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Committee for Medicinal Products for Veterinary Use (CVMP)

Concept paper on use of aminoglycosides in animals in the European Union: development of resistance and impact on human and animal health

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Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

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1. Introduction

Aminoglycosides have a broad antibacterial spectrum with good activity against Gram negative species and less activity against Gram positive species. This class of antimicrobials has no effect against anaerobic bacteria.

Aminoglycosides were among the first antibiotics discovered and used clinically. In the 1980s their use as monotherapy for Gram negative sepsis in humans was replaced by new antimicrobials with a broad-spectrum effect against Gram negative bacteria and which are less oto- and nephrotoxic (e.g. cephalosporins, carbapenems, and fluoroquinolones). In subsequent years aminoglycosides have often been combined with beta-lactam antibiotics for the treatment of severe sepsis/septic shock to broaden the antibacterial spectrum.

These antimicrobials are extensively used in veterinary medicine (EMA/ESVAC, 2013). The most frequent use is therapy for serious infections such as septicaemias, digestive tract infections (e.g. neomycin for *Escherichia coli*), respiratory and urinary infections in many animal species (cattle, pigs, sheep, goats, horses, dogs and cats). In particular gentamicin is indicated for *Pseudomonas aeruginosa* infections with few alternative treatments available. In the European Union (EU) approximately half of aminoglycoside use is in oral forms (premix or soluble in drinking water) and about half as injections (EMA/ESVAC, 2013). Aminoglycosides are also used in intramammary preparations. In the EU the most frequently used aminoglycosides are neomycin and dihydrostreptomycin. Other substances from the group used in food producing species (where maximum residue limits (MRLs) have been established) are: apramycin, gentamicin, kanamycin, paromomycin, neomycin, framycetin and streptomycin. Amikacin is also used for companion animals.

Following extensive use of aminoglycosides in humans, food-producing and companion animals resistance has emerged. Resistance can be mediated by transmissible genes or chromosomal mutation. The common mechanism of resistance is the production of aminoglycoside modifying enzymes. Resistance mechanisms are complex and differ between the different aminoglycoside molecules, and generally there is less cross resistance when compared to other classes of antimicrobials.

Many of these resistance mechanisms can be located in mobile elements increasing the likelihood of spread of aminoglycoside resistance as well as co-resistance. Recently, a new type of mechanism, post-transcriptional methylation of the 16SrRNA, has been reported. This results in high-level resistance to aminoglycosides.

The emergence of 16SrRNA methylases in bacteria of animal origin was first discovered in Spain in 2005 in an *Escherichia coli* isolate of pig origin harbouring the *armA* gene (Gonzalez-Zorn et al., 2005). Since then the same mechanism has been detected in *Escherichia coli* isolates from pigs, chicken, cows, and companion animals (dogs and cats) in different countries (Chen et al., 2007; Davis et al., 2010; Deng et al., 2011; Du et al., 2009; Hopkins et al., 2010; Liu et al., 2008).

2. Problem statement

In recent years, there has been an increased focus on the need to mitigate the risk associated with antimicrobial resistance (AMR). The European Council has emphasized the need to strengthen the surveillance for AMR and antimicrobial use in the veterinary sector, and for the promotion of the prudent use of antimicrobials. Emerging aminoglycoside resistance in bacteria of animal and human

origin have raised concern as to whether aminoglycoside use in veterinary medicine could have a negative impact on public and animal health.

3. Discussion

The World Health Organisation (WHO) has classified aminoglycosides as Critically Important Antimicrobials (CIA) (AGISAR, 2009).

In humans aminoglycosides are one of the few remaining treatment options for enterococcal endocarditis, multidrug resistant tuberculosis and infections caused by Gram negative pathogens, particularly *Enterobacteriaceae* and *Pseudomonas* spp. Aminoglycosides are used for infection control purposes beyond curative therapy, e.g. gastrointestinal decolonization procedures in intensive care units (Huttner et al., 2013). Aminoglycosides are important for the therapy of common infections and are widely used in food producing species and companion animals. Loss of efficacy of aminoglycosides could have a serious negative impact on animal health and welfare.

The reflection paper should address the impact of use of aminoglycosides in animals on public and animal health.

4. Recommendation

The CVMP recommends drafting a reflection paper on aminoglycosides to critically review recent information on their use in food producing and companion animals in the EU, their effect on development of resistance to this class of antimicrobial agents in bacterial species that are of importance for human and animal health, and the potential impact on animal and human health.

The reflection paper should include information on:

- The use of aminoglycosides in veterinary medicine;
- The use of aminoglycosides in human medicine;
- Mechanisms of resistance in relevant bacteria;
- Occurrence of resistance in bacteria from food producing and companion animals;
- Possible links between the use of aminoglycosides in animals and resistance in bacteria of animal origin;
- Impact on animal health;
- Impact on human health.

5. Proposed timetable

The end of the consultation period for the concept paper is October 2014. The preparation of a reflection paper will take place during 2015.

6. Resource requirements for preparation

The development of the reflection paper will require the appointment of one Antimicrobials Working Party (AWP) rapporteur, and physical and virtual meetings of the AWP rapporteur and experts.

7. Impact assessment (anticipated)

The reflection paper will provide information on the development of antimicrobial resistance to aminoglycosides and provide further clarification on the need and priority of risk management measures. In addition the reflection paper may detect gaps in our knowledge and identify subjects for further research.

8. Interested parties

Veterinarians, veterinary pharmaceutical industry, farmers, consumers and regulators.

9. References to literature, guidelines, etc.

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