EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2022
EMA/CVMP/VICH/840/1999
Committee for Veterinary Medicinal Products (CVMP)

VICH GL13 Efficacy of anthelmintics: specific recommendations for ovines (Revision 1)

Draft

Draft agreed by VICH Steering Committee	May 2022
Adoption by CVMP for release for consultation	15 June 2022
Start of public consultation	24 June 2022
End of consultation (deadline for comments)	1 November 2022

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International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL13 (ANTHELMINTICS OVINES)
May 2022
Revision at Step 9
For consultation at Step 4

EFFICACY OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR OVINES (REVISION 1)

Revision at Step 9

Recommended for Consultation at Step 4 of the VICH Process
in May 2022
by the VICH Steering Committee

This Guideline has been developed by the appropriate VICH Expert Working Group will be subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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EFFICACY OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR OVINES

INTRODUCTION

These guidelines for ovines were developed by the Working Group established by the Veterinary International Cooperation on Harmonization (VICH), Anthelmintic Guidelines and subsequently revised in 2022. They should be read in conjunction with the VICH Efficacy of Anthelmintics: General Requirements (VICH GL7) which should be referred to for discussion of broad aspects for providing pivotal data to demonstrate product anthelmintic effectiveness. The present document is structured similarly to VICH GL7 with the aim of simplicity for readers comparing both documents.

The aim of the guidelines for ovines is (1) to be more specific for certain specific issues for ovines not discussed in VICH GL7; (2) to highlight differences with VICH GL7 on efficacy data requirements and (3) to give explanations for disparities with VICH GL7.

It is also important to note that technical procedures to be followed in the studies are not the aim of this guideline. We recommend to the sponsors to refer to the pertinent procedures described in detail in other published documents e.g. WAAVP Second Edition of Guidelines for Evaluating the Efficacy of Anthelmintics in Ruminants (Bovine, Ovine, Caprine) Veterinary Parasitology 58: 181-213, 1995, and updated versions as they are published.

A. General Elements

1 - The Evaluation of Effectiveness Data

Only controlled tests based on parasite counts of adults/larvae are acceptable both for the dose determination and dose confirmation studies, since critical tests generally are not considered to be reliable for ruminants. Egg counts/larval identification is the preferred method to evaluate the effectiveness in field studies. Long-acting or sustained-release products should be subject to the same evaluation procedures as other therapeutic anthelmintics. Adequate parasite infection should be defined in the protocol according to regional prevalence or historical data and/or statistical analysis.

2 - Use of Natural or Induced Infections

Dose determination studies generally should be conducted using induced infections with either laboratory strains or recent field isolates. If no infection model exists for a parasite species (*Protostrongylidae*, cestodes, *Dicrocoelium* spp.), the use of natural infections instead of induced infections is justified.

Dose confirmation studies should be conducted using naturally infected animals, however, induced infections or superimposed induced infections can also be used. This procedure will allow a wide range of parasites to be present. For claims against 4th stage larvae, induced infections must be used. For claims against hypobiotic larvae, only natural infections can be considered. Sponsors should aim for a maximum period of accumulation of hypobiotic larvae for the particular parasite species being targeted in trial animals. This will be area or regionally dependent. Specific details on area or regional situations should be obtained from experts on a case by case basis, if needed. In all cases, animals need to be housed (to preclude reinfection) for a minimum of 2 weeks before treatment.

Persistent efficacy studies should be conducted using induced infections with recent field isolates. The history of the parasites used in the induced infection studies should be included

in the final report.

3 - Number of Infective Parasitic Forms Recommended for Induced Infections

The number to be used is approximate and will depend on the isolate that is used. The final number of larvae used in the infection should be included in the final report. Table 1 shows the range of numbers recommended for parasites with existing infection models.

