Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection

PL 18157/0009

UKPAR

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Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection

PL 18157/0009

LAY SUMMARY

On 28th September 2009, the MHRA granted Beacon Pharmaceuticals Limited a Marketing Authorisation (licence) for Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection (PL 18157/0009).

This medicine contains the active ingredient colistimethate sodium. Colistimethate is an antibiotic. It belongs to a group of antibiotics called polymyxins. Like all antibiotics, Colistimethate is only active against some bacteria, so it is only suitable for treating some types of infection.

Colistimethate is given by injection to treat the following infections:

• Some serious infections where other antibiotics are not suitable. These infections include some types of pneumonia and some bladder or kidney infections.

• Certain chest infections in patients with cystic fibrosis.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection outweigh the risks; hence Marketing Authorisations have been granted.
Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection (PL 18157/0009) to Beacon Pharmaceuticals Limited on 28th September 2009. This product is a prescription only medicine used in adults to treatment of the following infections where sensitivity testing suggests that they are caused by susceptible bacteria:

- Intravenous administration for the treatment of some serious infections caused by Gram negative bacteria, including those of the lower respiratory tract and urinary tract, when more commonly used systemic antibacterial agents may be contra-indicated or may be ineffective because of bacterial resistance.

This application for Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection is submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Colomycin Injection 1,000,000 Units first authorised to Forest Laboratories UK Limited in June 1986.

The product contains the active substance colistimethate sodium, a derivative of colistin, a cationic cyclic polypeptide belonging to the polymyxin group of antibiotics produced by certain strains of *Bacillus polymyxa* var *colistinus*. It has been in clinical use for over 40 years and is classified as an antibacterial for systemic use.

Colistin has been used in the treatment of severe Gram-negative infections, especially those due to *Pseudomonas aeruginosa*. Colistin is given parenterally, as colistimethate sodium, by slow intravenous injection or infusion. The usual doses are 1 to 2 million units three times daily for adults weighing more than 60 kg; children weighing up to 60 kg may be given 50,000 units/kg daily in three divided doses. Doses and dosage intervals should be adjusted in patients with renal impairment. Colistimethate sodium may be given by inhalation in respiratory infections as an adjunct to systemic antibacterial therapy. Children under 2 years are given 0.5 to 1 million units twice daily by inhalation and adults and children over 2 years are given 1 to 2 million units twice daily, up to a maximum of 2 million units three times daily for frequent recurrent infections.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Colistimethate sodium

INN/Ph.Eur name: Colistimethate sodium
Chemical name: pentasodium [[4-[[3-hydroxy-1-[[1-[[3-(1-hydroxyethyl)-12,15-bis(2-methylpropyl)-2,5,8,11,14,17,20-heptaoxo-6,9,18-tris[2-(sulfonatomethylamino)ethyl]-1,4,7,10,13,16,19-heptazacyclotricos-21-yl]amino]-1-oxo-4-(sulfonatomethylamino)butan-2-yl]amino]-1-oxobutan-2-yl]amino]-3-(6-methyloctanoylamino)-4-oxobutyl]amino]methanesulfonate

Structural formula:

```
R-C-L-Dbu-L-Thi-L-Dbu-L-Dbu-L-Dbu-D-Leu-L-Leu - L-Dbu - L-Dbu - L-Dbu - L-Thi

N^N

\text{Dbu is 2,4-diaminobutanoic acid; R is 5-methylheptyl in colistin A and 5-methylhexyl in colistin B}
```

Molecular formula: $C_{58}H_{105}N_{16}Na_5O_{28}S_5$

Appearance: Dry, white to slightly yellow powder.

Solubility: Has an appreciable solubility in water.

Molecular weight: 1749.8190

An appropriate specification based on the European Pharmacopoeia has been provided.

All aspects of the manufacture of the active substance colistimethate sodium from its starting materials are controlled by a Certificate of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substance colistimethate sodium.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.
Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

**DRUG PRODUCT**

**Other ingredients**
None.

**Product development**
The objective of the development programme was to produce a product that could be considered a generic medicinal product of Colomycin Injection 1,000,000 Units (Forest Laboratories UK Limited, June 1986).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished product versus the reference product Colomycin Injection 1,000,000 Units (Forest Laboratories UK Limited).

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

In-process controls are satisfactory based on process validation data and controls on the finished product. The applicant has committed to perform process validation on future commercial-scale batches.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis for all working standards used have been provided and are satisfactory.

