Concept paper on Use of pleuromutilins in food-producing animals in the European Union: development of resistance and impact on human and animal health

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1. Introduction

Pleuromutins are antibacterial agents that inhibit protein synthesis by binding to the 50S subunits of ribosomes of bacteria. They are active against Gram-positive bacteria, anaerobic bacteria and Mycoplasma. Pleuromutins (tiamulin and valnemulim) are mainly used in veterinary medicine, especially in swine and to a lesser extent in poultry and rabbits. In pigs, tiamulin and valnemulim are used to treat swine dysentery (Brachyspira hyodysenteriae), spirochaetal diarrhoea (Brachyspira pilosicoli), porcine proliferative enteropathy (Lawsonia intracellularis), enzootic pneumonia and other infections where Mycoplasma is involved. Pleuromutins are also used to treat the polyetiological disease porcine respiratory disease complex (PRDC), and more rarely, leptospirosis. In poultry pleuromutins have been used to control Mycoplasma infections and Brachyspira infections (avian intestinal spirochaetosis). In rabbits tiamulin is used to treat epizootic rabbit enteropathy.

A special concern is the reported increase of the MICs of tiamulin and valnemulim for porcine Brachyspira hyodysenteriae (B. hyodysenteriae) isolates. There is a limited number of antimicrobials available for the treatment of swine dysentery and resistance to alternative antimicrobials (macrolides, lincosamides) is common.

Since 2005, a specific clone of meticillin resistant Staphylococcus aureus (MRSA), ST398, is increasingly reported worldwide in livestock, especially swine. Most often animals are only colonized with MRSA ST398, but clinical infections may also occur. Zoonotic infections in humans in contact with colonized animals are well documented, including severe cases. Recently, decreased susceptibility of MRSA ST398 to tiamulin has been reported.

2. Problem statement

Pleuromutins are very important antimicrobials for the control of swine dysentery in pigs. As resistance to the other antimicrobials for this indication is common, the recent reports on the increased MICs of tiamulin and valnemulim against B. hyodysenteriae is a concern, as there might be a lack of treatments available for this disease in the future. In addition, reports on plasmid-borne resistance to pleuromutins in MRSA could be of concern, as plasmids might be transmitted between bacterial strains or species.

3. Discussion (on the problem statement)

Due to the lack of commercial vaccines, control and treatment of swine dysentery involves the use of antimicrobial drugs. Eradication strategies used also mostly include targeted antimicrobial treatments. In several countries the treatment of this disease has been complicated by the emergence of antimicrobial resistance. Resistance to macrolides (tylosin) and lincosamides seems to be very high in many countries and the most active agents are the pleuromutins, where most isolates are reported to be susceptible. Recently isolates with reduced susceptibility to pleuromutins have emerged among B. hyodysenteriae. Pleuromutins are often used as group medication and for prevention of disease, thus exposure of animal microbiota to pleuromutins including zoonotic agents is high. Options for prevention of a further emergence and spread of resistance against the last option left to treat B. hyodysenteriae infections needs to be discussed as this could have substantially impact on animal health and welfare as well as having economic consequences in farming.

Plasmid-borne genes, which confer a multiresistance phenotype that includes resistance to pleuromutins, lincosamides and streptogramins A in MRSA ST398 isolates from swine have been described. Transfer of such plasmids between different bacteria and different hosts, including humans...
could potentially occur. To date only one product containing pleuromutilins (retapamulin) is authorized in humans for topical use. A new product is being developed for oral and intravenous administration to humans with serious multidrug-resistant skin infections, including MRSA. Investigations exploring pleuromutilins for the treatment of *Mycobacterium tuberculosis* infections in humans are ongoing. Therefore, potential implications of the emergence of resistance to pleuromutilins in the livestock associated MRSA ST398 need to be considered.

4. **Recommendation**

The CVMP recommends drafting a reflection paper on pleuromutilins to critically review recent information on their use in food producing animals in the EU, its 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 pleuromutilins in veterinary medicine
- The use of pleuromutilins in human medicine
- Mechanisms of resistance in relevant bacteria
- Occurrence of resistance in bacteria from food producing animals
- Possible links between the use of pleuromutilins in animals and resistance in bacteria of animal origin
- Impact on animal health
- Impact on human health

5. **Proposed timetable**


6. **Resource requirements for preparation**

The development of the reflection paper will require the appointment of one SAGAM rapporteur and physical and virtual meetings of the SAGAM rapporteur and experts. Additional expertise on control of swine dysentery in pigs might be required.

7. **Impact assessment (anticipated)**

The reflection paper can provide information on the development of antimicrobial resistance to pleuromutilins 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


Kadlec K, Pomba CF, Couto N, Schwarz S. Small plasmids carrying vga(A) or vga(C) genes mediate resistance to lincomycin, pleuromutilins and streptogramin A antibiotics in methicillin-resistant Staphylococcus aureus ST398 from swine. J Antimicrob Chemother. 2010 Dec;65(12):2692-3.