Table 1 - Number of Infective Stages Used to Produce Adequate Infections in Sheep for Anthelmintic Evaluation

Parasite Anatomical Location *Genus Species*	Range of eggs/larvae
Abomasum	
Haemonchus contortus	400 – 4,000
Teladorsagia circumcincta	6,000 – 10,000
Trichostrongylus axei	3,000 – 6,000
Intestines	
Cooperia curticei	3,000 – 6,000
T. colubriformis & *T. vitrinus*	3,000 – 6,000
Nematodirus spp.	3,000 – 6,000
Oesophagostomum spp.	500 – 1,000
Chabertia ovina	800 – 1,000
Bunostomum trigonocephalum	500 – 1,000
Strongyloides papillosus	80,000
Gaigeria pachyscelis	400
Trichuris spp.	1,000
Lungs	
Dictyocaulus filaria	1,000 – 2,000
Liver	
Fasciola hepatica (metacercaria)	
	100 - 200 (chronic)
	1,000 – 1,500 (acute)

4 - Recommendations for the Calculation of Effectiveness

4.1 Criteria to Grant a Claim

To be granted a claim the following pivotal data should be included:

a) Two dose confirmation studies conducted with a minimum of six adequately infected non-medicated animals (control group) in each study. The infection of the animals in the study will be deemed adequate based on historical, parasitological and/or statistical criteria.

b) The differences in parasite counts between treated and control animals should be statistically significant ($p \leq 0.05$).

c) Percent efficacy should be 90% or higher and calculated and interpreted using the procedures described in Section 4.2 of VICH GL7.

4.2 Number of Animals (Dose Determination, Dose Confirmation and Persistency trials)

The minimum number of animals required per experimental group is a critical point. Although the number of animals will depend on the possibility to process the data statistically according to adequate statistical analysis, it has been recommended, to achieve harmonization, that the inclusion of at least 6 animals in each experimental group is a minimum.

In cases where there are several studies none of which have 6 adequately infected animals

in the control group (for example, important rare parasites), the results obtained could be pooled to accumulate 12 animals in the studies; and statistical significance calculated. If the difference is significant ($p<0.05$), effectiveness may be calculated and if the infection is deemed adequate, the claim may be granted. Sampling techniques and estimation of worm burden should be similar among laboratories involved in the studies to allow adequate and meaningful extrapolation of the results to the population.

4.3 Adequacy of Infection

The minimum adequate number of helminths in individual control animals should be defined in the protocol. However, final conclusions regarding adequacy of infection will be made as part of the final report based on statistical analysis, historical data, literature review, or expert testimony. The range of ovine helminths (adults) that has been considered adequate to grant a claim will vary according to the species. Generally, a minimum of 100 nematodes in individual control animals is considered an adequate infection. Lower individual counts are to be expected with *Bunostomum* spp., *Oesophagostomum* spp., *Trichuris* spp., *Gaigeria pachyscelis* and *Dictyocaulus filaria*. For *Fasciola* spp. minimum counts of 20 adults are considered adequate.

4.4 Label Claims

For adult claims as a general rule, the treatment should not be administered earlier than 21 to 25 days after infection; optimum for most species is 28 to 32 days. Major exceptions are *Oesophagostomum* spp. (28 to 41 days), *Bunostomum* spp. (52 to 56 days), *Strongyloides papillosus* (14 to 16 days) and *Fasciola* spp. (8 to 12 weeks).

For L4 claims, treatments should be given on the following days after infection: 3 to 4 days for *Strongyloides papillosus*, 5 to 6 days for *Haemonchus* spp., *Trichostrongylus* spp. and *Cooperia* spp., 7 days for *T.(O.) circumcincta*, 8 to 10 days for *Nematodirus* spp., and *D. filaria* and 15 to 17 days for *Oesophagostomum* spp. The term immature on the labelling is not acceptable for these claims.

For early immature *Fasciola* spp., treatments should be given 1 to 4 weeks after infection and for late immatures at 6 to 8 weeks.

5 - Treatment Procedures

The method of administration (oral, parenteral, topical, slow-release etc.), formulation and extent of activity of a product will influence the protocol design. It is advisable to consider the weather and animal relationship with regard to effectiveness of topical formulations. Slow-release products should be tested over the entire proposed effective time unless additional information suggests that this is unnecessary, e.g. blood levels demonstrate steady state at all points of the proposed therapeutic period.

When the drug is to be administered in the water or in a medicated feed, it should be done as much as possible following the labelling recommendations. Palatability studies may be required for medicated feed. Samples of medicated water or feed should be collected to confirm drug concentration. The amount of medicated product provided to each animal should be recorded to ensure that the treatment satisfies the label recommendations. For products used topically, the impact of weather (e.g. rainfall, UV light), and coat length should be included in the evaluation of the effectiveness of the product.

