**For the use of a Registered Medical Practitioners or a Hospital or a Laboratory only**

# CRITIMYCIN 2 MIU

(Colistimethate Sodium for Injection I.P. 2 Million IU)

## COMPOSITION

Each vial contains:
Colistimethate Sodium I.P. (Sterile)…..2,000,000 IU
(IU: International Units)
Excipients…….q.s.

## INDICATION

Treatment of Pseudomonas aeruginosa lung infection in patients with cystic fibrosis.

## POSOLOGY AND METHOD OF ADMINISTRATION

SYSTEMIC TREATMENT
The dose to be administered and the treatment duration should take into account the severity of the infection as well as the clinical response. Therapeutic guidelines should be adhered to. The dose is expressed in international units (IU) of colistimethate sodium (CMS). A conversion table from CMS in IU to mg of CMS as well as to mg of colistin base activity (CBA) is included at the end of this section.

Posology
The following dose recommendations are made based on limited population-pharmacokinetic data in critically ill patients:

*Adults and adolescents*
Maintenance dose 9 million IU/day in 2-3 divided doses
In patients who are critically ill, a loading dose of 9 MIU should be administered.
The most appropriate time interval to the first maintenance dose has not been established. Modelling suggests that loading and maintenance doses of up to 12 MIU may be required in patients with good renal function in some cases. Clinical experience with such doses is however extremely limited, and safety has not been established.
The loading dose applies to patients with normal and impaired renal functions including those on renal replacement therapy.

*Renal impairment*
Dose adjustments in renal impairment are necessary, but pharmacokinetic data available for patients with impaired renal function is very limited.

The following dose adjustments are suggested as guidance.

Dose reductions are recommended for patients with creatinine clearance < 50 ml/min:
Twice daily dosing is recommended.

| **Creatinine clearance (ml/min)** | **Daily dose** |
|---|---|
| < 50- 30 | 5.5- 7.5 MIU |
| <30- 10 | 4.5- 5.5 MIU |
| <10 | 3.5 MIU |

MIU = million IU

Haemodialysis and continuous haemo(dia)filtration
Colistin appears to be dialyzable through conventional haemodialysis and continuous venovenous haemo(dia)filtration (CVVHF, CVVHDF). There are extremely limited data from population PK studies from very small numbers of patients on renal replacement therapy. Firm dose recommendations cannot be made. The following regimes could be considered.

Haemodialysis
No-HD days: 2.25 MIU/day (2.2-2.3 MIU/day).
HD days: 3 MIU/day on haemodialysis days, to be given after the HD session. Twice daily dosing is recommended.

CVVHF/ CVVHDF
As in patients with normal renal function. Three times daily dosing is recommended.

*Hepatic impairment*
There are no data in patients with hepatic impairment. Caution is advised when administering colistimethate sodium in these patients.

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

*Paediatric population*
The data supporting the dose regimen in paediatric patients are very limited. Renal maturity should be taken into consideration when selecting the dose. The dose should be based on lean body weight.

Children ≤ 40kg
75,000-150,000 IU/kg/day divided into 3 doses.
For children with a body weight above 40 kg, use of the dosing recommendation for adults should be considered.

The use of doses >150,000 IU/kg/day has been reported in children with cystic fibrosis.

There are no data regarding the use or magnitude of a loading dose in critically ill children.

No dose recommendations have been established in children with impaired renal function.

*Intrathecal and intraventricular administration*
Based on limited data, the following dose is recommended in adults:
Intraventricular route
125,000 IU/day
Intrathecally administered doses should not exceed those recommended for intraventricular use.

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

Method of administration
Critimycin is administered intravenously as a slow infusion over 30 – 60 minutes. Patients with a totally implantable venous access device (TIVAD) in place may tolerate a bolus injection of up to 2 million units in 10ml given over a minimum of 5 minutes.

Colistimethate sodium undergoes hydrolysis to the active substance colistin in aqueous solution. For dose preparation, particularly where combination of multiple vials is needed, reconstitution of the required dose must be performed using strict aseptic technique.

If any particle is visible in the vial after reconstitution of content, please do not use the solution.

The reconstituted solution should be used immediately or used within 24 hours when stored at 2°C to 8°C.

**Dose conversion table:**
In the EU, the dose of colistimethate sodium (CMS) must be prescribed and administered only as International Units (IU). The product label states the number of IU per vial.

Confusion and medication errors have occurred because of the different expressions of dose in terms of potency. The dose is expressed in the US, and other parts of the world, as milligrams of colistin base activity (mg CBA).

The following conversion table is prepared for information and the values must be considered nominal and approximate only.

