7 December 2017
EMA/CVMP/EWP/158889/2017
Committee for Medicinal Products for Veterinary Use (CVMP)

Concept paper for the revision of the guideline on the summary of product characteristics for anthelmintics

Draft

Agreed by Efficacy Working Party (EWP-V)	September 2017
Adopted by CVMP for release for consultation	8 December 2017
Start of public consultation	15 December 2017
End of consultation (deadline for comments)	31 March 2018

The proposed guideline will replace the current CVMP guideline on the summary of product characteristics for anthelmintics (EMEA/CVMP/EWP/170208/2005).

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

Keywords	anthelmintic, resistance, veterinary, SPC

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1. Introduction

The current guideline on the Summary of Product Characteristics (SPC) for anthelmintics (EMEA/CVMP/EWP/170208/2005) recommends standard warnings aimed at delaying the development of anthelmintic resistance. The scope of the guideline is currently limited to products for sheep, goats, cattle and horses, and proposes standard text for sections 4.4 and 4.9 of the SPC.

Since its introduction in February 2008, the guideline has been applied to most new applications and renewal procedures and possibly also, on the occasion of variations.

In April 2017, the CVMP adopted a Reflection Paper on anthelmintic resistance in the EU (EMA/CVMP/EWP/573536/2013), with a series of recommendations for actions aimed at reducing the risk of resistance emergence. Among the actions proposed, the reflection paper recommends the revision of the guideline on the SPC for anthelmintics and highlights several issues more specifically.

2. Problem statement

The scope of the guideline should be extended to host species other than ruminants and horses, e.g. to pigs and companion animals. In those additional species, resistance emergence is reported in some helminths in given geographical areas.

The provisions of the current guideline do not sufficiently promote the sustainable integration of anthelmintic treatments and herd management strategies, in order to reduce the overall selection pressure and to maintain unexposed, susceptible parasite populations i.e., *refugia*. This would notably consist of targeted (selective) treatment of individual animals based on an appropriate diagnosis, or of pasture management measures.

In the general context of targeted treatment, clearer SPC recommendations are also needed on the correct use of fixed combination products containing substances with different activity spectra.

The guideline revision should also address the SPCs of multi-active products (i.e. products containing a combination of substances with different mechanisms of action but targeting the same worm species), which are under development. Furthermore, there is a lack of SPC guidance in relation to anthelmintic products with claims for efficacy against worms with acquired resistance to other anthelmintic classes.

In a general manner, the revision should aim to provide clear harmonized text, with the purpose to prompt a rational use of anthelmintic products, while not unnecessarily extending or overloading the SPC text. Furthermore, the guidance should be flexible, so as to take into account the fact that resistance prevalence, mechanisms and detection are evolving matters.

3. Discussion (on the problem statement)

The scope of the guideline should be extended to other species, e.g. pigs and non-food producing species. Due to the limited information currently available, future guidance in relation to other species would be restricted to general, standard recommendations aiming at delaying resistance emergence or at informing the user on reported resistance situations.

A consensus should be sought in regard of the definition of the terms “infection” and “infestation”. It appears that both are used in SPCs for a same parasite type.

Section 4.2 (Indications)

- Appropriate statements should be proposed to clarify that the use of fixed combination products with the purpose of extending the activity spectrum, is restricted to situations where each of the active substances is required at the time of administration.

Section 4.4 (Special warnings)

- Several herd/pasture management strategies have been identified that could help delaying the development of anthelmintic resistance. The elaboration of standard general advice encouraging appropriate pasture or habitat management, as a direct way to favour *refugia*, and/or as the necessary adjunct to targeted and less frequent use, should be considered.
- Emphasis should be put on promoting targeted treatment at an individual or at herd level. The product literature should encourage users to administer treatment based on the confirmation of the parasite species, life cycle stage and worm burden, on the observed clinical signs, and/or on solid epidemiological information. SPC recommendations for routine or systematic treatment (e.g. at some period of the year or in some defined animal categories) should no longer be accepted unless clearly justified both from an epidemiological and prudent use point of view.

