15 October 2021
EMA/CVMP/AWP/266787/2021
Committee for Medicinal Products for Veterinary Use (CVMP)

Concept paper on an update to the CVMP's reflection paper on the use of macrolides, lincosamides and streptogramins (MLS) in food-producing animals in the European Union: development of resistance and impact on human and animal health

Agreed by AWP	23 August 2021
Adopted by CVMP for release for consultation	7 October 2021
Start of public consultation	15 October 2021
End of consultation (deadline for comments)	31 January 2022

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

Keywords	Antibiotics, antimicrobials, macrolides, lincosamides, streptogramins, ketolides, antimicrobial resistance, concept paper, animals, veterinary medicine, reflection paper

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. Introduction

The CVMP's reflection paper on the use of macrolides, lincosamides and streptogramins in food-producing animals in the EU was published in November 2011 (EMA/CVMP/SAGAM, 2011). Macrolides are regarded as critically important antibiotics in both human and veterinary medicine and, owing to shared sites of action and resistance mechanisms, lincosamides and streptogramins were reviewed alongside. Nearly a decade has now elapsed and it is important to review the status of these classes, in particular considering their importance to treat zoonotic campylobacter infections in humans and their ability to select for certain multi-resistance genes which have been detected in isolates from animals in Europe. Furthermore, both the (approved) indications and the volumes of use of these antibiotic classes have changed. Therefore, an update of the reflection paper is now recommended.

Aspects of the paper relating to the importance of these antibiotic classes in animals and humans and the potential for transmission of antimicrobial resistance (AMR) are of relevance for the AMEG (Antimicrobial Advice Ad Hoc Expert Group) categorisation. Furthermore, to expand the One Health approach, the use in companion animals together with their role and that of the environment in transmission of AMR should also be considered.

2. Problem statement

In the 6th revision of the WHO's categorisation of Critically Important Antimicrobials (WHO, 2019), macrolides and ketolides have been prioritized as a highest priority critically important antimicrobials (HP-CIA) for human medicine. Considering the importance of this class also in veterinary medicine and the specific circumstances of the European region, the revised AMEG categorisation of antibiotics (EMA/CVMP/CHMP, 2019) placed macrolides in its Category C ("Caution"). Although the criteria and purposes of these two categorisations differ, in view of the considerations at international level and constantly evolving patterns of AMR and antimicrobial usage both in veterinary and human medicine in the EU, it is important that the CVMP's reflections on these antibiotic classes are kept up to date. Several mechanisms confer cross-resistance between macrolide, ketolide, lincosamide and streptogramin classes variously; therefore, there is a rationale for reviewing in the same paper the impacts of antibiotic resistance related to the use of these three classes in animals.

Furthermore, increasing attention is being paid to the way in which antimicrobials excreted from treated animals degrade and spread within the environment, potentially contributing to the emergence, selection and dissemination of AMR. In line with the EU's Strategic Approach to Pharmaceuticals in the Environment adopted in 2019 (European Commission, 2019), and expanding the One Health approach, it is proposed to include consideration of environmental aspects in the updated reflection paper. In addition, whilst the previous reflection paper addressed food-producing animals only, companion animals should also now be brought within scope considering their therapeutic needs and relevant role in AMR transmission pathways.

3. Discussion (on the problem statement)

Macrolides are widely used for treatment of diseases that are common in food producing animals. This class has been categorised as critically important for veterinary medicine (VCIA) in the OIE list of antimicrobials of veterinary importance, updated in June 2021 (OIE, 2021). In the EU, macrolides are among few alternative antibiotics for treatment of haemorrhagic digestive tract disease in pigs (*Lawsonia intracellularis)* and for foot-rot in sheep and goats. They are also important for the treatment of mycoplasma infections in pigs and poultry. Newer macrolides are among few alternatives for treatment of respiratory tract infections caused by bacteria that are resistant to alternatives in

AMEG's Category D ("Prudence"). Lincosamides are also widely used in veterinary medicine in companion and food-producing animals in the EU and internationally. OIE places them in the highly important (VHIA) category. Conversely, streptogramins and ketolides have not been approved for use in veterinary medicines in the EU; although streptogramins are classified as important antimicrobials (VIA) by the OIE and used in animals in third countries.

According to the latest ESVAC report (EMA/ESVAC, 2020), from 2011 to 2018 the sales of macrolides for use in food-producing animals in the EU have declined by 34% whilst the sales of lincosamides have remained relatively stable.

