MONOGRAPH

# Colistimethate Sodium Monograph - Paediatric

| | |
|---|---|
| **Scope (Staff):** | Medical, Pharmacy, Nursing |
| **Scope (Area):** | All Clinical Areas |

**Child Safe Organisation Statement of Commitment**

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

**This document should be read in conjunction with this DISCLAIMER**

⚠ HIGH RISK MEDICINE ⚠

**QUICKLINKS**



## DRUG CLASS

Polymyxin antibacterial (also known as polymyxin E)[1-4]

Colistimethate sodium is a High Risk Medicine.

## INDICATIONS AND RESTRICTIONS

- Intravenous colistimethate sodium is used in the treatment of multi-drug resistant Gram-negative bacterial infections due to *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*.[3, 5, 6]
- Inhaled colistimethate sodium is used in the treatment of airway colonisation or infection due to resistant strains of *Pseudomonas aeruginosa* or in patients who do not respond to (or who don't tolerate) nebulised tobramycin.[1, 8]

**Nebulised: Monitored (orange) antibiotic**

- If the use is consistent with a standard approved indication, this must be communicated to ChAMP by documenting the specific indication on all prescriptions (inpatient and outpatient).
- The ChAMP team will review if ongoing therapy is required and/or if the order does not meet ChAMP Standard Indications

- If use is not for a standard approved indication, phone approval must be obtained from ChAMP before prescribing.

**IV: Restricted (red) antibiotic**

ChAMP approval is required prior to prescription.

## CONTRAINDICATIONS

- Hypersensitivity to colistimethate sodium, colistin, polymyxin E or any component of the formulation.[4, 6, 7, 9]

## PRECAUTIONS

**Intravenous colistimethate sodium should be prescribed as milligrams of colistin base whilst nebulised colistimethate sodium should prescribed as international units.**[3, 7]

Colistimethate sodium and colistin base are not interchangeable, care must be taken **not** to use these terms interchangeably.[6, 7] The following table may be a useful guide.

| International units of Colistimethate sodium | Colistin base[1, 4, 7] |
|---|---|
| 1 million international units | 33.33 mg |
| 2 million international units | 66.66 mg |

***Intravenous:***

- Use of colistimethate sodium in patients with myasthenia gravis may worsen symptoms.[3, 4, 6, 7]
- Use of colistimethate sodium in patients with neurological disease may increase the risk of neurotoxicity. Additionally, renal impairment increases the risk of neurotoxicity. Dose adjust accordingly and use with caution.[7]
- Each 150 mg IV vial contains 1.09 mmol of sodium.[2]
- Use with caution in renal impairment.[6]
- Use in neonates is associated with an increased risk of electrolyte disturbance (e.g. hypomagnesaemia, hypokalaemia, hypocalcaemia, hyponatraemia). Close dose monitoring is required in neonates as neurotoxicity may present as apnoea's or seizures.[7]

***Inhaled:***

- Bronchospasm may occur - ensure a short acting bronchodilator is administered prior to administration of each dose.[1, 3, 7]
- Reconstituted solution must be used immediately as colistimethate sodium hydrolyses rapidly, forming a compound that may cause lung toxicity.[4, 7]

## FORMULATIONS

Listed below are products available at PCH, other formulations may be available, check with pharmacy if required:

- 150 mg **colistin base** powder for injection.
- 1 million international units of **colistimethate sodium** powder for reconstitution and nebulisation.

Imprest location: Formulary One

## DOSAGE & DOSAGE ADJUSTMENTS

***Intravenous:***

**Neonates**

- Not routinely used in neonates. Contact Infectious Disease or Clinical Microbiology for advice.[7]
- Doses of 2.5 mg – 5 mg/kg/DAY in divided doses given every 6 to 12 hours have been used.[7]

**Children ≥ 4 weeks old:**

All doses are expressed as colistin base and should be calculated based on ideal body weight. Refer to: **Dosing in Overweight and Obese Children** for information on calculation of ideal body weight [6, 7]

- **Usual dose:** 2.5 to 5 mg/kg/DAY (to a maximum of 450 mg DAILY) in three divided doses.[1, 3, 7]
- **Cystic Fibrosis patients:** Doses up to 8 mg/kg/DAY (to a maximum of 450mg DAILY) in three divided doses have been used, but are associated with more severe toxicity.[1, 7]
- **Note:** Close monitoring for nephrotoxicity and neurotoxicity is required for **all** patients receiving colistimethate sodium.

***Inhalation:***

**Neonates**

Not routinely used in neonates. Contact Infectious Diseases or Clinical Microbiology for advice.

