IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0100/001/007
Case No: 2045705

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Forest Laboratories UK Ltd

Bourne Road, **Bexley**, **Kent DA5 1NX**, **England**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Colomycin Injection 500 000 International Units. Powder for solution for injection, infusion or inhalation.

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **24/02/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Colomycin Injection 500 000 International Units.
Powder for solution for injection, infusion or inhalation.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500,000 International Units Colistimethate Sodium.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection, infusion or inhalation.

Sterile white powder in a 10ml colourless glass vial with a blue 'flip-off' cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Colomycin is indicated in the treatment of the following infections where sensitivity testing suggests that they are caused by susceptible bacteria:

Treatment by inhalation of *Pseudomonas aeruginosa* lung infection in patients with cystic fibrosis (CF).

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.

4.2 Posology and method of administration

SYSTEMIC TREATMENT
Colomycin 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 *(see section 6.6, Special precautions for disposal of a used medicinal product or waste materials derived from such a product and other handling of the product)*.

The dose is determined by the severity and type of infection and the age, weight and renal function of the patient. Should clinical or bacteriological response be slow the dose may be increased as indicated by the patient's condition.

Serum level estimations are recommended especially in renal impairment, neonates and cystic fibrosis patients. Levels of 10–15 mg/l (approximately 125-200 units/ml) colistimethate sodium should be adequate for most infections.
A minimum of 5 days treatment is generally recommended. For the treatment of respiratory exacerbations in cystic fibrosis patients, treatment should be continued for up to 12 days.

Children and adults (including the elderly):

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.

Over 60kg: 1-2 million units three times a day. The maximum dose is 6 million units in 24 hours.

Anomalous distribution in patients with cystic fibrosis may require higher doses in order to maintain therapeutic serum levels.

Renal impairment: In moderate to severe renal impairment, excretion of colistimethate sodium is delayed. Therefore, the dose and dose interval should be adjusted in order to prevent accumulation. The table below is a guide to dose regimen modifications in patients of 60kg bodyweight or greater. It is emphasised that further adjustments may have to be made based on blood levels and evidence of toxicity.

SUGGESTED DOSAGE ADJUSTMENT IN RENAL IMPAIRMENT

Grade	Creatinine clearance (ml/min)	Over 60kg bodyweight
Mild	20-50	1-2 million units every 8hr
Moderate	10-20	1 million units every 12-18 hr
Severe	<10	1 million units every 18-24 hr

AEROSOL INHALATION
For local treatment of lower respiratory tract infections Colomycin powder is dissolved in 2-4 ml of water for injections or 0.9% sodium chloride intravenous infusion for use in a nebuliser attached to an air/oxygen supply *(see section 6.6, Special precautions for disposal of a used medicinal product or waste materials derived from such a product and other handling of the product).*

In small, uncontrolled clinical trials, doses of from 500,000 units twice daily up to 2 million units three times daily have been found to be safe and effective in patients with cystic fibrosis.

The following recommended doses are for guidance only and should be adjusted according to clinical response:
Children <2 years: 500,000-1 million units twice daily
Children >2 years and adults: 1-2 million units twice daily

4.3 Contraindications

Hypersensitivity to colistimethate sodium (colistin) or to polymyxin B.

Patients with 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 sodium concentrations should be monitored.
Bronchospasm may occur on inhalation of antibiotics. This may be prevented or treated with appropriate use of $beta_2$-agonists. If troublesome, treatment should be withdrawn.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Neuromuscular blocking drugs and ether should be used with extreme caution in patients receiving colistimethate sodium.

4.6 Pregnancy and lactation

There are no adequate data from the use of colistimethate sodium in pregnant women. Single dose studies in human pregnancy show that colistimethate sodium crosses the placental barrier and there may be a risk of foetal toxicity if repeated doses are given to pregnant patients. Animal studies are insufficient with respect to the effect of colistimethate sodium on reproduction and development *(see section 5.3, Preclinical safety data)*. Colistimethate sodium should be used in pregnancy only if the benefit to the mother outweighs the potential risk to the foetus.

Colistimethate sodium is secreted in breast milk. Colistimethate sodium 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

Systemic treatment

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.

Neurotoxicity may be associated with overdose, failure to reduce the dose in patients with renal insufficiency and concomitant use of either curariform agents or other 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.

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 dosage in patients with renal impairment or during concomitant use of other nephrotoxic drugs. 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.

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

Local irritation at the site of injection may occur.

Inhalation treatment

Inhalation may induce coughing or bronchospasm.

Sore throat or mouth has been reported and may be due to *Candida albicans* infection or hypersensitivity. Skin rash may also indicate hypersensitivity, if this occurs treatment should be withdrawn.