Macrolides are categorised as HPCIA by the WHO, primarily considering their use to treat campylobacter infections, particularly in children; however, considering their use in the EU they have been placed in the AMEG category C. Lincosamides and streptogramins are categorised as highly important antimicrobials by WHO. In the EU/EEA, the consumption of macrolides, lincosamides and streptogramins in humans in the community has statistically decreased in the period from 2010-2019 (ECDC, 2020).

Changes in the consumption patterns of these antimicrobial classes could indicate a change in their importance to treat specific infections, may reflect an overall decline in antimicrobial consumption in a sector, or could be associated with other factors. This should be investigated.

Resistance to macrolides can emerge in zoonotic pathogens such as *Campylobacter* spp. and methicillin-resistant *Staphylococcus* spp. (MRS), which can be transmitted directly from animals to humans via food and/or contact. In addition, transferable macrolide-resistance genes can emerge in commensals e.g. *Enterococcus* spp. colonising animals, and can potentially be transferred to bacteria colonising or infecting humans. In addition to food-producing species, companion animals may play an important role as a reservoir of macrolide resistant bacteria or resistance genes that could be transmitted via direct contact to humans (Iannino *et al.*, 2019).

At present, resistance to macrolides in *C. jejuni* from animals and humans remains low in Europe; but is higher in *C. coli*, in certain MSs (EFSA/ECDC, 2020). Recently attention has been on emergence of a transferrable resistance mechanism, encoded by the *erm*B gene, which confers high level resistance to macrolides, lincosamides and streptogramin B in *Campylobacter* spp. In Europe, *erm*B has been reported in *C. coli* from poultry in Spain and Belgium (Elhadidy *et al.*, 2019; Florez-Cuadrado *et al.*, 2017). Another resistance pattern of particular concern relates to the *cfr* gene which confers resistance to phenicols, lincosamides, oxazolidinones, pleuromutilins and streptogramin A. This gene has been detected in livestock associated MRSA (LA-MRSA) from pigs in Belgium 2016 (EFSA/ECDC, 2018). These mechanisms amongst others, and the plasmids on which they are borne, favour co-selection and confer resistance to important antimicrobial classes.

Resistance to macrolides also occurs in pathogens of importance in animal health. High levels of resistance to macrolides and lincosamides have been determined for *Brachyspira* spp. Consequently, in CVMP referral procedures the benefit-risk balance in relation to the use of certain veterinary medicinal products containing tylosin, lincomycin, and lincomycin/spiramycin against swine dysentery caused by *B. hyodysenteriae* was considered to be negative and the indication was removed. Referral procedures for macrolide and lincosamide products have also considered the dosing regimens and indications relating to other target pathogens. Significant resistance to macrolides and lincosamides has appeared among staphylococci isolated in pigs and dogs and streptococci isolated in cattle. Resistance to macrolides can also emerge in other animal pathogens such as Pasteurellaceae and *Mycoplasma* spp. Knowledge on susceptibility patterns in target pathogens could be updated based on latest surveillance

data and scientific publications (Gautier-Bouchardon, 2018; Michael *et al*., 2018; Ruzauskas *et al.*, 2016).

4. Recommendation

A review of an update to the CVMP reflection paper on macrolides, lincosamides and streptogramins. The updated reflection paper will include information on:

- General drug characteristics (including pharmacodynamics and pharmacokinetics)
- Resistance mechanisms and susceptibility testing
- Sales and use of macrolides, lincosamides and streptogramins in veterinary medicine
- The use of macrolides, ketolides, lincosamides and streptogramins in human medicine
- Occurrence of resistance in bacteria from animals and humans
- Possible links between the use of macrolides, lincosamides and streptogramins in animals and resistance in bacteria of animal origin
- MLS residues, antimicrobial resistant bacteria (ARB) and antimicrobial resistant genes (ARGs) in the environment (emission and fate to and within environmental compartments)
- Transmission of antibiotic resistance or resistance determinants between animals, humans and the environment
- Impact of resistance on animal and human health
- Review of the implementation and, if possible, impacts of the recommendations made in the first reflection paper
- Recommendations

5. Proposed timetable

October 2021	Concept paper released for consultation
January 2022	Deadline for comments from interested parties
Q3 2023	Revised reflection paper released for consultation

6. Resource requirements for preparation

The revision of the reflection paper will involve two AWP co-rapporteurs. Correspondingly, rapporteurs will be appointed from the Environmental Risk Assessment Working Party (ERAWP) and the Infectious Disease Working Party (IDWP), as required.