**Children ≥ 4 weeks to < 2 years:**

- **Usual dose:** 0.5 to 1 million international units inhaled twice daily.[5]
  - Dose may be increased to three times daily for recurrent infections.[1]

**Children ≥ 2 years old:**

- **Usual dose:** 1 to 2 million international units inhaled twice daily for three weeks.[1, 3, 4]
  - The dose may be increased to 2 million international units inhaled 3 times daily for refractory *Pseudomonas aeruginosa* infection for up to 3 months.[1, 3, 4]
  - Chronic colonisation: 1-2 million international units inhaled twice daily.[1, 3, 4]

**Dose adjustment for toxicity:**

- In cases of CNS toxicity (e.g. dizziness, numbness, paraesthesia, tingling, itch) discuss with Infectious Diseases. A dose reduction may reduce symptoms.[7]
- In cases of nephrotoxicity, colistimethate sodium treatment should be withheld.[7]

**Renal impairment:**

- eGFR calculator
- Colistimethate sodium should be avoided in renal impairment wherever possible due to an increased risk of toxicity and worsening of renal impairment.[4, 6]
- eGFR > 80 mL/minute/1.73m$^2$ = normal dosing
- eGFR 50 to 79 mL/minute/1.73m$^2$ = 2.5 to 3.8 mg/kg/DAY in two divided doses
- eGFR 30 to 49 mL/minute/1.73m$^2$ = 2.5 mg/kg/DAY in one OR two divided doses
- eGFR 10 to 29 mL/minute/1.73m$^2$ = 1.5 mg/kg/dose every 36 hours
- eGFR < 10 mL/minute/1.73m$^2$ = avoid use.[6]

Contact pharmacy for advice on dose adjustment in patients on renal replacement therapy.

- As systemic absorption of colistimethate sodium following nebulisation is low, dose adjustment is not routinely recommended. However caution should be taken if inhaled colistimethate sodium is used in patients with renal impairment or failure.[7]

**Hepatic impairment:**

- Colistimethate sodium should be used cautiously in patients with hepatic impairment however no dosage adjustments are required.[5-7]

## RECONSTITUTION & ADMINISTRATION

***Reconstitution - Intravenous:***

- Reconstitute each 150 mg vial with 2 mL of water for injection to give a final concentration of 75 mg/mL (powder volume 0.3 mL).[2, 4]
- This should be swirled gently (**not** shaken) to avoid frothing.[2, 6]

***Reconstitution - Inhaled:***

**Using Tadim® for inhalation via conventional nebuliser:**

- Turn the vial upside down and tap lightly to loosen any powder sticking to the side of the vial.
- Carefully lift the red flip-up top (do not remove) where indicated by the “Flip up ▼” to right angles with the top. Using the flip-up top as a hinge, pull backwards to remove the plastic top and the metal seal.
- Remove the rubber stopper.
- Draw up 2 mL of water for injection and add to the vial. This may cause frothing (which is normal), do not shake the vial as this will cause excessive frothing.

- Replace the rubber stopper and roll the vial between both hands after adding the water for injection. It may take 5-10 minutes for the colistimethate sodium to fully dissolve.
- Withdraw the required volume of solution and add to the nebuliser bowl/chamber. If an additional vial is required to make up the required dose – repeat steps one to six.(4)
- Use the solution immediately following reconstitution as colistimethate sodium hydrolyses increasing the risk of pulmonary toxicity. Discard any remaining solution. (1, 4, 6, 7)
- If using I-neb AAD nebuliser, refer to the product information for alternative reconstitution information.(4)

***Administration - Intravenous:***

**IV injection:**

- After reconstitution, give via slow IV injection over 3 to 5 minutes.(2, 6, 7)

**IV infusion:**

- After reconstitution, dilute further to a suitable volume with compatible fluid and infuse over 30 minutes.(7)
- For patients with any degree of renal impairment, consider using a slower rate of infusion (e.g. over 1 to 2 hours).(2)

***Reconstitution – Inhaled:***

- A short acting bronchodilator must be administered prior to each dose of inhaled colistimethate sodium due to risk of bronchospasm.(3, 7)
- Colistimethate sodium should be administered over 10 to 15 minutes after other inhaled drugs (such as bronchodilator, hypertonic saline, dornase alfa).(3, 6)

## COMPATIBILITY *(LIST IS NOT EXHAUSTIVE)*

***Intravenous*:**

- Glucose 5%
- Glucose/sodium chloride solutions
- Hartmann's
- Sodium chloride.(2)

**Compatible at Y-site:**

*Compatibilities of IV drugs* must be checked when two or more drugs are given concurrently.

***Inhaled:***

- Water for Injection.
- Sodium chloride 0.45% and 0.9%.(4)

Note: To prepare a sodium chloride 0.45% solution a 1:1 mixture of water for injections and sodium chloride 0.9% can be used to reconstitute the colistimethate sodium vial.(4)

## MONITORING

***Intravenous:***

- Renal function, urine output and full blood picture should be monitored at baseline and regularly during treatment.[3, 5, 6]
- Therapeutic drug monitoring has been recommended but is not widely available. Contact ChAMP or Infectious Diseases for further information.

***Inhaled:***

- The first dose of inhaled colistimethate sodium must be administered in the hospital or in outpatient clinic under supervision to ensure that the patient does not suffer from any significant adverse effects such as coughing or bronchospasm.[3]
- Lung function must be measured before and after the initial dose of colistimethate sodium and patients should be monitored for bronchospasm.[5]

## ADVERSE EFFECTS

***Intravenous:***

**Common:** nephrotoxicity (includes increased serum creatinine, haematuria, proteinuria, oliguria and rarely tubular necrosis), neurotoxicity (e.g. paraesthesia, dizziness, muscle weakness, ataxia, confusion, visual effects), presyncope.