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. Measures to increase the rate of elimination of colistin e.g. mannitol diuresis, prolonged haemodialysis or peritoneal dialysis may be tried, but effectiveness is unknown.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use.
ATC Code: JOIX B01

Mode of action
Colistimethate sodium 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 lipopolysaccharide that become substituted with ethanolamine or aminoarabinose. Naturally resistant Gram-negative bacteria, such as *Proteus mirabilis* and *Burkholderia cepacia*, show complete substitution of their lipid phosphate by ethanolamine or aminoarabinose.

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

Breakpoints
The suggested general MIC breakpoint to identify bacteria susceptible to colistimethate sodium is $\leq$ 4mg/l.

Bacteria for which the MIC of colistimethate sodium is $\geq$ 8mg/l should be considered resistant.

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*
Citrobacter species
Escherichia coli
Haemophilus influenzae
Pseudomonas aeruginosa
Species for which acquired resistance may be a problem
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

**In-vitro* results may not correlate with clinical responses in the case of Acinetobacter spp.

5.2 Pharmacokinetic properties

Absorption

Absorption from the gastrointestinal tract does not occur to any appreciable extent in the normal individual.
When given by nebulisation, variable absorption has been reported that may depend on the aerosol particle size, nebuliser system and lung status. Studies in healthy volunteers and patients with various infections have reported serum levels from nil to potentially therapeutic concentrations of 4mg/l or more. Therefore, the possibility of systemic absorption should always be borne in mind when treating patients by inhalation.

Distribution

After the administration to patients with cystic fibrosis of 7.5 mg/kg/day in divided doses given as 30-min intravenous infusions to steady state the C max was determined to be 23±6 mg/l and C min at 8 h was 4.5±4 mg/l. In another study in similar patients given 2 million units every 8 hours for 12 days the C max was 12.9 mg/l (5.7 – 29.6 mg/l) and the C min was 2.76 mg/l (1.0 – 6.2 mg/l). In healthy volunteers given a bolus injection of 150mg (2 million units approx.) 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. One study in cystic fibrosis patients gives 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 sodium is largely excreted in the urine, dose reduction is required in renal impairment to prevent accumulation. Refer to the table in s*ection 4.2., Posology and administration.*

After intravenous administration to healthy adults the elimination half-life is around 1.5 hrs. In a study in cystic fibrosis patients given a single 30-minute intravenous infusion the elimination half-life was 3.4 ± 1.4 hrs.

The elimination of colistimethate sodium following inhalation has not been studied. A study in cystic fibrosis patients failed to detect any colistimethate sodium in the urine after 1 million units were inhaled twice daily for 3 months.

Colistimethate sodium kinetics appear to be similar in children and adults, including the elderly, provided renal function is normal. Limited data are available on use in neonates which suggest kinetics 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 resorption occurred at 9.3 mg/kg.

There are no other preclinical safety data of relevance to the prescriber which 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

Mixed infusions, injections and nebuliser solutions involving colistimethate sodium should be avoided.

6.3 Shelf Life

Before opening: 3 years

Reconstituted solutions:

Solutions for infusion or injection:
Chemical and physical in-use stability for 28 days at 4^{o}C has been demonstrated.

From a microbiological point of view, solutions should be used immediately. If not used immediately in-use storage times and conditions prior to use are the responsibility of the user. They would normally be no longer than 24 hours at 2 to 8°C, unless reconstituted and diluted under controlled and validated aseptic conditions.

Solutions for nebulisation:
Solutions for nebulisation have similar in-use stability and should be treated as above. Patients self-treating with nebulised antibiotic should be advised to use solutions immediately after preparation. If this is not possible, solutions should not be stored for longer than 24hrs in a refrigerator.

6.4 Special precautions for storage

Do not store above 25°C. Keep the vials in the outer carton.
For storage of solutions following reconstitution refer to *section 6.3., Self life*.

6.5 Nature and contents of container

Type I glass vials with a blue ‘flip-off’ cap supplied in cartons of ten vials.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Parenteral administration
The normal adult dose of 2 million units should be dissolved in 10-50ml of 0.9% sodium chloride intravenous infusion or water for injections to form a clear solution. The solution is for single use only and any remaining solution should be discarded.

Inhalation
The required amount of powder is dissolved preferably in 2-4ml 0.9% sodium chloride solution and poured into the nebuliser. Alternatively, water for injections may be used. The solution will be slightly hazy and may froth if shaken. Usually jet or ultrasonic nebulisers are preferred for antibiotic delivery. These should produce the majority of their output in the respirable particle diameter range of 0.5-5.0 microns when used with a suitable compressor. The instructions of the manufacturers should be followed for the operation and care of the nebuliser and compressor.

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

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

7 MARKETING AUTHORISATION HOLDER

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Bexley
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United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0100/001/007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 June 2005

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10 DATE OF REVISION OF THE TEXT

December 2008