provided for release and shelf life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been 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

Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion is supplied in packs of 1 or 10 x 10 ml, type III glass vials complete with rubber stoppers and aluminium seals. The vials are packaged, with the product information leaflet, into cardboard outer cartons.

Specifications and Certificates of Analysis for all packaging components used have been provided and are satisfactory. The vials satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support the applied shelf-life of 2 years, with storage instructions ‘Do not store above 25°C. Store the vial in the outer carton in order to protect from light. Do not freeze’. The reconstituted solution for intravenous injection or infusion should be used immediately. If not used immediately, reconstituted solution may be kept for up to 24 hours, stored in a refrigerator (2 to 8°C). For full details and instructions for reconstitution, refer to section 6.6 of the SmPC.
Quality Overall Summary
A satisfactory quality overall summary is provided, which has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information
The approved Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) and labelling texts are satisfactory. The MAH has submitted text versions of the PIL and labelling only and has committed to submitting mock-up livery to the relevant regulatory authorities, as appropriate.

The PIL text is in line with the SmPC and is satisfactory. User-testing of the PIL text has been accepted based on bridging to the successful user-testing of the ‘parent’ PIL for Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection (PL 18157/0009). The text, content and layout of the proposed PIL are considered to be sufficiently similar to the approved PIL for the stated product. The bridging is accepted.

Conclusion
The quality grounds for this application are considered adequate. There are no objections to approval of Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that this is an application for a generic version of a product that has been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of colistimethate sodium, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the UK product, Colomycin Injection 1 million International Units powder for solution for injection, infusion or inhalation (Forest Laboratories UK Limited).

The MAH has provided adequate justification for not submitting a detailed 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. There are no environmental concerns associated with the method of manufacture or formulation of the product.

There are no objections to approval of Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INTRODUCTION

Colistimethate sodium, more commonly referred to as colistin, is a naturally occurring polymyxin antibacterial agent that has been in clinical use for more than 50 years. However, due to its limited spectrum of activity (aerobic Gram negative species), need for parenteral administration, limited distribution in the body compartments and adverse event profile (narrow therapeutic window), it has never been widely used for the systemic therapy of bacterial infections. It is usually reserved for patients who cannot receive other parenteral antibacterial agents that might be suitable for the infection to be treated. For example, patients hypersensitive to numerous other agents and those infected with organisms that are resistant to alternatives.

Since the 1980s, although explored as far back as the 1960s, nebulised colistin has become established as a treatment for patients with cystic fibrosis who are colonised with Pseudomonas aeruginosa.

Polymyxins are cyclic cationic peptides that appear to have surface detergent properties that destroy the cytoplasmic membrane of bacteria by altering their osmotic properties. This increase in permeability of the cellular membrane causes the death of the cell. If the bacteria become resistant to the polymyxins through mutation or adaptation mechanisms, the drug cannot penetrate the external membrane of the bacteria to reach the cytoplasmic membrane. They mainly act on the bacterial wall of the Gram-negative micro-organisms. At low concentrations, the polymyxins are bacteriostatic, and bactericidal at high concentrations.

Colistin is closely related to polymyxin B. Colistin’s antimicrobial action spectrum and mode of action are similar to that of polymyxin B, the sulphate is slightly less active and colistimethate even less active. The MICs for more sensitive species are between 0.01 and 4 μg/ml. Both colistin and polymyxin B are active against the majority of Escherichia coli and P. aeruginosa strains, but all Enterobacter, Salmonella, Shigella, Pasteurella, Brucella and Bordetella. Proteus, Serratia, Providencia and Edwardsiella strains are resistant at
concentrations >200 μg/ml. Anaerobes, members of the *Neisseria* genus and all the Gram-positive aerobes are resistant. Polymyxins are not clinically effective against Gram-positive micro-organisms or fungi.

In terms of secondary pharmacodynamics, colistin has long been known to exert an effect on nerve conduction that appears to be related to an ability to inhibit acetylcholine release at somatic nerve endings in skeletal muscle. Weakness and paralysis can result if plasma concentrations are allowed to increase unnecessarily and/or if colistin is co-administered with other drugs (e.g. curariform agents) that have this effect. An exacerbation of myasthenia gravis is also possible. However, colistin’s effect on sensory nerves and its ability to trigger vertigo and ataxia seem to be mediated by a different mechanism that has not been elucidated.