**CMS conversion table**

| Potency | | ≈ mass of CMS (mg) * |
|---|---|---|
| **IU** | **≈ mg CBA** | |
| 12 500 | 0.4 | 1 |
| 150 000 | 5 | 12 |
| 1 000 000 | 34 | 80 |
| 4 500 000 | 150 | 360 |
| 9 000 000 | 300 | 720 |

* Nominal potency of the drug substance = 12,500 IU/mg

## CONTRAINDICATIONS

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

## SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Consideration should be given to co-administering intravenous colistimethate sodium with another antibacterial agent whenever this is possible, taking into account the remaining susceptibilities of the pathogen(s) under treatment. As the development of resistance to intravenous colistin has been reported in particular when it is used as a monotherapy, co-administration with other antibacterial should also be considered in order to prevent the emergence of resistance.

There are limited clinical data on the efficacy and safety of intravenous colistimethate sodium. The recommended doses in all subpopulations are equally based on limited data (clinical and pharmacokinetic/ pharmacodynamics data). In particular there are limited safety data for the use of high doses (> 6MIU/day) and the use of a loading dose, and for special populations (patients with renal impairment and the paediatric population). Colistimethate sodium should only be used when other, more commonly prescribed antibiotics are not effective or not appropriate.

Renal function monitoring should be performed at the start of treatment and regularly during treatment in all patients. The dose of colistimethate sodium should be adjusted according to creatinine clearance. Patients who are hypovolaemic or those receiving other potentially nephrotoxic drugs are at increased risk of nephrotoxicity from colistin. Nephrotoxicity has been reported to be associated with cumulative dose and treatment duration in some studies. The benefit of prolonged treatment duration should be balanced against the potentially increased risk of renal toxicity.

Caution is advised when administering colistimethate sodium to infants < 1 year of age as renal function is not fully mature in this age group. Further, the effect of immature renal and metabolic function on the conversion of colistimethate sodium to colistin is not known.

In case of an allergic reaction, treatment with colistimethate sodium must be discontinued and appropriate measures implemented.

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. Monitoring should be performed for perioral paraesthesia and paraesthesia in the extremities, which are signs of overdose.

Colistimethate sodium is known to reduce the presynaptic release of acetyl-choline at the neuro-muscular junction and should be used in patients with myasthenia gravis with the greatest caution and only if clearly needed.

Respiratory arrest has been reported following intramuscular administration of colistimethate sodium. Impaired renal function increases the possibility of apnoea and neuromuscular blockade following administration of colistimethate sodium.

Colistimethate sodium should be used with extreme caution in patients with porphyria.

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti-bacterial agents and may occur with colistimethate sodium. They may range from mild to life-threatening in severity. It is important to consider this diagnosis in patients who develop diarrhoea during or after the use of colistimethate sodium. Discontinuation of therapy and the administration of specific treatment for Clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

Intravenous colistimethate sodium does not cross the blood brain barrier to a clinically relevant extent. The use of intrathecal or intraventricular administration of colistimethate sodium in the treatment of meningitis was not systematically investigated in clinical trials and is supported by case reports only. Data supporting the posology are very limited. The most commonly observed adverse effect of CMS administration was aseptic meningitis.
Bronchospasm may occur on inhalation of antibiotics. This may be prevented or treated with appropriate use of beta2-agonists. If troublesome, treatment should be withdrawn.

**DRUG-INTERACTION**

Concomitant use of intravenous colistimethate sodium with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with great caution.

Caution should be taken with concomitant use with other formulations of colistimethate sodium as there is little experience and there is a possibility of summative toxicity.

No in vivo interaction studies have been performed. The mechanism of conversion of colistimethate sodium to the active substance, colistin, is not characterised. The mechanism of colistin clearance, including renal handling, is equally unknown. Colistimethate sodium or colistin did not induce the activity of any P 450 (CYP) enzyme tested (CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4/5) in in vitro studies in human hepatocytes.

The potential for drug-drug interactions should be borne in mind when Colomycin is coadministered with drugs known to inhibit or induce drug metabolising enzymes or drugs known to be substrates for renal carrier mechanisms.

Due to the effects of colistin on the release of acetylcholine, non-depolarising muscle relaxants should be used with caution in patients receiving colistimethate sodium as their effects could be prolonged.

Co-treatment with colistimethate sodium and macrolides such as azithromycin and clarithromycin, or fluoroquinolones such as norfloxacin and ciprofloxacin should be undertaken with caution in patients with myasthenia gravis.

Concomitant use of other medicinal products with neurotoxic and/ or neurotoxic potential with Colistimethate sodium should be avoided. Included are the aminoglycoside antibiotics such as amikacin, gentamycin, netilimicin and tobramycin. Concomitant use with cephalosporin antibiotics may increase risk of nephrotoxicity.

## FERTILITY, PREGNANCY AND LACTATION

There are no adequate data from the use of colistimethate sodium in pregnant women. Single dose studies in human pregnancy showed that colistimethate sodium crosses the placental barrier and there may be a risk of fetal 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. Colistimethate sodium should not be used in pregnancy unless the benefit to the mother outweighs the potential risk to the fetus.
Colistimethate sodium is secreted in breast milk. Colistimethate sodium should be administered to breastfeeding women only when clearly needed.

