EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Questions and answers on veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally

Outcome of a referral procedure under Article 35 of Directive 2001/82/EC (EMEA/V/A/111)

On 21 April 2016, the European Medicines Agency (the Agency) completed a review of the effectiveness of and antimicrobial resistance to all veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally. The Agency's Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the overall benefit-risk balance for the aforementioned products is negative, due to a lack of clinical relevance and in view of over-exposure of colistin that could pose a potential risk to animal and human health from an acceleration of the occurrence of colistin resistance. The CVMP recommended that all marketing authorisations for veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally should be withdrawn throughout the European Union (EU).

What is colistin?

Colistin belongs to the polymyxin group of antibiotics. Colistin is used for the treatment and prevention of diseases caused by sensitive bacteria (e.g. *Escherichia coli*) in pigs, poultry, rabbits, cattle, sheep and goats. Combinations of colistin with other antimicrobials are available for group treatments of gastro-intestinal and respiratory infections in food-producing animals in different European Member States. These include veterinary medicinal products containing combinations of colistin with 14 different antimicrobial substances, belonging to different classes e.g. β-lactams, tetracyclines, macrolides, sulfonamides and trimethoprim (see Annex I on the 'All documents' tab).

Why were veterinary medicinal products containing colistin in combination with other antimicrobial substances reviewed?

Following a request from the European Commission, in July 2013 the CVMP and CHMP adopted scientific advice and detailed considerations on colistin[1]. This advice critically reviewed information on

[1] Request for scientific advice on the impact on public health and animal health of the use of antibiotics in animals, answer to the first request from the European Commission (EMA/363834/2013)
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/07/WC500146812.pdf

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the use of colistin in food-producing animals in the EU, its effect on the development of resistance to this category of antimicrobial agents in bacterial species that are of importance for human and animal health and the possible impact on human and animal health.

In May 2014 the European Commission initiated a referral procedure under Article 35 of Directive 2001/82/EC for all veterinary medicinal products containing colistin as sole active substance for oral administration to food-producing species (EMEA/V/A/106). The procedure was concluded and on 16 March 2015 the European Commission adopted a Decision[2] restricting the indications, target species, and duration of treatment of the concerned products, as well as adding prudent use warnings to the product information.

On 4 May 2015, the European Commission initiated a referral procedure under Article 35 of Directive 2001/82/EC for all veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally. The CVMP was requested to review the marketing authorisations and the available data in order to ensure responsible use of the substance in protecting animal health and limiting the possibility of future risk to public health.

Which data has the CVMP reviewed?

Proprietary data, scientific references and expert reports were provided in this Article 35 referral procedure in support of some indications of some of the products included in the scope of the procedure. In addition, the marketing authorisation holders were asked to justify the benefits of using a colistin combination product over the use of monotherapy for the treatment of the respective conditions, particularly taking into account the CVMP guideline on pharmaceutical fixed combination products[3] (EMEA/CVMP/83804/2005).

What are the conclusions of the CVMP?

Based on the evaluation of the currently available data, the CVMP concluded that no benefit could be demonstrated when using colistin combination products instead of monotherapy and no feasible risk mitigation measures could be identified to address the identified potential risk for human health, as even limited use of colistin combination products was considered unnecessary. Therefore the CVMP recommended that all marketing authorisations for all veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally should be withdrawn.

The European Commission issued a decision on 14 July 2016.

Use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health (EMA/755938/2012)
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146813.pdf

[2] Commission Decision concerning, in the framework of Article 35 of Directive 2001/82/EC of the European Parliament and of the Council, the marketing authorisations for all veterinary medicinal products containing "Colistin" to be administered orally ((2015)1916 of 16/03/2015) http://ec.europa.eu/health/documents/community-register/html/vo25478.htm

[3] CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004645.pdf