The mechanism of action of colistin on renal function is not well understood although some studies have shown a decrease in creatinine and urea clearance during therapy.

**INDICATIONS**

Colistimethate sodium is indicated in the treatment of the following infections caused by susceptible aerobic Gram-negative bacteria (see SmPC section 5.1):

- Hospital acquired pneumonia (HAP)
- Complicated urinary tract infections

It is recommended that colistimethate sodium should be selected when antibacterial agents that are commonly used to treat these infections are not considered to be appropriate for the individual patient and/or the causative pathogen(s) (see SmPC sections 4.4 and 5.1). Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The indications are satisfactory.

**POSOLOGY AND METHOD OF ADMINISTRATION**

Full details concerning the posology are provided in the SmPC. The posology is satisfactory.

**CLINICAL PHARMACOLOGY**

The clinical pharmacology of colistimethate sodium is well-known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for these applications.

Following administration, colistimethate sodium is hydrolysed to the active moiety polymyxin E1 and polymyxin E2 (colistin). It has been estimated that approximately 30% of the colistimethate sodium is converted to colistin (Couet *et al*., 2011). The half-life of colistin is longer than the half-life of colistimethate sodium (Plachouras 2009).

The volume of distribution of colistimethate sodium has been shown to be increased in critically ill patients possibly due to fluid retention and the presence of α1-acid glycoprotein, an acute-phase reactant that is generally elevated in critically ill patients to which colistimethate sodium binds (Markou *et al*., 2008; Varghese *et al*., 2010). In such circumstances, doses up to 6 million IU may not be adequate to achieve therapeutic concentrations in an appropriate time period and a higher dose may be required.
Colistimethate sodium is excreted unchanged in the urine where the hydrolysis to the active moiety continues (Couet et al, 2011). Colistin is excreted by the non-renal route (Markou et al, 2008). Excretion is dependent on the patient’s ideal body weight and creatinine clearance (Garonzik 2011).

**Clinical efficacy**

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. The efficacy of colistimethate sodium is well-established from its extensive use in clinical practice.

Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion is to be administered as an intravenous solution and contains the same active substance, in the same concentration, as the reference product, Colomycin Injection 1 million International Units powder for solution for injection, infusion or inhalation (Forest Laboratories UK Limited). Thus, in accordance with the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98), Section 5.1.6 Parenteral solutions, the applicant is not required to submit a bioequivalence study.

**Clinical safety**

No new safety data have been submitted and none are required for this type of application. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of colistimethate sodium is well-known.

**CLINICAL OVERVIEW**

A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

**PRODUCT INFORMATION:**

**Summary of Product Characteristics (SmPC)**

The approved SmPC is acceptable.

**Product Information Leaflet (PIL)**

The final PIL text is in line with the approved SmPC and is satisfactory.

**Labelling**

The labelling text is satisfactory.

**CONCLUSIONS**

Sufficient clinical information has been submitted to support this application. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was, therefore, recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview.

The applicant’s Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion has been demonstrated to be a generic version of the UK reference product, Colomycin Injection 1 million International Units powder for solution for injection, infusion or inhalation (Forest Laboratories UK Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC is consistent with that for the UK reference product and is satisfactory.

The PIL text is in line with the SmPC and is satisfactory. User-testing of the PIL text has been accepted based on bridging to the successful user-testing of the ‘parent’ PIL for Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection (PL 18157/0009). The results show that the 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.

The approved labelling text complies with statutory requirements.

The MAH has submitted text versions only for the PIL and labelling and has committed to submitting mock-up livery to the relevant regulatory authorities, as appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Colistimethate Sodium 1 Million International Units (I.U.) Powder for solution for injection or infusion and the UK reference product, Colomycin Injection 1 million International Units powder for solution for injection, infusion or inhalation (Forest Laboratories UK Limited), are interchangeable. Extensive clinical experience with colistimethate sodium is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.
### Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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