



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 July 2013
EMA/363834/2013

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

Introduction

On 15 February 2013 the European Commission submitted to the European Medicines Agency a request for advice on the impact on public health and animal health of the use of antibiotics in animals¹.

The first request is as follows:

1. Advice on 'old' antibiotics or new antibiotics belonging to 'old' classes of antibiotics that have been re-introduced or have a new use to treat multi-resistant bacteria in humans, in particular colistin and tigecycline. EMA should consider in particular:
 - a) Possible links between the use of those substances in animals (where relevant) and resistance in bacteria of animal origin;
 - b) The impact of use of those substances or other related antibiotics in animals on human health and whether restricting or not their use as veterinary medicines would have an impact on the development of resistance in bacteria causing infections in humans.

The overall answer to the question 1 (parts "a" and "b") were prepared by the Antimicrobial Advice ad hoc Expert Group (AMEG). The AMEG is composed of representatives and experts from the European Medicines Agency (EMA) and its Committee for Medicinal Products for Veterinary Use and Antimicrobials Working Party (AWP/CVMP) and its Committee for Medicinal Products for Human Use and Infectious Disease Working Party (IDWP/CHMP), the European Food Safety Authority (EFSA), the European Centre for Disease Prevention and Control (ECDC) and the Joint Interagency Antimicrobial Consumption and Resistance Analysis Report (JIACRA). The AMEG used as the basis to answer the questions on tigecycline and colistin the draft assessments prepared by the CVMP Antimicrobial Working Party to which experts of the CHMP Infectious Diseases Working Party had provided input. The final answer was endorsed during the CVMP (16-18 July 2013) and CHMP (22-25 July 2013) plenary meetings.

¹ Available from http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142070.pdf



Answers to the request

Scope of the request

The organisms that currently lead to a therapeutic impasse are Gram-negative bacteria, in particular Enterobacteriaceae such as *Escherichia coli* and *Klebsiella pneumoniae*, and non-fermenting bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. The antibacterial spectrum of the two antimicrobial compounds covered below, tigecycline and colistin, include these target organisms.

Due to the limited time available to respond to the European Commission first question, the scope of this scientific advice will be limited to colistin and tigecycline, the two substances mentioned in the request from the European Commission. The AMEG has confirmed that these are the most important substances within the definition provided by the European Commission. Other antibiotics not authorised for use in animals but used off label, may be included when preparing the response to question 3.

Tigecycline

- a) Possible links between the use of those substances in animals (where relevant) and resistance in bacteria of animal origin;

Tigecycline is currently not approved in veterinary medicine, and the extent of off label use of this substance is not quantified although there is some anecdotal evidence of use in dogs and cats. There is no available evidence of links between the use of tigecycline in animals and resistance to tigecycline. There is evidence from human use that tigecycline resistance emerges rapidly and a similar scenario could arise following use in animals, allowing the potential for transfer of resistant organisms or resistance determinants to animals (and humans). Tigecycline resistance is selected by tigecycline use. In addition tigecycline resistance might be impacted by use of other antimicrobials, such as fluoroquinolones, but the possible influence on development of tigecycline resistance from the use of these antimicrobials in animals is not known.

- b) The impact of use of those substances or other related antibiotics in animals on human health and whether restricting or not their use as veterinary medicines would have an impact on the development of resistance in bacteria causing infections in humans.

For tigecycline, which is currently not approved for use in veterinary medicine, only limited need for use in dogs and cats has been identified. The impact on human health from use of tigecycline in animals is dependent on the amount used and is therefore thought to be limited.

The use of tigecycline has been proposed as one of the treatment alternatives for dogs and cats to treat infections caused by multidrug resistant bacteria which are increasing. There is currently no reported use of glycylyclines in food animal species and no clear need identified in these species. There are no MRLs for tigecycline therefore it cannot currently be used under *the Cascade* for food producing species (article 11 of Directive 2001/82/EC of the European Parliament and of the Council relating to veterinary medicinal products).

The proposals for risk management, including restrictions of use, are:

Taking into account the importance of glycylyclines for public health and the potential for emergence of multidrug resistance, under the current circumstances it is proposed that glycylycline use in animals should be restricted. Currently no need for any approval of a veterinary medicinal product containing tigecycline is foreseen. Should, in the future, a need for such medicinal products for animals be identified, authorisations could only be considered on the basis of a positive benefit risk assessment

where the risk for transfer of resistance to humans is included in the assessment. With the available information on the need for tigecycline in humans and the estimated risk level, it appears unlikely that the benefit risk balance for such a product is going to be established as positive. Furthermore, whether a veterinary authorisation would increase the potential extent of use of tigecycline in animals under *the Cascade* when compared to use of the human authorised product should be considered.