## 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.

## 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 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.

Neurotoxicity has been reported often in association with overdose, failure to reduce dose in patients with renal insufficiency and concomitant use of either neuromuscular blocking drugs 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.

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.

## 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.

## PHARMACOLOGICAL PROPERTIES

### Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, other antibacterials, polymyxins
ATC code: J01X B01

Mechanism of action

Colistin is a cyclic polypeptide antibacterial agent belonging to the polymyxin group. Polymyxins work by damaging the cell membrane and the resulting physiological effects are lethal to the bacterium. Polymyxins are selective for aerobic Gram-negative bacteria that have a hydrophobic outer membrane.

Resistance

Resistant bacteria are characterised by modification of the phosphate groups of lipopolysaccharide, which 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 between colistin (polymyxin E) and polymyxin B is expected. Since the mechanism of action of the polymyxins is different from that of other antibacterial agents, resistance to colistin and polymyxin by the above mechanism alone would not be expected to result in resistance to other drug classes.

PK/PD relationship

Polymyxins have been reported to have a concentration-dependent bactericidal effect on susceptible bacteria. fAUC/ MIC is considered to be correlated with clinical efficacy.

| **EUCAST Breakpoints** | Susceptible (S) | Resistant (R) [a] |
|---|---|---|
| *Acinetobacter* | S≤2 | R>2 mg/L |
| *Enterobacteriaceae* | S≤2 | R>2 mg/L |
| *Pseudomonas* spp | S≤4 | R>4 mg/L |

[a] *Breakpoints apply to dosage of 2-3 MIU x 3. A loading dose (9 MIU) 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 baumannii*<br>*Haemophilus influenza*<br>*Klebsiella spp*<br>*Pseudomonas aeruginosa* |
| **Species for which acquired resistance may be a problem** |
| *Stenotrophomonas maltophilia*<br>*Achromobacter xylosoxidans (formerly Alcaligenes xylosoxidans)* |
| **Inherently resistant organisms** |
| *Burkholderia cepacia* and related species.<br>*Proteus* species<br>*Providencia* species<br>*Serratia* species |

**Pharmacokinetic properties**

Absorption

The information on the pharmacokinetics of colistimethate sodium (CMS) and colistin is limited. There are indications that pharmacokinetics in critically ill patients differ from those in patients with less severe physiological derangement and from those in healthy volunteers. The following data are based on studies using HPLC to determine CMS/colistin plasma concentrations.

After infusion of colistimethate sodium the inactive pro-drug is converted to the active colistin. Peak plasma concentrations of colistin have been shown to occur with a delay of up to 7 hours after administration of colistimethate sodium in critically ill patients. 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

The volume of distribution of colistin in healthy subjects is low and corresponds approximately to extracellular fluid (ECF). The volume of distribution is relevantly enlarged in critically ill subjects. Protein binding is moderate and decreases at higher concentrations. In the absence of meningeal inflammation, penetration into the cerebrospinal fluid (CSF) is minimal, but increases in the presence of meningeal inflammation.
Both CMS and colistin display linear PK in the clinically relevant dose range.

Elimination

It is estimated that approximately 30% of colistimethate sodium is converted to colistin in healthy subjects, its clearance is dependent on creatinine clearance and as renal function decreases, a greater portion of CMS is converted to colistin. In patients with very poor renal function (creatinine clearance <30 ml/min), the extent of conversion could be as high as 60 to

70%. CMS is eliminated predominantly by the kidneys via glomerular filtration. In healthy subjects, 60% to 70% of CMS is excreted unchanged in the urine within 24 hours.

The elimination of the active colistin is incompletely characterised. Colistin undergoes extensive renal tubular reabsorption and may either be cleared non-renally or undergo renal metabolism with the potential for renal accumulation. Colistin clearance is decreased in renal impairment, possibly due to increased conversion of CMS.
Half-life of colistin in healthy subjects and those with cystic fibrosis is reported to be around 3h and 4h, respectively, with a total clearance of around 3L/h. In critically ill patients, halflife has been reported to be prolonged to around 9-18h.

**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 fetuses 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 PI.

**EXPIRY DATE**
Do not use later than date of expiry

**STORAGE**
Store below $25^0$C. Protect from light and moisture.
Keep medicine out of reach of children.

**PRESENTATION**
Critimycin 2 MIU is packed in a single dose vial and is placed in printed carton.

**MARKETED BY**
torrent PHARMA
TORRENT PHARMACEUTICALS LTD.
Indrad – 382721, Dist. Mehsana, INDIA.

**IN/CRITIMYCIN 2 MIU/AUG-19/02/PI**