  Current recommendations in section 4.4 should be reviewed. In particular, the sentence "[…avoid…] too frequent and repeated use of anthelmintics from the same class, over an extended period of time" could be perceived as unclear and too general and therefore, may not be effective; in addition, it is of note that the benefit of anthelmintic class rotation in terms of resistance prevention seems not to have been formally demonstrated.
- The current guideline states that suspected cases of resistance should be further investigated using appropriate tests (e.g. FECRT). This recommendation is still appropriate but could be completed by advice to investigate the underlying mechanism, where a suitable method is available and where this is relevant to treatment.
- The current recommendation to investigate cases of suspected lack of expected efficacy (SLEE) could be extended e.g. to encourage users to perform systematic post-treatment check-ups when possible, and to report SLEEs when appropriate.

Section 4.9 (Amounts to be administered, administration route)

- The current advices in sections 4.4 and 4.9 for careful weighing and administration technique in order to avoid underdosing might be collated in section 4.9, in one or a few clear and brief sentences.
- There may be a need for specific warnings relating to given product formulations. For example, the conditions to optimize the consistency of efficacy of pour on formulations could be addressed. Also, recommendations could be considered in relation to the frequency and optimal timing of administration of long-acting formulations.

Section 5.1 (Pharmacodynamic properties)

- In line with the SPC guideline for pharmaceuticals, information on resistance should be included in section 5.1. The information required to populate this section (e.g. prevalence, mechanisms and genetics, reported cross-resistance), and the type and amount of supporting data, might be specified for anthelmintic products, taking into account the evolving character of such matters.
- The future guideline should consider the information in the CVMP Question and Answer document on the information contained in section 5.1 of the SPC (EMA/CVMP/757903/2016),

stating that this section should not contain information that would constitute a new indication or a widening/restriction of an approved indication.

- It should be considered whether to make specific recommendations regarding the information to be included in section 5.1 (and/or possibly also in other sections) in the case of multi-active products (i.e. products containing a combination of substances with different mechanisms of action but targeting the same worm species).

Section 6.2 (Pack sizes)

- The availability of appropriate pack sizes is linked to the risk of misuse by animal owners; this issue should be addressed when elaborating the guideline.

It will be useful also, to define in which SPC section, and under which form, claims may be made for efficacy against worms with acquired resistance to other anthelmintic classes. Notably this should take into account the fact that in principle, there is always a possibility that multiple resistance emerges involving also the active substance under assessment.

4. Recommendation

The CVMP recommends a revision of the existing guideline, in view of concerns in regard of resistance development, and in order to clarify some aspects that are currently not adequately addressed in the current guideline.

5. Proposed timetable

7 December 2017	Concept paper adopted by CVMP for release for consultation
31 March 2018	Deadline for comments from interested parties
2019 (tbc)	Expected date for adoption of the draft revised guideline by EWP-V
2019 (tbc)	Expected date for adoption of the draft revised guideline by CVMP for release for consultation

6. Resource requirements for preparation

Preparation of the revision would involve one rapporteur assisted by two co-rapporteurs. Preparation of the draft revised guideline will require discussion at approximately 4 EWP-V plenary meetings.

Drafting group meetings (virtual) will be organised, as needed.

7. Impact assessment (anticipated)

The revised guideline is not intended to increase the requirements for marketing authorisation applications regarding the type or amount of data. It is expected to assist applicants and assessors in preparing clear product literature, with a view to promoting the correct use and accurately informing the user.

8. Interested parties

Veterinary pharmaceutical industry and consultants, regulatory authorities, veterinarians and veterinary scientific associations (e.g. European Veterinary Parasitology College (EVPC), Federation of

Veterinarians of Europe (FVE), World Association for the Advancement of Veterinary Parasitology (WAAVP), International Federation for Animal Health Europe (IFAH-Europe), as well as other professionals concerned with the use of anthelmintics and with anthelmintic resistance from the use anthelmintics in veterinary medicine.

9. References to literature, guidelines, etc.

CVMP Guideline on the Summary of Product Characteristics for anthelmintics (EMEA/CVMP/EWP/170208/2005)

CVMP Reflection paper on anthelmintic resistance (CVMP/EWP/573536/2013)

CVMP Question and answer on the information contained in section 5.1 of the SPC on pharmacodynamic properties for pharmaceutical products (EMA/CVMP/757903/2016)

SPC guideline for pharmaceuticals, Notice to Applicants, Volume 6C