**Infrequent:** neurotoxicity (increased incidence in CF patients prescribed high dose).[7]

**Rare:** hypersensitivity reactions (including skin rash), slurred speech, apnoea, psychosis, sensory disorder, visual impairment.[3, 5]

***Inhaled:***

There is minimal systemic absorption of colistimethate sodium when administered by inhalation. However, it should be kept in mind that this may occur and to monitor for adverse effects as per systemic administration, in particular nephrotoxicity or hypersensitivity reactions such as rash.[4]

**Common:** arthralgia, asthenia, impaired balance, fever, headache, tinnitus, coughing, bronchospasm, chest tightness, decrease in $FEV_1$, taste disturbances, nausea, vomiting, dysphonia.[4, 5]

**Infrequent:** anxiety, decreased appetite, diarrhoea, drowsiness, ear congestion, flatulence, oral disorders, proteinuria, seizures.[4, 5]

**Rare:** Thirst.

## STORAGE

***Intravenous:***

**Vial:** store below 25°C.[2, 4]

***Inhaled:***

**Vial:** store below 25°C[4]

- Once reconstituted, vials should be used immediately as it contains no antimicrobial preservative and there is an increased risk of lung toxicity due to hydrolysis of the medication with storage.[3, 4, 6, 7]
- If this is not possible, they can be stored at 2° C to 8° C and used within 24 hours.[4]

## INTERACTIONS

This medication may interact with other medications; consult PCH approved references (e.g. Clinical Pharmacology), a clinical pharmacist or PCH Medicines Information Service on extension 63546 for more information.

***Please note: The information contained in this guideline is to assist with the preparation and administration of **colistimethate sodium**. Any variations to the doses recommended should be clarified with the prescriber prior to administration***

## Related CAHS internal policies, procedures and guidelines

Antimicrobial Stewardship Policy

ChAMP Empiric Guidelines and Monographs

KEMH Neonatal Medication Protocols

## References

1. Royal Australian College of General Practitioners, Pharmaceutical Society of Australia, Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists. AMH: Children's Dosing Companion. Adelaide: Australian Medicines Handbook Pty Ltd; 2022.
2. Symons K. Ermer J. (editors). Australian injectable drugs handbook. Collingwood: The Society of Hospital Pharmacists of Australia; 2022.
3. Australian Medicines Handbook. Adelaide, S. Aust.: Australian Medicines Handbook; 2023 [cited 2023 30th October]. Available from: https://amhonline-amh-net-au.pklibresources.health.wa.gov.au/.
4. MIMS Australia. MIMS online [full product information]. St Leonards, N.S.W: CMP Medica Australia.; 2023 [cited 2023 31th October].
5. Paediatric Formulary Committee. BNF for Children: 2023. London: BMJ Group Pharmaceutical Press; 2023.
6. Clinical Pharmacology powered by ClinicalKey [Internet]. Elsvier. 2023 [cited 2023 December 11th]. Available from: https://www-clinicalkey-com.pklibresources.health.wa.gov.au/pharmacology/.
7. Up To Date - Paediatric Drug information [Internet]. Lexicomp. 2023 [cited 2023 December 11th]. Available from: https://www-uptodate-com.pklibresources.health.wa.gov.au/contents/table-of-contents/drug-information/pediatric-drug-information.
8. Taketomo CK, Hodding JH, Kraus DM. Pediatric and Neonatal dosage handbook with international trade names index. 26th edition ed. Ohio: Lexi-comp; 2019-2020.
9. IBM Micromedex [Internet]. Truven Health Analytics. 2023 [cited 2023 December 11th]. Available from: http://www-micromedexsolutions-com.pklibresources.health.wa.gov.au/micromedex2/librarian.

This document can be made available in alternative formats on request.

| | | | |
|---|---|---|---|
| File Path: | *W:\Safety & Quality\CAHS\CLOVERS MEDICAL Pharmacy\Procedures Protocols and Guidelines\ChAMP\Word* | | |
| Document Owner: | Head of Department – Infectious Diseases | | |
| Reviewer / Team: | Children's Antimicrobial Management Program Pharmacist | | |
| Date First Issued: | November 2013 | Last Reviewed: | December 2023 |
| Amendment Dates: | December 2017 | Next Review Date: | January 2027 |
| Approved by: | Medication Safety Committee | Date: | December 2023 |
| Endorsed by: | Drug and Therapeutics Committee, Chair | Date: | January 2024 |
| Aboriginal Impact Statement and Declaration (ISD) | | Date ISD approved: | 31/08/2023 |
| Standards Applicable: | NSQHS Standards:  <br>NSMHS: N/A<br>Child Safe Standards: N/A | | |

**Printed or personally saved electronic copies of this document are considered uncontrolled**