European Medicines Agency
Veterinary Medicines and inspections

London, 12 July 2007
Doc. Ref. EMEA/CVMP/EWP/170208/2005

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS (CVMP)

GUIDELINE ON THE SUMMARY OF PRODUCT CHARACTERISTICS FOR ANTHELMINTICS

DRAFT AGREED BY EFFICACY WORKING PARTY (EWP)	May 2006
ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	June 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	December 2006
AGREED BY EFFICACY WORKING PARTY	April 2007
ADOPTION BY CVMP	July 2007
DATE FOR COMING INTO EFFECT	February 2008

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EXECUTIVE SUMMARY

Helminths resistant to the application of anthelmintics have been an issue since the first use of these products in ruminants (sheep, goats and cattle) and horses. The recognition of the existence or possible development of resistance to anthelmintics must be considered in the use of any of these products in these target animal species. The intent of this guideline is to draw attention of anyone involved in the anthelmintic treatment to the fact that the development of resistance is directly affected by the use of anthelmintics. It recommends adding standard warnings in the summary of product characteristics (SPC) of anthelmintics authorised 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 (see below for a definition of resistance). 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, acetylcholine receptor agonists [imidazothiazoles/tetrahydropyrimidines] and macrocyclic lactones [avermectins/milbemycins]). In extreme cases, such as when populations of gastro-intestinal nematodes develop resistance to all 3 major classes of anthelmintics, resistance may threaten the animal welfare and production, due to ineffective therapy. 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.

There are many factors that contribute to the selection of resistant helminths, but currently, the most widely accepted ones 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.). These actions are risk factors because the development of resistant organisms within a population relies on the selection for individual parasites that possess genes that confer survival fitness. These genes may or may not be rare when use of an anthelmintic starts, but the frequency may increase based on the amount of pressure placed on the population by use of anthelmintics. Unfortunately, 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.

The importance of anthelmintic resistance has also been addressed in Commission Directive 2006/130 which establishes criteria for an exemption from a veterinary prescription for products used in food-producing animals. One of these criteria is that there should not be a risk to human or animal health as regards to the development of anthelmintic resistance [1]. Adding appropriate standard warnings to the SPC of anthelmintics authorised for ruminants and horses could also contribute in delaying the development of resistance to anthelmintics in these animal species.

2. SCOPE

The scope is to provide guidance on the warnings to be placed in the SPC of anthelmintics in relation to resistance. This guideline only applies to the SPC of veterinary medicinal products (VMP) containing anthelmintics authorised for the following target animal species: sheep, goats, cattle or horses.

3. LEGAL BASIS

Directive 2001/82/EC as amended by Directive 2004/28/EC [2] 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 [2], guidelines on the efficacy requirements for anthelmintics [3-7], the guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor uses or minor species [8] as well as the guideline on the SPC for pharmaceuticals [9].

4. MAIN GUIDELINE TEXT

The use of anthelmintics to control helminth diseases in cattle, sheep, goats, and horses is indicated for the health and well-being of the animals. This use must be judicious, however; and based on sound veterinary scientific principles. Knowledge of the epidemiology of the helminths and the effects of these parasites on the animals are points to consider. Furthermore, the application of treatments should always be done with an appreciation of the long term effects of the use of the products on the parasite populations. Indeed, one of the consequences of the use of anthelmintics is the possible selection for resistant individual parasites within a population susceptible to the anthelmintic. Over time, it may be possible to allow this subpopulation of parasites to be selected as the dominant parasite population, reducing the effectiveness of the particular anthelmintic. Strategies to limit this selection process should be practiced. Therefore, special warnings have been developed to call attention to some specific principles that should be observed whenever these products are used in either sheep, goats, cattle or horses.

The following standard sentences should be included in the SPC of anthelmintics authorised for one or more of the above-mentioned target species, where appropriate:

Section 4.4. Special warnings for each target species:

- *The following warnings should always be included:*
    - "Care should be taken to avoid the following practices because they increase the risk of development of resistance and could ultimately result in ineffective therapy:
        - Too frequent and repeated use of anthelmintics from the same class, over an extended period of time.
        - Underdosing, which may be due to underestimation of body weight, misadministration of the product, or lack of calibration of the dosing device (if any).
    - "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".

- *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 in Europe, using appropriate tests, for at least one species of gastro-intestinal nematodes or for a particular helminth species (except gastro-intestinal nematodes), 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, that many natural infections are mixed ones, and that "resistance" refers to at least one species of gastro-intestinal nematodes:*
    - "Resistance to <*active(s) substance(s)/class(es) of anthelmintic*> has been reported in <*gastro-intestinal nematodes/helminth species*> in <*target animal species*>. Therefore, the use of this product should be based on local (regional, farm) epidemiological information about susceptibility of the <*nematodes/helminth species*> and recommendations on how 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 administration of a correct dose, body weight should be determined as accurately as possible; accuracy of the dosing device should be checked".

- "If animals are to be treated collectively rather than individually, they should be grouped according to their bodyweight and dosed accordingly, in order to avoid under- or over-dosing".

DEFINITIONS

Resistance: genetically determined decline in the susceptibility of a population of helminths against an anthelmintic substance [10].

REFERENCES (scientific and / or legal)

[1] Commission Directive 2006/130/EC on the establishment of criteria for exempting certain veterinary medicinal products for food-producing animals from the requirement for a veterinary prescription. Official Journal L – 349/15, 12.12.2006.

[2] 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.

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

[4] CVMP/VICH/833/99: Efficacy of anthelmintics: specific recommendations for equines.

[5] CVMP/VICH/839/99: Efficacy of anthelmintics: specific recommendations for bovines.

[6] CVMP/VICH/840/99: Efficacy of anthelmintics: specific recommendations for ovines.

[7] CVMP/VICH/839/99: Efficacy of anthelmintics: specific recommendations for caprines.

[8] EMEA/CVMP/EWP/117899/2004: Guideline on Efficacy and Target Animal Safety data requirements for Veterinary Medicinal Products intended for Minor Uses or Minor Species.

[9] EMEA/CVMP/065/05: Guideline on the Summary of the Product Characteristics for Pharmaceutical Veterinary Medicinal Products.

[10] Sangster NC, Gill J. Pharmacology of anthelmintic resistance. Parasitology Today, Vol. 15, 1999, pp. 141–146.