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GUIDELINE ON THE SPC FOR ANTHELMINTICS

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EXECUTIVE SUMMARY

This guideline is to draw attention of anyone involved in the anthelmintic treatment of ruminants (sheep, goats and cattle) and horses to the problem of resistance and to help limiting resistance development. It recommends adding standard warnings in the SPC of anthelmintics authorized for these target species, if appropriate.

1. INTRODUCTION (background)

Resistance to anthelmintics is an increasing problem in sheep, goats and horses worldwide and is an emerging problem in cattle. Information on anthelmintic resistance in other animal species is currently more limited. Resistance is reported mainly in gastro-intestinal nematodes (*e.g. Teladorsagia circumcincta* and *Haemonchus contortus* in sheep and goats, Cyathostominae in horses and *Cooperia spp*. in cattle) and, to a lesser extent, in liver fluke (*Fasciola hepatica*) in sheep. In Europe, scientific reports indicate an increase of helminth resistance, to different extents, to all three major classes of anthelmintics (benzimidazoles, imidazothiazoles and macrocyclic lactones). In some European regions, the situation has become so dramatic that anthelmintic resistance threatens the economic viability of some types of animal production : in some UK sheep flocks, for example, populations of gastro-intestinal nematodes have developed resistance to all 3 major classes of anthelmintics [1]. Given that development of new anthelmintics with a novel mode of action in the near future is unlikely to occur, maintaining the efficacy of established anthelmintics appears as a priority. For a review on anthelmintic resistance in Veterinary Medicine, see [2].

In general, genes conferring resistance to a particular anthelmintic appear to exist as rare alleles within a helminth population prior to the first exposure to the anthelmintic. The way anthelmintics are used will determine effectiveness of selection pressure for these resistance genes, thereby favouring, or not, the development of resistance within a population.

Currently, the most widely recognized factors contributing to the development of resistance are the too frequent and repeated use of anthelmintics from the same class over an extended period of time as well as underdosing (which may occur following incorrect administration, underestimation of bodyweight, etc.).

When resistance appears to one anthelmintic in a class, other anthelmintics in the same class (sharing the same mode of action) will generally also be affected.

Adding appropriate standard warnings to the SPC of anthelmintics authorised for ruminants and horses could contribute in delaying the development of resistance to anthelmintics in these animal species.

2. SCOPE

This guideline focuses on the problem of anthelmintic resistance. The objective of it is to draw attention of anyone involved in the anthelmintic treatment of ruminants (sheep, goats and cattle) and horses to the problem of resistance and to help limiting resistance development. This guideline only applies to the SPC of veterinary medicinal products (VMP) containing anthelmintics authorised for (at least one of) the above-mentioned target animal species. .

3. LEGAL BASIS

Directive 2001/82/EC as amended by Directive 2004/28/EC [3] requires that data on the potential emergence of resistant organisms of relevance for clinical use are necessary in the case of veterinary medicinal products, and that, where necessary, measures to limit resistance development from the intended use of the veterinary medicinal product should be proposed (Annex I, Part IV, Chapter I, Section A.2.).

This guideline should be read in conjunction with Directive 2001/82/EC as amended by Directive 2004/28/EC [3], guidelines on the efficacy requirements for anthelmintics [4, 5] as well as the guideline on the SPC for pharmaceuticals [6].

4. MAIN GUIDELINE TEXT

In order to draw attention to the possibility of resistance development when using anthelmintics and to help limiting the development of resistance, the following standard sentences are proposed to be included in the SPC of anthelmintics authorized for either sheep, goats, cattle or horses, where appropriate:

Section 4.4. (Special warnings for each target species):

- The following warnings should always be included:
    - "Strategies that should be avoided because they might lead to an increased risk of development of resistance to anthelmintic drugs include:
        - Too frequent and repeated use of anthelmintics from the same class over an extended period of time
        - Underdosing"
    - "Suspected clinical cases of resistance to anthelmintics should be further investigated using appropriate tests (*e.g*. Faecal Egg Count Reduction Test). Where the results of the test(s) strongly suggest resistance to a particular anthelmintic, an anthelmintic belonging to another pharmacological class and having a different mode of action should be used"
    - "Selection of resistant genes leading to the development of resistance can ultimately result in ineffective anthelmintic therapy."

- *When resistance to (an) active substance(s) contained in the VMP or to (an) active substance(s) from the same class of anthelmintic is demonstrated, using appropriate tests, for at least <u>one species of gastro-intestinal nematodes</u> in Europe, the following standard sentence should be used, taking into account that the different species of gastro-intestinal nematodes are not distinguishable from each other under field conditions, and that many natural infections are mixed ones:*

  "Resistance to <active(s) substance(s)> or to <active substance(s) from the same class of anthelmintic> has developed in gastro-intestinal nematodes in <target animal species> in Europe. Before using this product, seek professional advice on current use recommendations to ensure good control of helminths and to limit further selection for resistance to anthelmintics".

- *When resistance to (an) active substance(s) contained in the VMP or to (an) active substance(s) from the same class of anthelmintic is demonstrated, using appropriate tests, for a particular helminth species (<u>except gastro-intestinal nematodes</u>) in Europe, the following standard sentence should be used:*

  "Resistance to <active(s) substance(s)> or to <active substance(s) from the same class of anthelmintic> has developed in <helminth species> in <target animal species> in Europe. Before using this product, seek professional advice on current use recommendations to ensure good control of helminths and to limit further selection for resistance to anthelmintics".

Section 4.9. Amount(s) to be administered and administration route:

The following warnings should be included, where appropriate:

- "To ensure a correct dosage, body weight should be determined as accurately as possible".
- "For the treatment of a group of animals of the same or of a similar age, the dosing should be done according to the heaviest animal of this group".

DEFINITIONS

Resistance: resistance in a given parasite population is a greater frequency of individuals that are able to tolerate treatment than in a normal population of the same parasite species and is inheritable. [7].

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[3] Directive 2001/82/EC on the Community code relating to veterinary medicinal products, as amended by Directive 2004/28/EC, Official Journal L – 136, 30/04/2004, pp. 58 –84.

[4] Volume 7A: The Rules Governing Medicinal Products in the European Union, Guidelines "Veterinary Medicinal Products: General, efficacy, environment, risk assessment", European Commission, DG Enterprise, 1999, pp. 153-190.

[5] CVMP/VICH/832/99-corr: Efficacy requirements for anthelmintics: overall guidelines.

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[7] Prichard, R.K., Hall, C.A., Kelly, J.D., Martin, I.C.A., Donald, A.D. 'The problem of anthelmintic resistance in nematodes', *Australian Veterinary Journal*, Vol. 56, 1980, pp. 239-250.