**Container-Closure System**
The product is packaged in a Type III glass 10ml vial closed with a rubber stopper and an aluminium cap.
The product is packaged in cartons of 1 or 10 vials.

Specifications and Certificates of Analysis for the packaging types used have been provided. All primary product packaging complies with the European Pharmacopoeia and relevant regulations regarding use of materials in contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set. For the reconstituted product, it is recommended that it should be used immediately. If not used immediately, then it has a shelf-life of 24 hours in a refrigerator (2 to 8°C), or 8 hours when stored at temperatures not exceeding 25°C. This is satisfactory.

General storage conditions are ‘Do not store above 25°C’, ‘Store the vial in the outer carton in order to protect from light’ and ‘Do not freeze’.
ADMINISTRATIVE

Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)
This is pharmaceutically satisfactory.

Labelling
These are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
This is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet 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 it contains.

MAA Form
This is pharmaceutically satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
PRECLINICAL ASSESSMENT

This application for Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Colomycin Injection 1,000,000 Units first authorised to Forest Laboratories UK Limited in June 1986.

No new preclinical data have been supplied with this application and none are required for applications of this type.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
No bioequivalence studies have been performed and none are required for this application, as the product is administered as a parenteral aqueous solution, distributed rapidly \textit{in vivo}.

EFFICACY
No new data has been provided.

SAFETY
No new data has been provided.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORM (MAA)
This is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
This is consistent with that for the reference product and is satisfactory.

DISCUSSION
A bioequivalence study with the reference product is not required for this product and can be justified as a generic medicinal product considering the quantitative and qualitative composition of the product and the route of administration.

MEDICAL CONCLUSION
The grant of a marketing authorisation is recommended for this application.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection 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.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
Colistimethate sodium is a well-known drug and has been used for many years. Bioequivalence has been demonstrated between the applicant’s Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection and the reference product Colomycin Injection 1,000,000 Units (Forest Laboratories UK Limited).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product Colomycin Injection 1,000,000 Units.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data submitted supports the claim that the applicant’s product and the reference product are interchangeable. Extensive clinical experience with colistimethate sodium is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
**Colistimathate Sodium 1 Million I.U. Powder for Solution for Injection**

**PL 18157/0009**

**STEPS TAKEN FOR ASSESSMENT**

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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 24th June 2003.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant, the MHRA considered the application valid on 18th August 2005.</td>
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<tr>
<td>3</td>
<td>Following assessment of the application, the MHRA requested further information relating to the clinical dossier on 25th July 2006. The MHRA requested further information relating to the quality dossier on 15th June 2006.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 2nd August 2007 for the clinical section. Further information was provided by the applicant on 23rd June 2006 for the quality section.</td>
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<tr>
<td>5</td>
<td>The application was determined on 28th September 2009.</td>
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Colistimathate Sodium 1 Million I.U. Powder for Solution for Injection

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**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Colistimethate Sodium 1 Million I.U. (International Units)

3 PHARMACEUTICAL FORM
Powder for Solution for Injection
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 where sensitivity testing suggests that they are caused by susceptible bacteria:

- Intravenous administration for the treatment of some serious infections caused by Gram-negative bacteria, including those of the lower respiratory tract and urinary tract, when more commonly used systemic antibacterial agents may be contra-indicated or may be ineffective because of bacterial resistance.

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

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology
The dosage is determined by the severity and type of infection, the sensitivity of the causative bacteria and the age, weight and renal function of the patient. General guidance is given below. Should clinical or bacteriological response be slow, the dose may be increased as indicated by the patient's condition. Anomalous distribution in CF patients may require higher doses in order to maintain therapeutic serum levels.

Estimation of serum levels is particularly recommended for patients with renal impairment, neonates and patients with cystic fibrosis. Serum levels of 10 - 15 mg/l (approximately 125-200 units/ml) should be adequate for most infections.

A minimum of 5 days treatment is generally recommended.

Adults (including the elderly)(Over 60kg): 1-2 million units three times a day. The maximum dose is 6 million units in 24 hours.

Children (up to 60kg): 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.

Renal Impairment: In moderate or severe renal impairment, excretion of Colistimethate is delayed. Therefore, the dose and the dose interval should be adjusted in order to prevent accumulation. The table below is a guide to dose regimen modifications. It is stressed that adjustments may still have to be made on evaluation of the individual patient.

