1 NAME OF THE MEDICINAL PRODUCT

COLIRACIN

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
1,000,000 units (1 MIU) of colistimethate sodium (also known as colistin sulfomethate sodium).

3 PHARMACEUTICAL FORM

Powder for concentrate for infusion
IM, IV

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Antibiotic for treatment of infections caused by micro-organisms sensitive to colistin.

4.2 Posology and method of administration

Coliracin injection is usually administered IM or IV.
Coliracin must be reconstituted before use.

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

The recommended dosage in children and adults up to 60kg is 50,000 units/kg/day to maximum of 75,000 units/kg/day. The total daily dose should be divided into three doses given at approximately 8-hour intervals. Serum levels should be measured if used in the newborn.
The recommended dosage in patients over 60 kg: 1-2 million units three times a day. The maximum dose is 6 million units in 24 hours.
Dosage should be in line with relevant treatment guidelines. Limited pharmacokinetic data from critically ill patients suggest that use of a loading dose and higher than standard doses may be appropriate. For severe infections and in critically ill patients doses up to 9 million IU 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 .

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

IV Administration:
Each dose of Coliracin can be diluted in 50 ml and administered by intravenous infusion over a 30 minutes. Patients with a totally implantable venous access device (TIVAD) in

place may tolerate injection of up to 2 million units in 10 ml given over a minimum of 5 minutes.

Conversion table from CMS (colistimethate sodium) in IU (international units) to mg of CMS as well as to mg of colistin base activity (CBA):

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		

Impaired Renal Function
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 following dose adjustments are suggested:
Mild - Ccr between 20-50ml/min; BUN>60mg/100ml (>10nmol/l)
Adult dosage: 1-2 million units every 8 hours
Pediatric dosage: 12500-16000 units/kg every 8 hours
Moderate - Ccr between 10-20ml/min; BUN>100mg/100ml (>16.5nmol/l)
Adult dosage: 1 million units every 12-18 hours
Pediatric dosage: 12500 units/kg every 12-18 hours
Severe - Ccr less than 10ml/min; BUN>200mg/100ml (>33 nmol/l)
Adult dosage: 1 million units every 18-24 hours
Pediatric dosage: 8000 units/kg every 18-24 hours

It is important to stress that adjustments may still have to be made upon evaluation of the individual patient. Blood level determinations are recommended: 10-15mcg/ml should be adequate.

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

Older people
No dose adjustments in older patients with normal renal function are considered necessary.

4.3 Contraindications
Hypersensitivity to the active substance colistimethate sodium or other polymyxins.

4.4 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 (> 6 MIU/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 (see section 4.2). Patients who are hypovolaemic or those receiving other potentially nephrotoxic drugs are at increased risk of nephrotoxicity from colistin (see sections 4.5 and 4.8). 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 (see section 4.9).

Colistimethate sodium is known to reduce the presynaptic release of acetylcholine at the neuromuscular 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 (see section 4.8). 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.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of intravenous colistimethate sodium with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with the greatest 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 Coliracin is co-administered 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 (see section 4.4).
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 (see section 4.4).

4.6 Fertility, pregnancy and lactation

Fertility

There are no data on the effects of colistimethate sodium on human fertility. Effects on male and female fertility have not been evaluated in animal studies.

Pregnancy

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

Lactation

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

4.7 Effects on ability to drive and use machines

Neurotoxicity, characterised by dizziness, confusion or visual disturbances have been reported following parenteral administration of colistimethate sodium. If these effects occur patients should be warned against driving or operating machinery.

4.8 Undesirable effects

The 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 very common (≥1/10): common (≥1/100 to <1/10): uncommon (≥1/1,000 to <1/100): rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), not known (cannot be estimated from the available data).

Body System	**Frequency**	**Reported adverse reaction**
Immune system disorders	Not known	Hypersensitivity reactions such as skin rash and angioedema
Nervous system disorders	Very Common	Neurotoxicity such as, facial, mouth and peri-oral paraesthesia, headache, and muscle weakness
	Not known	Dizziness Ataxia
Skin and subcutaneous tissue disorders	Very Common	Pruritus
Renal and urinary disorders	Very Common	Renal impairment demonstrated by increased blood creatinine and / or urea and / or decreased creatinine renal clearance
	Rare	Renal failure

General disorders and administration site conditions	Not known	Injection site reaction

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

Overdosage may cause renal insufficiency, renal failure, apnoea, muscle weakness, vertigo, slurred speech, vasomotor instability, visual disturbances, confusion and psychosis.

No antidote is available.

Management of overdose is by means of supportive treatment and measures designed to increase clearance of colistimethate sodium such as inducing an osmotic diuresis with mannitol, peritoneal dialysis or prolonged haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, other antibacterials, polymyxins ATC code: J01XB01

General properties

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>2mg/L
Enterobacteriaceae	S≤2	R>2mg/L
Pseudomonas spp	S≤4	R>4mg/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
Haemophilus influenzae
Klebsiella spp
Pseudomonas aeruginosa

Species for which acquired resistance may be a problem

Stenotrophomonas maltophilia
Achromobacter xylosoxidans (formerly Alcaligenes xylosoxidans)

Inherently resistant organisms

Burkholderia cepacia and related species
Proteus spp
Providencia spp
Serratia spp

5.2 Pharmacokinetic properties

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.

Absorption

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

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.

Biotransformation

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.

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 nonrenally 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, half-life has been reported to be prolonged to around
9-18h.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
None

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

6.3 Shelf life
The expiry date of the unopened vials is indicated on the packaging materials.
See also sections 6.4, 6.6.

6.4 Special precautions for storage
Unopened vials of Coliracin are stable until the date indicated when stored below 25ºC, protected from light.
For storage conditions of the reconstituted/diluted product see section 6.6.

6.5 Nature and contents of container
A white powder dispensed in 10 ml colorless glass vials with rubber stopper.
Box of 50 vials.

6.6 Special precautions for disposal and other handling

For reconstitution Coliracin should be dissolved in aseptic conditions before use in 6-8 ml of 0.9% sodium chloride or water for injection to form a clear solution. Following reconstitution, the solution should be diluted to a suitable volume with 0.9% sodium chloride solution. The solution should be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear, colorless and free from particles. The solution is for single use and any remaining solution should be discarded.

Coliracin solution should preferably be freshly prepared and used immediately, but can be stored for no longer than 24h at 2-8 ºC. From a microbiological point of view solutions should be used immediately, unless reconstituted under controlled aseptic conditions.

7 REGISTRATION HOLDER

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