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REVISED GUIDELINE ON THE SPC FOR ANTIMICROBIAL PRODUCTS

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REVISED GUIDELINE ON THE SPC FOR ANTIMICROBIAL PRODUCTS

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EXECUTIVE SUMMARY

This revised guideline on the SPC for antimicrobial products provides updated guidance for instructions on the information to be included in the Summary of Product Characteristics of the veterinary medicinal product containing antimicrobial substances. The revision replaces *the guideline on the SPC for antimicrobial products* (EMEA/CVMP/612/01-FINAL) and takes into account the developments during the recent years and the feedback obtained from the users on the previous guideline which was adopted in 2002. Importance of including guidance on Prudent Use in the Summary of Product Characteristics is emphasized. The revised guideline should serve to harmonise the Summary of Product Characteristics for antimicrobial products throughout the EU.

1. INTRODUCTION

This note for guidance should be read together with directive 2001/82/EEC, the Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/627/01-FINAL), the Guideline for the conduct of efficacy studies for intramammary Products for Use in Cattle (EMEA/CVMP/344/99-FINAL-Rev.1), the Guideline on the summary of product characteristics for pharmaceutical veterinary medicinal products included in Volume 6C of the Rules Governing Medicinal Products in the European Union, VICH GL27 Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance (CVMP/VICH/644/01-FINAL) and any guideline derived from this.

The Summary of Product Characteristics (SPC) should contain the necessary information making it possible to use the antimicrobial veterinary medicinal product effectively and safely while at the same time minimising the risk of development of antimicrobial resistance. This document indicates items considered being relevant from this point of view and therefore should be addressed in the SPC. In the SPC the elements of Prudent Use should also be included; for this purpose examples of standard phrases are presented.

2. SCOPE

This guideline provides additional instructions about the information which should be included in the SPC of the veterinary medicinal products which contain antimicrobial substances. Defining a harmonised approach for presenting the necessary information is considered useful particularly for mutual recognition and decentralised procedures.

3. LEGAL BASIS

Summary of Product Characteristics (SPC) should contain the information in accordance with requirements detailed in the article 14 of the Directive 2001/82/EC of the European Parliament and of the Council as amended.

This guideline supersedes the previous SPC guideline on the SPC for antimicrobial products (EMEA/CVMP/612/01-FINAL).

GENERAL CONSIDERATIONS FOR THE PREPARATION OF THE SPC

The following headings refer to the respective sections of the SPC. Sections, where specific guidance related to veterinary medicinal products containing antimicrobial substances is not necessary, do not appear in this guidance document.

4. CLINICAL PARTICULARS

4.2 Indications for use, specifying the target species

The target bacterial species shall be listed within each target animal species and indication for use. The target bacterial species should be listed alphabetically in the following order: aerobic Gram-positive bacteria, aerobic Gram-negative bacteria, anaerobic bacteria, and other micro-organisms.

4.5 Special precautions for use

i) Special precautions for use in animals

Recommendations for prudent use

Recommendations for prudent use to retain the therapeutic efficacy and to minimise the spread of resistance should be given. These recommendations may be different for products indicated for food animals and those indicated for companion animals. In food animals the main focus is on the higher pressure for selection of resistance e.g. by treatment of animal groups or flocks and the potential spread of food-borne pathogens. In the SPC, also improvement of management and strategies for eradication can be mentioned as further means to control infections. In companion animals resistance may be spread as pets and humans live in close contact and direct transfer of bacteria or resistance determinants is possible. Information on measures to reduce such transfer could be included.

If, in view of maintaining the efficacy of antimicrobials, the use of certain antimicrobials should be restricted, one or more of the following standard phrases can be incorporated, taking official and local antimicrobial policies into account. This is particularly important for products with a high potential to select for antimicrobial resistant bacteria of human and animal health concern.

> "The <*antimicrobial*> should be used for treatment of severe infections only"
>
> "The <*antimicrobial*> should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials."
>
> This standard phrase should be revised in a case-by-case basis. If it relates to the product containing a substance which belongs to higher generation the use of antimicrobials from previous generation which are likely to create less resistance should be taken into account, for instance in case of 3rd generation cephalosporin-containing product when 1st generation containing products can be used:
>
> "…poorly, to other classes of antimicrobials or first generation cephalosporins."
>
> "Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria."
>
> "Due to the likely variability (time, geographical) in the occurrence of resistance of bacteria for <*antimicrobial*>, bacteriological sampling and susceptibility testing are recommended."
>
> "Whenever possible, the <*antimicrobial*> should only be used based on susceptibility testing"
>
> "Official and local antimicrobial policies should be taken into account when the product is used."

"Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the <*antimicrobial*> and may decrease the effectiveness of treatment with <*the following specified antimicrobial(s)*>, due to the potential for cross resistance."

Depending on the application of VICH GL27, additional sentences could be included.