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Adult Dose</th>
<th>Child Dose</th>
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<tbody>
<tr>
<td>20-50</td>
<td>1-2 million units every 8hr</td>
<td>12,500-16,000 units/kg every 8 hr</td>
</tr>
<tr>
<td>10-20</td>
<td>1 million units every 12-18 hr</td>
<td>12,500 units/kg every 12-18hr</td>
</tr>
<tr>
<td>&lt;10</td>
<td>1 million units every 18-24 hr</td>
<td>8,000 units/kg every</td>
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Method of Administration
Colistimethate Sodium can be given as a 50ml intravenous infusion over a period of 30 minutes. Patients with a totally implantable venous access device (TIVAD) in place may tolerate a bolus injection of up to 2 million units 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 polymyxin B.
Myasthenia gravis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Use with extreme caution in patients with porphyria.

Nephrotoxicity or neurotoxicity may occur if the recommended parenteral dose is exceeded.
Use with caution in renal impairment (see Section 4.2 - Posology and method of administration). It is advisable to assess baseline renal function and to monitor during treatment. Serum colistimethate concentrations should be monitored.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Curariform muscle relaxants should be used with extreme caution in patients receiving colistimethate sodium.
Concomitant use of colistimethate sodium with other medicinal products of neurotoxic and/or nephrotoxic potential should be avoided. These include the aminoglycoside antibiotics such as gentamicin, amikacin, netilmicin and tobramycin. There may be an increased risk of nephrotoxicity if given concomitantly with cephalosporin antibiotics.

4.6 PREGNANCY AND LACTATION
There are no adequate data from the use of Colistimethate sodium in pregnant women. Animal studies in rats and mice do not indicate teratogenic properties. 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.

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

Colistimethate is secreted in breast milk, and should be administered to breastfeeding women only when clearly needed.

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 likelihood of adverse events may be related to the age, renal function and condition of the patient.

In cystic fibrosis patients neurological events have been reported in up to 27% of patients. These are generally mild and resolve during or shortly after treatment.

Adverse effects on renal function have been reported, usually following use of higher than recommended doses in patients with normal renal function, or failure to reduce the dose in patients with renal impairment or during concomitant use of other nephrotoxic antibiotics. The effects are usually reversible on discontinuation of therapy.
In cystic fibrosis patients treated within the recommended dosage limits, nephrotoxicity appears to be rare (less than 1%). In seriously ill hospitalised non-CF patients, signs of nephrotoxicity have been reported in approximately 20% of patients.

Neurotoxicity has been reported often in association with overdose, failure to reduce dose in patients with renal insufficiency and concomitant use of either curariform agents or drugs with similar neurological effects. Reducing the dose may alleviate symptoms. Effects may include apnoea, transient sensory disturbances (such as facial paraesthesia and vertigo) and, rarely, vasomotor instability, slurred speech, visual disturbances, confusion or psychosis.

Hypersensitivity reactions including skin rash have been reported. If these occur treatment should be withdrawn. Local irritation at the site of injection may occur.

4.9 OVERDOSE
Overdose can result in neuromuscular blockade that can lead to muscular weakness, apnoea and possible respiratory arrest. Overdose can also cause acute renal failure characterised by decreased urine output and increased serum concentrations of BUN and creatinine. There is no specific antidote. Manage by supportive treatment and measures to increase the rate of elimination of colistimethate e.g. mannitol diuresis, prolonged haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Antibacterials for systemic use.
ATC Code: JOIX B01.

Mode of Action
Colistimethate (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 agents that work by damaging the cell membrane. The resulting physiological affects are lethal to the bacterium. Polymyxins are selective for Gram negative bacteria that have a hydrophobic outer membrane.

Resistance
Resistant bacteria are characterised by modification of the phosphate groups of lipopolysaccharides due to substitution with ethanolamine or aminoorabinose. Naturally resistant Gram-negative bacteria, such as *Proteus mrrabilis* and *Burkholderia cepacia*, show complete substitution of their lipid phosphate by ethanolamine or aminoorabinose.

Cross-resistance between Colistimethate and polymyxin B would be expected. Since the mechanism of action of the polymyxins is different from that of other antibiotics, resistance to colistimethate and polymyxin by the above mechanism alone would not be expected to result in resistance to other drug classes.

