



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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European Medicines Agency completes review of polymyxin-based medicines

Recommendations issued for safe use in patients with serious infections resistant to standard antibiotics

On 23 October 2014 the European Medicines Agency (EMA) completed a review of the safety and effectiveness of products containing the antibiotics colistin or colistimethate sodium (known as polymyxins) and recommended changes to their product information to ensure safe use in the treatment of serious infections that are resistant to standard antibiotics.

Polymyxin-based products have been available since the 1960s, but their use quickly decreased due to the availability of antibiotics with fewer potential side effects. Due in part to this limited use, colistimethate sodium has retained activity against a number of bacteria which have become resistant to commonly used antibiotics. This has led to a resurgence in recent years in the use of polymyxins in patients with few other options. However, current experience has raised concerns that the existing product information, in particular relating to dosing and the way the medicine is handled in the body (pharmacokinetics), might need updating. The European Commission therefore requested the EMA to review the available data and make recommendations on whether the marketing authorisations for these medicines should be changed and the product information amended appropriately.

The Agency's Committee for Medicinal Products for Human Use (CHMP) reviewed the available data about the pharmacokinetics, effectiveness and safety of these medicines. The review considered products given by injection or inhaled as a liquid into the lungs (systemic use) containing colistimethate sodium, which is converted to the active substance colistin in the body. Products taken by mouth (which mainly contain colistin and are not absorbed into the body in significant amounts but act locally on the gut) and those applied externally were not covered in this review.

The CHMP concluded that injection or infusion (drip) of colistimethate sodium should be reserved for the treatment of serious infections due to susceptible bacteria, in patients whose other treatment options are limited. The medicine should be given with another suitable antibiotic where possible. The Committee recommended that doses should always be expressed in international units (IU) but because doses of colistimethate sodium can be expressed in different ways a conversion table should be included in the product information. Critically ill patients should be given a higher starting dose (loading dose) to provide an effective level of the antibiotic in the body more quickly. Although data were very limited, the Committee recommended doses for use in patients with kidney problems and in children, and provided



guidance on dosage in adults when given directly into fluid surrounding the brain or spinal cord (intrathecal or intraventricular injection).

CHMP concluded that colistimethate sodium may also be given by inhalation or in a nebuliser to treat ongoing (chronic) infections with the bacterium *Pseudomonas aeruginosa* in patients with cystic fibrosis. (Products for inhalation as a dry powder have a different dosage and distribution in the body, and were not affected by the conclusions of the review.)

The CHMP opinion was forwarded to the European Commission, which issued a final decision valid throughout the EU on 16 December 2014.

Information to patients

- Colistin and colistimethate sodium are older antibiotics (belonging to the class called polymyxins) that are sometimes used for infections that have become resistant to newer treatments. Colistimethate sodium is given by injection or inhaled, and becomes colistin inside the body.
- The available information on colistimethate sodium has been reviewed and recommendations have been made on its safe use and appropriate dosage.
- Injection or infusion (drip) of colistimethate sodium should only be used to treat serious infections in patients with few other treatment options, normally combined with another antibiotic. Colistimethate sodium may also be inhaled as a liquid vapour to treat lung infection in patients with cystic fibrosis.
- The product information for medicines containing colistimethate sodium will be updated as required to take these recommendations into account.
- Patients who have any questions about their treatment should consult their doctor or pharmacist.

Information to healthcare professionals

The Agency's recommendations are based on a review of the available clinical, pharmacological and pharmacokinetic data, although significant gaps still exist, particularly with regard to the pharmacokinetics in special populations such as children and patients with renal impairment. Research currently underway may provide further information on pharmacodynamics and pharmacokinetics of these medicines to improve the evidence-base behind any dose recommendations. However, it was considered that in the interim the product information should be updated throughout the EU to reflect what was currently known.

- Doses should always be expressed in IU of colistimethate sodium. To address the differences in the way in which the strength of colistimethate sodium and colistin are expressed in the EU and in other regions such as the USA and Australia, which has led to errors in reporting in the medical literature and could potentially lead to serious medication errors, the following table will be included in the product information:

Colistimethate sodium (IU)	Colistimethate sodium (mg)	Colistin-base activity (CBA) (mg) ¹
12 500	1	0.4
150 000	12	5
1 000 000	80	34
4 500 000	360	150
9 000 000	720	300

¹ Nominal potency of the drug substance = 12.500 IU/mg

- **Intravenous** colistimethate sodium is indicated in adults and children including neonates for the treatment of serious infections due to aerobic Gram-negative pathogens in patients with limited treatment options. Consideration should be given to co-administration with another antibacterial agent whenever this is possible.
- Dosage should be in line with relevant treatment guidelines. Based on the limited available evidence the recommended dose in adults is 9 million IU daily in 2 or 3 divided doses as a slow intravenous infusion; in critically ill patients a loading dose of 9 million IU should be given. Doses should be reduced according to creatinine clearance in patients with renal impairment.
- In children, the suggested dose is 75,000 to 150,000 IU/kg daily, in 3 divided doses.
- Intravenous colistimethate sodium does not cross the blood-brain barrier to a significant extent. Where appropriate, adult doses of 125,000 IU for intraventricular administration and no more than this for intrathecal administration are recommended.
- Use of intravenous colistimethate sodium together with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with great caution.
- When given **by inhalation**, colistimethate sodium solutions may be used for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adults and children with cystic fibrosis. The recommended dose in adults is 1 to 2 million IU given 2 to 3 times a day, and in children 0.5 to 1 million IU twice daily, adjusted according to the severity of the condition and the response.

A parallel review is currently underway, looking at the quality of the products and the way the potency of colistimethate sodium is measured and tested, and may result in further changes to the product information once complete.

More about the medicine

Polymyxins are a group of antibiotics that includes colistin and colistimethate sodium (a 'prodrug' that is converted to colistin in the body), which have been available in the EU since the 1960s for the treatment of susceptible infections. Currently, products containing colistimethate sodium for use by injection or by inhalation as a solution or as a mist (nebulised) are approved under various trade names in Austria, Belgium, Bulgaria, Croatia, the Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, Netherlands Poland, Portugal, Romania, Slovakia, Spain, Sweden and United Kingdom. In addition, colistimethate sodium has been approved in the EU for inhalation as a dry powder under the trade name Colobreathe.

More about the procedure

The review of polymyxin-based medicines was initiated on 16 September 2013 at the request of the European Commission, under Article 31 of Directive 2001/83/EC. Colistin and its prodrug colistimethate sodium are the only polymyxins approved for clinical use in the EU, and the review was limited to products used by injection or inhalation (all formulated as colistimethate sodium).

Products containing colistin are available for use by mouth or for external application but are not included in this review, as they are not considered to produce significant amounts of the active substance in the body.

The review of these data was conducted by the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which considered them and formulated the Agency's final opinion. The CHMP opinion was forwarded to the European Commission, which issued a final decision valid throughout the EU on 16 December 2014.

A parallel review under Article 5(3) of Regulation (EC) No 726/2004 is currently also under way, looking at the quality of the products and the way the potency of colistimethate sodium is measured and tested, and may result in further changes to the product information once complete.

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