EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory tools (SPC and Product Literature)

Current regulatory requirements when authorising anthelmintics

Current standard information included in the SPC / PL

Presented by Stephan Steuber on 13 June 2016
Veterinary Specialist in Parasitology, *dipl*EVPC
Federal Office of Consumer Protection and Food Safety (BVL), Berlin, Germany

Scope:

- Current regulatory requirements for Marketing Authorisation of anthelmintics (Focus on Resistance)
- Current standard information included in the PL (SPC, Package Leaflet) in relation to resistance
- Potential shortcomings related to standard SPC information

I. Current regulatory requirements for marketing authorisation of anthelmintics (Focus on Resistance)

VICH GL7 (Efficacy requirements for anthelmintics: general requirements)

- Dose determination studies using the dose limiting parasite species in a dose range of 0, 0.5, 1 and 2 x of the anticipated dose, at least 6 adequately infected animals (per group
- Minimum 2 controlled dose confirmation studies per species and stages to verify efficacy (non resistant strain), at least 6 adequately infected animals per group.
- For broad spectrum anthelmintics with residual activity at least 2 studies are necessary per species to demonstrate persistence claims.
- Field studies or a multicentre study, considering (i) the animal species, geographic location and regional situation. A minimum of 25 % animals serves as a control (untreated or treated with a registered anthelmintic)
- **Claims for resistant endoparasites: not yet available!**

II. Current regulatory requirements for marketing authorisation of anthelmintics (Focus on Resistance)

Efficacy for anthelmintics: specific recommendations

VICH GL12/13/14 : anthelmintics bovines, ovines, and caprines:

VICH GL15 : anthelmintics horses:

VICH GL16 : anthelmintics porcine:

VICH GL19/20: anthelmintics felines and canines:

- **Guidance for claims for resistant endoparasites: not yet available!**

III. Alternative Guidelines for evaluating the efficacy of anthelmintics in ruminants (W.A.A.V.P., 2nd Edition, 1995)

5.4 Anthelmintic resistant trials to determine the efficacy of a product against nematodes resistant to other anthelmintics. One controlled efficacy study only against a specific resistant strain.

Trial design recommended to determine activity of a product against a specific resistant strain

Group no.	Parasite	Treatment
1	Resistant strain	Test product
2	Resistant strain	Commercial product
3	Resistant strain	Untreated control
4	Susceptible strain	Test product
5	Susceptible strain	Commercial product
6	Susceptible strain	Untreated control

III. Examples

III.1 Startect Dual® *National Procedure, UK*

Drench: 2mg derquantel and 0.2 mg abamectin/ml for sheep

4.2 Indications for use, specifying the target species

Dictyocaulus filarial (adult): This product is effective against strains of parasites resistant to benzimidazoles, levamisole, macrocyclic lactones, and combinations of these.

III.2 Flukiver Combi® *Decentralised Procedure*

Drench: 10 mg closantel and 15 mg/kg mebendazole for sheep

4.2 Indications for use, specifying the target species

Haemonchus contortus (adults, immatures, inhibited stages and BZ-resistant strains)

III. Examples

III.3 Zolvix® *Centralised Procedures*

Drench: 25 mg Monepantel/ml for sheep

5.1 Pharmacodynamic properties:

ZOLVIX was shown to be effective against strains of gastro-intestinal parasites……resistant to (pro)-benzimidazoles, levamisole, morantel, M L and *H. contortus* strains resistant to salicylanilides. … The product was shown to be effective against 4th stage larvae of a strain of *H. contortus* in a laboratory study where a combination of abamectin with derquantel was not effective.

Guideline on the Summary of Product Characteristics for Anthelmintics (2008)

The following warnings should always be included in section 4.4. Special warnings for each target species:

"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."

Guideline on the Summary of Product Characteristics for Anthelmintics (2008)

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"

Guideline on the Summary of Product Characteristics for Anthelmintics (2008)

The following warnings should be included in section 4.9. Amount(s) to be administered and administration route, 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 overdosing”.

Potential shortcomings related to SPC information

- Compliance?
- The current resistance situation is sometimes not correctly reflected in the SPC. (update?)
- Grouping according to the BW of the animals in order to avoid under- or overdosing is sometimes difficult to follow.
- Recommendations is very general: repeated use of anthelmintics from the same class, over an extended period of time.
- Classification of an active substance to a certain group having the same mode of action might be a challenge for some farmers.
- The Faecal Egg Count Reduction Test is still not used to any relevant extent in common animal husbandry. For certain helminth species (cestodes, liver flukes) resistance is difficult to identify using the FECRT.

Thank you for your attention

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
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