Breakpoints
The BSAC-recommended general MIC breakpoint to identify bacteria susceptible to Colistimethate is $\leq$ 4 mg/l. Bacteria for which the MIC of Colistimethate is $\geq$ 8 mg/l should be considered resistant.

Susceptibility
The prevalence of 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*
*Citrobacter* species
*Escherichia coli
*Haemophilus influenzae*
Species for which acquired resistance may be a problem

- *Pseudomonas aeruginosa*
- *Enterobacter* species
- *Klebsiella* species

Inherently resistant organisms

- *Brucella* species
- *Burkholderia cepacia* and related species.
- *Neisseria* species
- *Proteus* species
- *Providencia* species
- *Serratia* species

Anaerobes

All Gram positive organisms

*Note that the in-vitro demonstration of susceptibility may not reliably predict clinical efficacy for Acinetobacter species.*

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 Cmax was determined to be 23 (±6) mg/l and Cmin 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 Cmax was 12.9 mg/l (5.7 – 29.6 mg/l) and the Cmin 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 18mg/l were observed 10 minutes after injection.

Protein binding is low. Polymyxins persist in the liver, kidney, brain, heart and muscle. One study in CF patients estimated the steady-state volume of distribution as 0.09 l/Kg.

Biotransformation

Colistimethate sodium is converted to the base *in-vivo*. As 80% of the dose can be recovered unchanged in the urine, and there is no biliary excretion, it can be assumed that the remaining drug is inactivated in the tissues. The mechanism is unknown.

Elimination

The main route of elimination after parenteral administration is by renal excretion with 40% of a parenteral dose recovered in the urine within 8 hours and around 80% in 24 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.

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

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 and serum levels monitored.
5.3 PRECLINICAL SAFETY DATA

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

None

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, reconstituted Colistimethate sodium must not be mixed with other medicinal products.

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) or 8 hours when stored at temperatures not exceeding 25°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 Colistimethate sodium solution may be kept for up to 8 hours when not stored above 25°C or 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 Colistimethate sodium 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

Beacon Pharmaceuticals Ltd.
Tunbridge Wells
Kent TN1 1YG

8 MARKETING AUTHORISATION NUMBER(S)

PL 18157/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/09/2009

10 DATE OF REVISION OF THE TEXT

28/09/2009
The name of your medicine is Colistimethate sodium 1 Million I.U. Powder for Solution for Injection. It is referred to as Colistimethate in this leaflet.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, nurse or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell the doctor, nurse or pharmacist.

In this leaflet:
1. What Colistimethate is and what it is used for
2. Before you are given Colistimethate
3. How Colistimethate is given
4. Possible side-effects
5. Storing Colistimethate
6. Further information

1. WHAT COLISTIMETHATE IS AND WHAT IT IS USED FOR

Colistimethate is an antibiotic. It belongs to a group of antibiotics called polymyxins. Like all antibiotics, Colistimethate is only active against some bacteria, so it is only suitable for treating some types of infection. Colistimethate 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.
- Certain chest infections in patients with cystic fibrosis.

2. BEFORE YOU ARE GIVEN COLISTIMETHATE

Colistimethate is not suitable for everyone. Some people must not have this injection. Do not have the injection if:
- you are allergic to Colistimethate (also known as colistin) or to another antibiotic called polymyxin B
- you have a condition called myasthenia gravis.
If you are unsure about anything, ask your doctor before you have the injection.

Your doctor must be especially careful if:
- You have porphyria
- You have kidney problems
- You are pregnant or breastfeeding.
If you are unsure about anything speak to your doctor.

Taking other medicines
You must tell your doctor if you are taking any of the following medicines:
- Other antibiotics called aminoglycosides (such as gentamicin, tobramycin or kanamycin).
  Having Colistimethate 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 called curare-like drugs that are often used during general anaesthesia. Colistimethate 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.

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

Each vial of Colistimethate contains about 5mg of sodium. This means that you could receive up to 30mg sodium each day if you are having the maximum adult dose. Please take this into account if you are on a low sodium (salt) diet and let your doctor or pharmacist know about this.

Pregnancy and breastfeeding
- Colistimethate 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 enter the milk. If you cannot stop breastfeeding while you have the injections, you should watch your baby carefully for any signs of illness and tell your doctor if you notice anything wrong.

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

3. HOW COLISTIMETHATE IS GIVEN

The Colistimethate 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 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.

