

IN USE PRODUCT SAFETY ASSESSMENT REPORT FOR COLISTIMETHATE SODIUM

SUMMARY OF ASSESSMENT AND ITS FINDINGS

BACKGROUND

Colistimethate sodium (colistin sulfomethate sodium) is licensed in the UK to be given by two routes: by intravenous injection or infusion, or inhaled as nebulised solution. The National Reporting and Learning System (NRLS) have identified incidents of errors with colistin preparations. Those of particular concern include incidents in which the wrong strength had been prescribed, dispensed or administered.

In October 2014, the European Medicines Agency (EMA) completed a review of polymyxin-based medicines (colistin or colistimethate sodium) subsequent to concerns raised in relation to product information.¹ There were several findings from this review, including those with a particular reference to product safety. The review concluded that significant gaps exist in the literature in relation to dosing in special populations (for example, in children and patients with renal impairment) and that differences in expression of strength in the EU compared to other regions, such as the USA and Australia, have led to errors in international medical literature. In light of these findings, recommendations have been made to update European product information. These recommendations include consistent expression of doses in International Units (IU), consistent dosing recommendations across the product literature, and inclusion of a strength conversion table (IU's AND milligram's) to address confusion arising from international medical literature.

This UKMi assessment reviews UK licensed colistimethate sodium products given via the nebulised or parenteral route and summarises considerations associated with their in-use safety in NHS practice.

DETAILS OF PRODUCT (S) ASSESSED

The products assessed using the validated UKMi product assessment tool² are:

1. Promixin® 1 million International Units (IU) powder for solution for infusion; Profile Pharma Limited
2. Promixin® 1 million IU powder for nebuliser solution; Profile Pharma Limited
3. Colomycin® injection powder for solution for injection, infusion or inhalation; Forest Laboratories UK Limited: 1 million IU and 2 million IU
4. Colistimethate sodium 1 million IU powder for solution for injection; Beacon Pharmaceuticals

Assessments were carried out with reference to images supplied by the manufacturers or from various sources within the NHS, Summaries of Product Characteristics (SmPC) and packaging inserts.³⁻¹⁰

The assessment process is summarised at the end of the report.

CONCLUSION FOLLOWING APPLICATION OF VALIDATED ASSESSMENT TOOL

There are some risks associated with the prescribing, product selection and administration of colistimethate sodium products. In some instances the risk may be increased due to unfamiliarity of the polymyxin-based antibiotic medicine in comparison to standard antibiotics. Potential risks are identified below; mitigating and other necessary actions are considered in the next section.

Variations in licensing between products

There are variations in relation to the licensed route of administration for each of the four products assessed:

Product (manufacturer)	Licensed route of administration			
	Nebulised	Intravenous	Intrathecal	Intraventricular
Promixin 1 million International Units (IU) powder for solution for infusion (Profile Pharma Limited)		✓	✓	✓
Promixin® 1 million IU powder for nebuliser solution; (Profile Pharma Limited)	✓			
Colomycin® injection powder for solution for injection, infusion or inhalation; 1 million IU, 2 million IU (Forest Laboratories UK Limited)	✓	✓		
Colistimethate sodium 1 million IU powder for solution for injection (Beacon Pharmaceuticals)		✓		

Confusion can arise when selecting the most appropriate product for the specific route of administration being used. From the assessment, the packaging and presentation between the products are well differentiated but, in our view, there is a small potential for confusion between the Promixin® powder for solution for infusion and Promixin® powder for nebuliser solution (see product photo's below). Products intended for intravenous use but used 'off-label' as a nebuliser solution is an area of some potential contention; the specific pharmaceutical issues associated with it are beyond the scope of this paper. Regardless, the variations in licensing should be taken into account when selecting an appropriate product at the point of prescribing, dispensing, and administration.

Complex dosing

Errors of 'wrong dose or strength' have been reported and concerns have been raised by the EMA on dosing information in existing product literature.¹ In the EU, colistimethate sodium dosing information should be expressed as 'international units (IU)' but it may be expressed in some non-European countries as 'mg' which has led to errors. The EMA has recommended that a conversion table should be included in the product information of all EU products. From the assessment, it was identified that some product information for UK licensed products remain to be updated in-line with the EMA recommendations; at the time of writing this included the Forest Laboratories and Beacon Pharmaceuticals products.

Dosing recommendations for the intravenous route can be complex. In particular for patients below 60kg of weight, as dosing can be calculated on an IU/kg basis.¹¹ This is further compounded by the fact that the product strength is expressed in units of 'million IU', which can clearly cause confusion when calculating doses on a weight basis. For example, the BNF recommended intravenous dosing for patients weighing below 60kg is 50,000-75,000 IU/kg daily in 3 divided doses. For a patient of 55kg, a dose of 2.75-4.125 million IU would be required daily in 3 divided doses. This calculation requires a number of steps and, in our view, there is a significant risk of errors in calculation.