Drafting group (physical and virtual) meetings will be organised, as needed.

7. Impact assessment (anticipated)

The reflection paper will update information on the development of antimicrobial resistance to these substances 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, users of antibacterials in general including farmers, veterinary pharmaceutical industry, academia, consumers and regulators

9. References to literature, guidelines, etc.

ECDC, 2020. 'Antimicrobial consumption in the EU/EEA - Annual Epidemiological Report for 2019', https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-consumption-europe-2019

EFSA/ECDC, 2018. 'The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2016 ', EFSA Journal, Vol. 16(2):5182

EFSA/ECDC, 2020. 'The European Union Summary Report on Antimicrobial Resistance in zoonotic and indicator bacteria from humans, animals and food in 2017/2018', EFSA Journal, Vol. 18(3):6007

Elhadidy, M., W.G. Miller, H. Arguello, A. Álvarez-Ordóñez, K. Dierick, and N. Botteldoorn, 2019. 'Molecular epidemiology and antimicrobial resistance mechanisms of Campylobacter coli from diarrhoeal patients and broiler carcasses in Belgium', Transboundary and emerging diseases, Vol. 66 (1), pp.463-475.

EMA/CVMP/CHMP, 2019. 'Categorisation of antibiotics in the European Union (EMA/CVMP/CHMP/682198/2017)', https://www.ema.europa.eu/en/documents/report/categorisation-antibiotics-european-union-answer-request-european-commission-updating-scientific_en.pdf

EMA/CVMP/SAGAM, 2011. 'Reflection paper on the use of macrolides, lincosamides and streptogramins (MLS) in food-producing animals in the European Union: development of resistance and impact on human and animal health (EMEA/CVMP/SAGAM/741087/2009)', https://www.ema.europa.eu/en/use-macrolides-lincosamides-streptogramins-food-producing-animals-european-union-development

EMA/ESVAC, 2020. 'European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption. Sales of veterinary antimicrobial agents in 31 European countries in 2018 (EMA/24309/2020). Trends from 2010 to 2018. Tenth ESVAC report', https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2018-trends-2010-2018-tenth-esvac-report_en.pdf

European Commission, 2019. 'Options for a strategic approach to pharmaceuticals in the environment - Final report', https://op.europa.eu/en/publication-detail/-/publication/5371e7bd-25db-11e9-8d04-01aa75ed71a1/language-en

Florez-Cuadrado, D., M. Ugarte-Ruiz, G. Meric, A. Quesada, M. Porrero, B. Pascoe, J.L. Sáez-Llorente, G.L. Orozco, L. Domínguez, and S.K. Sheppard, 2017. 'Genome comparison of erythromycin resistant Campylobacter from turkeys identifies hosts and pathways for horizontal spread of erm (B) genes', Frontiers in microbiology, Vol. 8 p.2240.

Gautier-Bouchardon, A.V., 2018. 'Antimicrobial resistance in Mycoplasma spp', Microbiology spectrum, Vol. 6 (4), p.6.4. 07.

Iannino, F., S. Salucci, G. Di Donato, P. Badagliacca, G. Vincifori, and E. Di Giannatale, 2019. 'Campylobacter and antimicrobial resistance in dogs and humans:" One health" in practice', Veterinaria italiana, Vol. 55 (3), pp.203-220.

Michael, G.B., J.T. Bossé, and S. Schwarz, 2018. 'Antimicrobial resistance in Pasteurellaceae of veterinary origin', Microbiology spectrum, Vol. 6 (3), p.6.3. 02.

OIE, 2021. 'OIE List of antimicrobial agents of veterinary importance', https://www.oie.int/app/uploads/2021/06/a-oie-list-antimicrobials-june2021.pdf

Ruzauskas, M., N. Couto, A. Pavilonis, I. Klimiene, R. Siugzdiniene, M. Virgailis, L. Vaskeviciute, L. Anskiene, and C. Pomba, 2016. 'Characterization of Staphylococcus pseudintermedius isolated from diseased dogs in Lithuania', Polish Journal of Veterinary Sciences, Vol.

WHO, 2019. 'Critically Important Antimicrobials for Human Medicine (6th revision) 2018 - Ranking of medically important antimicrobials for risk management of antimicrobial resistance due to non-human use', https://www.who.int/foodsafety/publications/antimicrobials-sixth/en/