In dogs and cats assessment of the extent of the need to use tigecycline in exceptional circumstances where no veterinary-authorised alternative antibiotic is available is not currently possible. Further information on this use is needed to draw conclusions on measures to be taken in relation to off label use of tigecycline in companion animals. Off label use of veterinary antimicrobials will be further addressed when answering questions 3 and 4 from the European Commission.

Colistin

- a) Possible links between the use of those substances in animals (where relevant) and resistance in bacteria of animal origin;

Despite the abundant use of colistin in veterinary medicine for over 50 years, from the available information colistin resistance transmission via horizontal gene transfer or sustained clonal expansion has not been observed for the target Gram-negative organisms. However the rapid emergence of resistance in humans after oral use in the Intensive Care Unit (ICU) for selective digestive tract decontamination shows that resistance in Enterobacteriaceae can emerge following oral use. The lack of emergence of resistance should be addressed with caution since in depth epidemiological surveys in veterinary medicine are scarce. Large studies combining consumption and resistance are limited, because colistin susceptibility tests are not fully reliable.

There is a need to implement robust systems for surveillance of antimicrobial resistance to detect any potential increase of colistin resistance in animal bacteria in the future that could lead to a review of the current advice.

- b) The impact of use of those substances or other related antibiotics in animals on human health and whether restricting or not their use as veterinary medicines would have an impact on the development of resistance in bacteria causing infections in humans.

The level of resistance to colistin in animals is infrequently reported in surveillance programmes monitoring antimicrobial resistance (AMR) in relation to veterinary use of antimicrobials. From the information available, transfer of resistance to colistin products encoded by mobile genetic elements (such as plasmids) between bacteria or from animals to humans has not been demonstrated. The information on surveillance of resistance to colistin is limited, with only a few Member States providing harmonised resistance data.

Based on current evidence it is considered appropriate to maintain the use of colistin in veterinary medicine but to restrict indications to therapy or metaphylaxis and to remove all indications for prophylactic use in order to minimise any potential risk associated with a broader use. Adequate monitoring of off-label use should be put in place.

The proposals for risk management, including restrictions of use, are:

Revision of the SPC

Colistin should only be used for treatment (cure or metaphylaxis) of disease, and should not be used for prophylactic use.

The SPCs of veterinary products containing colistin should be revised to take fully into account responsible use considerations (indications, SPC warnings...). In the case of products containing colistin in combination with another antimicrobial, a scientific justification for the authorisation of a fixed combination would be required.

An Article 35 referral procedure under Directive 2001/82/EC as amended was completed in 2010 addressing the posology and withdrawal periods of colistin products for administration in drinking water. The benefit-risk balance for the colistin products involved was considered positive for gastrointestinal infections caused by non-invasive *E. coli* susceptible to colistin, however the balance was considered negative for treatment of gastrointestinal infections caused by *Salmonella* spp in calves, lambs, pigs and poultry.

Surveillance of usage

Use of colistin in Member States is currently monitored as part of the ESVAC project in terms of overall use. The monitoring system should be enhanced to provide figures on use per species, production type and weight class. This advice is particularly important for colistin but also relates to other veterinary antimicrobials and so will be further considered as part of the response to questions 3 and 4.

Surveillance of resistance

The proposed revised European Commission harmonised monitoring of AMR requires all Member States to perform standardised and quality controlled susceptibility testing of colistin on representative samples of zoonotic and indicator bacteria (*Salmonella* spp. and *E. coli*). The findings from such testing are voluntarily reported by some Member States but should be made compulsory for all Member States. This monitoring system should be linked to a system where a random selection of all identified resistant isolates are screened for new resistance mechanisms, in particular for emergence of transferrable resistance genes.

Surveillance of target animal pathogens from clinical cases should be implemented to ensure an early detection of any change in resistance patterns. There is currently no official surveillance of target animal pathogens; such a system should therefore be implemented. The practical challenges for surveillance are recognised and are not restricted to colistin. Further consideration will therefore be given as part of the response to questions 3 and 4.

Follow up of scientific advice

This advice is based on a preliminary risk assessment relying to a large extent on the current data available on resistance to colistin and its pattern of use. Should surveillance detect a substantial increase in resistance, the benefit risk balance for colistin use would need to be re-evaluated.

The answers provided above are based upon two assessments on the use of colistin and tigecycline and their specific recommendations for actions, which can be consulted in the Annex.

Annex

(Documents on use of tigecycline and colistin)