Furthermore, it is acknowledged that gaps exist in the evidence based literature in relation to dosing in special populations with significant adverse events having been reported due to inappropriate dosage reductions in patients with renal impairment.^{3,7,9} The BNF refers the reader to the manufacturer's product literature for renal dosing; this assessment concluded that the recommended dosing for renal impairment varied in the UK product literature, which could be potentially confusing when prescribing for this patient group.

Administration issues

The intrathecal route of administration is clearly high risk and use would only be expected under very rare

circumstances. The intravenous preparation is used more routinely and administration is complex, consisting of multiple preparation steps. The reconstitution and administration of the intravenous product could be regarded as high-risk using the [NPSA risk scoring tool](#) (use of a concentrate, potential complex calculation, complex method, reconstitution of powder in a vial, use of more than one vial, and potential use of a pump). Overall, it was felt there were variations between the manufacturers' product literature with respect to clarity of instructions for preparing the product for administration. As mentioned above, dosing calculations in specific population groups can be complicated due to the dose unit expression used for this product but this is further compounded by the fact that part vials may be required resulting in multiple calculations steps.

Equally, the nebulised preparation has complexities associated with use. The specifics for preparing this product for administration can vary depending on which colistimethate sodium product has been selected, as well as the type of nebuliser being used. During administration, certain precautions need to be taken to prevent exposure of the nebulised drug into the local environment. This may include the use of a Promixin disc, which is compatible with the I-neb AAD system and supplied with the Promixin product, or ensuring the room is well ventilated which may require tubing or filters to prevent waste aerosol from entering the environment. Nebulised colistimethate sodium may be used across a range of care settings, and hence there is potential for risk associated with this. For example, when home use is anticipated, the same issues of particle exposure during administration will be present.

POTENTIAL NEXT STEPS AND MITIGATION ACTIONS

Potential next steps and mitigation actions can be considered in two respects: those of particular relevance to the NHS, and those of relevance to manufacturers.

To support safe use in the NHS Healthcare providers should consider:

- Rationalisation of the current range of colistimethate sodium products held taking into account the variations in product licensing. This may include risk assessment of individual products before local purchasing and procurement decisions are made.
- Use of intravenous colistimethate sodium within the context of local guidance. This may include strategies to ensure safe prescribing in high risk patient groups, such as those with renal impairment, and recommendations of plasma concentration monitoring under certain circumstances. This is in addition to inclusion in local intravenous guides to support correct preparation and administration.
- Strategies to mitigate any risks of exposure of nebulised colistimethate sodium into the local environment and ensure administration is only within this context. These strategies should be included in local protocols, in addition to clear guidance on the use of any preparations for an 'off-label' nebulised route.
- Education of staff in relation to the nature of the problem with errors of 'wrong dose or strength' identified.
- Good patient counselling to ensure safe administration of nebulised colistimethate sodium in the home.

Suggested further actions for the manufacturers of colistimethate sodium products include ensuring product literature is updated in line with EU recommendations and instructions for preparation are as clear as possible to support correct preparation for administration. With reference to product packaging, the route of administration should be clear and reflect the licensed indications to support correct product selection.

This report was produced in June 2015 using photographic images (not physical products) of licensed products available at the time of assessment. Images were obtained primarily from pharmaceutical companies, but also from the Commercial Medicines' Unit PharmaQC database (<http://cmu.dh.gov.uk/medicines/pharmaqc-database/>) and from various sources within the NHS.

This report summarises product assessments undertaken by:
London Medicines Information Service (Northwick Park) and South West Medicines Information and Training. We are also grateful for the input of clinical specialists (respiratory, intensive care, microbiology) in completing this piece of work. For comments email lnwh-tr.medinfo@nhs.net

References:

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2. UKMi Product Safety Assessment tool. Available at:
<http://www.ukmi.nhs.uk/activities/patientSafety/default.asp?pageRef=19>
3. Profile Pharma Limited. Summary of Product Characteristics for Promixin, 1 million International Units (IU), Powder for Solution for Infusion. Revision of text: 10/4/2015.
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5. Profile Pharma Limited. Summary of Product Characteristics for Promixin, 1 million International Units (IU), Powder for Nebuliser Solution. Revision of text: 10/3/2015
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7. Forest Laboratories UK Limited. Summary of Product Characteristics for Colomycin Injection. Revision of text: August 2012.
8. Forest Laboratories UK Limited. Package leaflet: information for the user of Colomycin Injection. Updated: 31/10/2012.
9. Beacon Pharmaceuticals. Summary of Product Characteristics for Colistimethate Sodium 1 million I.U. Powder for Solution for Injection. Revision of text: 16/07/2014.
10. Beacon Pharmaceuticals. Patient information leaflet for Colistimethate Sodium 1 million I.U. Powder for Solution for Injection. Approved: March 2012.
11. Joint Formulary Committee. British National Formulary (online). London: BMJ Group and Pharmaceutical Press; 2015. Accessed: May 2015.

EXAMPLE PRODUCT PHOTOS