6 - Animal Selection, Allocation and Handling

Test animals should be clinically healthy and representative of the age, sex, and class for which the claim of the test anthelmintic is to be made. In general, the animals should be ruminating, and older than 3 months of age. Randomization to treatment group should be performed using

an adequate method that should be described in the protocol and final report. Blocking should only be employed if it is expected to reduce residual error in the study. If blocking is used, blocks should be included as a random effect in the statistical model. Nevertheless, blocking is not always the most appropriate method for reducing residual error. Alternative methods may therefore be considered e.g. a suitably selected covariate.

For induced infections, the use of helminth naive animals is recommended. Animals not raised in a helminth-free environment should be treated with an approved anthelmintic, chemically not related to the test drug, to remove pre-existing infections followed by faecal examination to determine that the animals are helminth free.

Animal housing, feeding and care should follow strict requirements of welfare, including vaccination according to local practices. This information should be provided in the final report. A minimum 7-day acclimatisation period is recommended. Housing and feed/water should be adequate according to the geographical location. Animals should be monitored daily to determine adverse reactions.

B. Specific Evaluation Studies

1 - Dose Determination Studies

No species specific recommendations.

2 - Dose Confirmation Studies

Confirmation studies are needed to support each claim: adult, larvae and when applicable hypobiotic larvae.

3 - Field Efficacy Studies

The field studies should be replicated in different geographic locations and in animal/production class(es) that represent the conditions of use for the indication being pursued. The protocol should state the number of experimental units per treatment group (sample size), describe allocation (proportion) to treatment groups, and include a brief description of how the sample size was determined. The protocol should also describe procedures for random selection of animals (number and percentage) to be sampled (if faecal samples will not be collected from all available animals in the study), as appropriate, and the methods to be used for both faecal collection and examination. Regardless of whether one or multiple parasites are being evaluated within a study, an appropriate sample size calculation or justification is necessary prior to study conduct.

Effectiveness against adult nematodes can be assessed by the reduction of faecal egg counts and should be performed using samples from the same animal before and after treatment in both study groups (control and treated). Post-treatment counts are generally made 10-14 days after treatment, but the timing of post-treatment counts will depend on the parasite species and class of anthelmintic evaluated. For example, due to the known effects of macrocyclic lactones on nematode egg suppression, post-treatment counts should be delayed until at least 14 days or longer. Efficacy should be calculated using post-treatment faecal egg counts from the treated and control (typically placebo or untreated control) groups. Additionally, a calculation of efficacy using pre- and post-treatment faecal egg counts may provide further information on field effectiveness. Furthermore, additional endpoints for evaluating field effectiveness should be considered as they are developed and generally accepted by experts in veterinary parasitology.

See also Sections 4.1 and 4.2 of VICH GL7.

4 - Persistent Efficacy Studies

Two basic study designs have been used to pursue persistent efficacy claims: one using a single challenge, another using multiple daily challenges following treatment. For both procedures, no standardised protocols have been developed. When conducting studies, protocols details should include among other things: determination of larval viability throughout the study, rationale for larval challenge and justification of slaughter time. Parasite naive sheep are recommended in these studies. A study design is recommended using multiple daily challenges, as this most closely mimics what occurs in nature.

A minimum requirement for a persistent efficacy claim (for each duration and helminth claim) should include 2 trials (with worm counts) each with a non-treated and one or more treated groups. At least 6 animals in the control group shall be adequately infected. Persistent efficacy claims will only be granted on a species-by-species basis.

In the protocol using multiple daily challenges, different groups of animals are treated and exposed to a daily natural or induced challenge for 7, 14, 21 or more days after the treatment, then at approximately 3 weeks after the last challenge (or earlier) the animals are examined for parasite burden. The challenge interval and schedule may vary for longer acting products, and should take into consideration the pharmacological properties of the product.

Persistent efficacy claims should be supported by a minimum 90% efficacy at each time point and calculated and interpreted using the procedures described in Sections 4.1 and 4.2 of VICH GL7. Persistent efficacy claims should be granted for the longest period between treatment and the last challenge where effectiveness criteria are met and all preceding time points tested meet the criteria as well.