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Committee for Medicinal Products for Veterinary Use (CVMP)

Questions and answers on the CVMP guideline on the "Testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats" (EMEA/CVMP/005/00-Rev.2)

The aim of this document is to provide clarification and harmonisation of the CVMP Guideline on "Testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats (EMEA/CVMP/005/00-Rev 2)", which was published in 2007.

Question 1:

What are the data requirements for a marketing authorisation of a generic ectoparasiticidal product for external topical use in dogs and cats which is only locally acting?

Answer:

The CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (CVMP/016/2000 Rev. 2) only concerns pharmaceutical forms acting systemically and, therefore, generic products like topical use ectoparasiticides with local activity are not covered by this guideline. Also, the guideline on ectoparasiticides for the treatment and prevention of flea and tick infestations does not cover generic products and can only be used partly for such applications. Therefore, the aim of this document is to provide guidance for the determination of efficacy and safety for generic ectoparasiticidal products that are for external or topical use only. Such applications are usually submitted under Art. 13(3) of Directive 2001/82/EC, as amended, as so called "hybrid applications".

Efficacy

Usually, the efficacy of a proposed antiparasitic product should be confirmed in two controlled clinical studies per parasite species on the target animal species. To reduce the number of clinical trials and to avoid unnecessary use of animals in experiments for "generic" antiparasitic products with local activity only, at least the following data package should be provided for dose confirmation:

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The efficacy of a proposed generic product should be confirmed in one controlled dose confirmation study (GCP) for each parasite species proposed for the generic product, on the target animal. Studies can be combined (max. two parasite species in one study), e.g. infestation with both *Ct. felis* and e.g. *I. ricinus* in one study.

The origin of tick and flea population used should be representative of the current European field situation. With respect to fleas, *Ct. felis* is known to be the most prevalent species on dogs and cats, and the flea species that can be routinely reared in laboratories.

The controlled clinical studies should be in accordance with the provisions of the above mentioned ectoparasiticide guideline. Insecticidal/acaricidal efficacy of at least 95% (fleas) and at least 90% (ticks), respectively, to be based on arithmetic means, should be achieved for the entire treatment period claimed by the applicant. Comparison to a reference product is not necessary as evaluation of efficacy is based on the threshold values specified in the guideline. The applicant needs to demonstrate the efficacy of the product in every target species for which a claim is made, e.g. in both dogs and cats. The evaluation of the persistent efficacy will be based on the proven duration of efficacy in the controlled clinical studies and cannot be longer than that of the reference product unless there is respective proof from both a second dose confirmation study for each parasite species and adequate field studies. Otherwise, field studies are not considered mandatory.

No extra study for flea allergy dermatitis (FAD) would be requested provided suitable persistence of efficacy against fleas was confirmed.

The option to confirm efficacy of a generic topically applied ectoparasiticide by using two controlled laboratory studies with the least susceptible tick species determined *in vitro* is not considered satisfactory, because there are currently no validated *in vitro* methods available for ticks, and correlation between *in vivo* and *in vitro* results is absent.

Tolerance

In general, local tolerance data should be provided according to the requirements of the “Guideline on target animal safety for veterinary pharmaceutical products (EMEA/CVMP/VICH/393388/2006)”.

Systemic tolerance should also be investigated if the composition of the generic product is different from the reference product, in particular if the absorption of the active substance(s) in a generic product is expected to be higher than that of the reference product (e.g. because of a different composition or concentration), unless otherwise justified.

Efficacy or tolerance studies are not considered necessary in the case that a generic product has the identical composition to the reference product (i.e. contains the same active substance(s) and excipient(s) in the concentrations as the reference product) and is to be administered at the same dose and route of administration. It should be confirmed that the pharmaceutical quality of the generic is identical to the reference product. In case there is a difference in the qualitative or quantitative composition, [clinical/dose confirmation] studies will normally be requested and may be waived only in case of very minor changes which could have no impact on the potential absorption, the rate and extent of distribution and persistence of the active substance(s).

Question 2:

By which mean (arithmetic or geometric) should efficacy be calculated in laboratory studies, using the Abbott's formula?

Answer:

CVMP considers the arithmetic mean the only appropriate tool for estimating efficacy of ectoparasiticides in the treatment and prevention of tick and flea infestations in controlled clinical studies in dogs and cats.

For such studies, there is no exceptional situation which would justify the use of geometric means, for the following reasons:

- The argument mostly used for justifying the use of geometric means is, that the distribution of parasite count data for treated animals is right-skewed (i.e. on the majority of animals there are only a few or no parasites left after treatment while only a few treated animals show a larger parasite burden), and the central tendency of right-skewed data is best described by their geometric mean.
- However, in laboratory studies for ticks and fleas all animals will be infested artificially with the same number of ectoparasites. In addition, randomisation of animals is performed after initial block ranking ensuring homogeneous infestation status within the groups. Thus – in contrast to endoparasites – skewed distributions can only be expected for treated groups after treatment, but not for untreated groups, and for none of the groups at the beginning of the trial.
- Efficacy estimates calculated by Abbott's formula and using geometric means tend to be biased upwards while the use of arithmetic means resulted on average in efficacy estimates very close to the true efficacy. This was shown by Dobson et al. (2009) by Monte Carlo simulation of faecal egg counts. It should be noted that this was true although the count data distributions were skewed. The simulation was on endoparasites; however, the conclusions are also valid for ectoparasites because efficacy is calculated in the same way. One can easily perform similar simulations involving counts typical for fleas and ticks, and this shows a similar bias upwards when using geometric means.
- An additional observation is that efficacy estimates based on geometric means tend to mask treatment failures. McKenna (1998) describes several trials - though on endoparasites in sheep, but the calculations are the same for ectoparasites - with large discrepancies between the efficacies based on geometric and arithmetic means. As a consequence, geometric mean based efficacies do not describe the proportion of parasites being killed and, thus, might be misinterpreted.

References:

Dobson RJ et al. (2009). Geometric means provide a biased efficacy result when conducting a faecal egg count reduction test (FECRT). Veterinary Parasitology 161, 162-167.

McKenna PB (1998). What do anthelmintics efficacy figures really signify? New Zealand Veterinary Journal 46, 82-83.