Sometimes, particularly in people with kidney problems, people with cystic fibrosis or in newborn babies, the doctor may measure the level of Colistimethate in the blood and adjust the dose accordingly.

The usual dose for adults is between 1 and 2 million units three times a day. The maximum dose is 6 million units in 24 hours.

The usual daily dose for children weighing up to 60 kg is 50,000 to 75,000 units/kg.

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

If you are being treated in hospital or at home by a doctor or nurse and think that you may have missed a dose or been given too much Colistimethate, please speak to your doctor or nurse. Too much Colistimethate can cause serious side effects.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Colistimethate 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.

The following side effects have also been reported:

- Reactions, such as irritation, at the injection site.
- Kidney problems. These are more likely in patients who already have poor kidneys, or who are given Colistimethate at the same time as other medicines that can affect the kidneys, or who are given a dose that is too high. These problems will normally get better if treatment is stopped, or the dose of Colistimethate is reduced.
- Neurological problems such as inability to breathe because of paralysis of the chest muscles, numbness or tingling (especially around the face), dizziness or loss of balance, rapid changes in blood pressure or blood flow (including faintness and flushing), slurred speech, problems with vision, confusion and mental problems (including loss of sense of reality). Side effects that affect the nervous system are more likely to occur when the dose of Colistimethate is too high, in people who have poor kidneys or in those who are also having curanform drugs or other medicines with a similar effect on how the nerves work.

If any of these side effects become troublesome or persist, or if you notice any side effects not listed in this leaflet, you should tell your doctor as soon as possible.

5. STORING COLISTIMETHATE

Keep out of the reach and sight of children. The vials of powder must not be stored above 25°C. The vials must be protected from light by storing in the outer carton. The vials must not be used after the expiry date printed on the carton and vial label. Do not freeze.

The solution of Colistimethate should be used immediately, or within 8 hours when stored at temperatures not exceeding 25°C or 24 hours in the refrigerator (2 to 8°C). The vials are for single use. Any unused solution should be discarded. Colistimethate should not be used if there is any discoloration or cloudiness of the solution.

6. FURTHER INFORMATION

Colistimethate is a creamy white powder for solution for injection 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. There are no other ingredients. The sodium content is 0.228 mEq per vial.

Manufacturer
Alfred Wassermann S.p.A., Contrada S. Emidio, 05020 Alviano, Italy.

Marketing Authorisation Holder
Beacon Pharmaceuticals Ltd., Tunbridge Wells, Kent TN1 1YG

Date of approval of this leaflet: Mm/yyyy

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.
Information for the Healthcare Professional

COLISTIMETHATE SODIUM 1 MILLION I.U. POWDER FOR SOLUTION FOR INJECTION

Please read this information carefully before using Colistimethate Sodium. Further information is contained in the Summary of Product Characteristics.

PRESENTATION

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

DOSE 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.

CONTRAINDICATIONS

Do not use in patients with known hypersensitivity to Colistimethate Sodium or polymyxin B or in patients with myasthenia gravis.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

PHARMACEUTICAL INFORMATION

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

Dosage (adjustment required in renal impairment):
Adults over 60kg (including the elderly): 1 – 2 million units three times daily. Maximum 8 million units in 24 hours.
Children (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.

Stability in solution: Up to 24 hours in a refrigerator (2-8°C) or 8 hours below 25°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-stereile.

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) or up to 8 hours when stored at temperatures not exceeding 25°C.

Nature of Container
10ml Type III glass vials with rubber stoppers and aluminium crimp seals. Each carton contains 1 or 10 vials.
For intravenous use. Sterile and non-pyrogenic. Use only as directed by a medical practitioner. For further information see the enclosed leaflet. To be used immediately, or within 24 hours if stored in the refrigerator (2-8°C) or 8 hours at temperatures not exceeding 25°C. For single use only. Discard any unused solution. Do not use unless the container is undamaged. Store below 25°C. Store vial in outer carton to protect from light. Do not freeze. Keep out of reach and sight of children.

MA Holder: Beacon Pharmaceuticals Ltd. Tunbridge Wells TN1 1YG. UK. PL No. 18157/0009

Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection

Colistimethate 1 Million I.U. Powder for Solution for Injection

Each vial contains 1 Million I.U. Powder for Solution for Injection
See leaflet for details of reconstitution.

For intravenous use
PL 18157/0009
Beacon Pharmaceuticals Ltd.