For (fluoro)quinolones a subset of the above precautionary phrases has been agreed that should be included in the SPC as described in the Reflection Paper on the use of fluoroquinolones in food producing animals - Precautions for use in the SPC regarding prudent use guidance (EMEA/CVMP/416168/06-FINAL)

4.9 Amounts to be administered and administration route

All deviations from optimal dosing and treatment duration of the antimicrobial product should be avoided. Underdosing of antimicrobials is considered to increase the possibility for development of antimicrobial resistance in bacteria. Too short treatment can reduce the efficacy of the antimicrobial. Also, an unnecessarily long antimicrobial treatment can be a factor to promote the development of resistance. The user of the product should comply with the posology as recommended, meaning that the correct quantity of the active substance or product is administered and that treatment is carried out for the entire period of time as indicated. The recommended duration of treatment included in this section of SPC is based on the efficacy and safety data of the product and should be as explicit as possible. Further guidance such as recommendations on the discontinuing of the treatment or re-evaluating diagnosis if no response of the animal is seen belong to good veterinary practice and should not be included in the SPC.

To ensure as far as possible that an accurate dose of the antimicrobial product is administered, it is recommended that the following statement is included.

"To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing."

For antimicrobials, administered through the drinking water or feed, the concentration in feed / water has to be adjusted in order to obtain the correct dosage. The following statement can be made.

"The uptake of medicated <*feed/water*> depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of <*antimicrobial*> has to be adjusted accordingly."

5. PHARMACOLOGICAL PROPERTIES

The information submitted in this paragraph should allow the prescriber to relate specific susceptibility data (animal, farm, region) on the bacterial isolates to the mode of action and the kinetic profile of the antimicrobial in order to allow a proper decision to be made on the use of the antimicrobial product, and to achieve an optimal antibacterial effect and minimal selection for resistance in a given situation.

5.1 Pharmacodynamic properties

General properties of the antimicrobial, e.g. classification and mode of action, i.e. if the substance is bactericidal or bacteriostatic, and its effect mainly time-dependant or concentration dependent, should be described.

The antibacterial spectrum relevant for the target animal species and approved indications should be stated. The order of the listed micro-organisms is the same as used in 4.2. If appropriate, MIC data should be provided for a representative sample of isolates of the target organisms from field materials from different geographic areas within the EU. For bactericidal substances, the minimum bactericidal

concentration (MBC) can also be stated. Naturally resistant bacterial species should only be mentioned if they are relevant in view of the indicated use.

Proportion of resistance in target pathogens should be reported. Clinical breakpoint MICs (µg/ml) should be used to categorise isolates as susceptible (S) or resistant (R). The source for the breakpoints used should be given. The known type(s) and mechanism(s) of acquired resistance in the target pathogens should be included. The existence of any cross-resistance within the class of antimicrobials and between classes of antimicrobials should also be stated.

Resistance among food-borne bacteria should be reported if relevant in the approved conditions of use. Epidemiological cut-off values (µg/ml) should be used to categorise isolates as susceptible (S) or resistant (R). The source for the epidemiological cut-off values used should be given.

5.2 Pharmacokinetic particulars

Pharmacokinetic particulars of the product should be described in sufficient detail for the clinical use. Relevant pharmacokinetic parameters such as Vd, Cmax, Tmax, elimination half-life, clearance and area under the concentration curve (AUC) should be mentioned. The degree of protein binding of the substance in the plasma should be given. Information about the concentrations of the antimicrobial at the site of infection should be provided if available. The surrogate markers from PK-PD modelling for dose determination and efficacy assessment of the active substance can be described if appropriate for the use of the antimicrobial.

If a dose-range is proposed (4.9), concentrations in plasma should be mentioned at least for the lowest and the highest dose.

If concentration in plasma is not applicable, free concentrations of the active substance in the relevant body compartments, should be mentioned.

If the active substance is transformed into an active metabolite and quantities are relevant from an efficacy point of view, data requirements are the same as for the parent compound.

Information on the excretion of the active substance at the defined dosage level into the gut of the animal where potential food borne pathogens may reside, if relevant in the approved conditions of use (antimicrobials for food-producing animals), should be given.

DEFINITIONS

N/a

REFERENCES (SCIENTIFIC AND / OR LEGAL)

- Directive 2001/82/EC of the European Parliament and of the Council as amended. Official Journal L 311, 28/11/2001 P. 0001 - 0066.
- Guideline on the summary of product characteristics for pharmaceutical veterinary medicinal products included in Volume 6C of the Rules Governing Medicinal Products in the European Union (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-6/c/spcpharmaceuticals_10-07-2006.pdf)
- Reflection Paper on the use of fluoroquinolones in food producing animals - Precautions for use in the SPC regarding prudent use guidance (EMEA/CVMP/416168/06-FINAL)
- Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/627/01-FINAL)

- Guideline for the conduct of efficacy studies for intramammary Products for Use in Cattle (EMEA/CVMP/344/99-FINAL-Rev.1)
- VICH GL27 Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance (CVMP/VICH/644/01-FINAL)