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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Veterinary Use (CVMP)

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

Concept paper agreed by Efficacy Working Party (EWP-V)	September 2017
Adopted by CVMP for release for consultation	7 December 2017
Start of public consultation	15 December 2017
End of consultation (deadline for comments)	31 March 2018
Revised concept paper agreed by Efficacy Working Party (EWP-V)	24 March 2021
Adopted by CVMP for release for consultation	15 April 2021
Start of second public consultation	22 April 2021
End of consultation (deadline for comments)	31 May 2021

Once drafted, 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	Antiparasitic, anthelmintic, ectoparasiticide, resistance, veterinary, SPC, product information

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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 (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.

A concept paper proposing the revision of the existing guideline on the SPC for anthelmintics was already released by the CVMP for public consultation in 2017; however, due to the Agency's relocation to Amsterdam, CVMP working parties had to discontinue their work. With the restart of work by CVMP working parties in 2020, and the new Regulation (EU) 2019/6 on veterinary medicinal products in force, more emphasis is now put on the need to limit the development of antiparasitic resistance. It is therefore proposed to extend the scope of the revision of the current guideline on the SPC for anthelmintics further, to also include other antiparasitic veterinary medicinal products.

A draft CVMP Reflection paper on resistance in ectoparasites is currently publicly available (EMA/CVMP/EWP/310225/2014). This reflection paper recommends that guidance should be developed as to what (scientifically supported) risk mitigation measures should be included in the SPC of these products.

2. Problem statement

There is a need to develop SPC guidance with a view to limit resistance development in the various types of parasites of veterinary importance, and not only in helminths.

Very few systematic monitoring systems currently exist in the EU that evaluate resistance prevalence in parasites, and published information in that regard is incomplete. Except for some helminth species, there is hardly any reliable diagnostic tool that can be used under practical field conditions, and knowledge on resistance mechanisms and selection is scarce. Nevertheless, resistance against antiparasitic substances contained in veterinary medicinal products is increasing worldwide, and providing a frame for the inclusion of appropriate information and instructions for use in their SPC is considered beneficial for all types of antiparasitic products.

Besides, it is expected that most recommendations will apply similarly to the different types of antiparasitic substances, and many products act against several types of parasites. Therefore, the scope of the current guideline should be enlarged to encompass all antiparasitic veterinary medicinal products, including notably, products acting against ectoparasites.

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

The provisions of the current guideline do not sufficiently promote the sustainable integration of antiparasitic treatments and herd or husbandry management strategies in order to reduce the overall selection pressure and to maintain unexposed, susceptible parasite populations, i.e. *refugia*. The

product information should better encourage targeted (selective) treatment of individual animals based on an appropriate diagnosis, together with pasture or husbandry 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 parasite species).

Furthermore, there is a lack of SPC guidance in relation to products with claims for efficacy against parasites with acquired resistance to other antiparasitic classes.

The revised guidance should also take into account the new requirements set out by Regulation (EU) 2019/6 in terms of structure of the SPC.

In a general manner, the revision should aim to provide a clear harmonised text, with the purpose to prompt a rational use of antiparasitic 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 all parasite species (i.e. include ectoparasites).

The guideline should include target species other than ruminants and horses, e.g. pigs, poultry and companion animals. Depending on the amount of scientific information currently available, future guidance in relation to other target species may be restricted to general, standard recommendations aimed at promoting prudent use 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.

Indications

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

Special warnings in relation to efficacy

- In farm animals, several herd/pasture management strategies have been identified that could help to delay the development of antiparasitic 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.
- In particular for ectoparasites, specific SPC instructions that focus on the need or possibility to target the parasite (or specific insect or acarid stages in the animal's surroundings) with appropriate products or devices could 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 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 antiparasitic class rotation in terms of resistance prevention seems not to have been formally demonstrated.

Similar general prudent use statements are actually used in the SPCs of ectoparasiticidal products, and should be discussed in order to come to an agreement on a standardised text, being as concrete as possible to the user, and to set a frame for more specific recommendations on targeted and evidence-based treatment schedules.

In the case of parasites in companion animals, prophylactic use is particularly common, and special attention should be payed to potential recommendations as to the appropriateness of such preventive use, while keeping in mind a potential zoonotic risk.

Where possible, the recommendations for more targeted treatment or prophylaxis should derive from specific data on the concerned product and parasite(s). The inclusion of general principles pertaining to good veterinary practice should be avoided.

- In the case of companion animals, the soundness of the general recommendation to treat all animals in the same household could be considered. While this may avoid unnecessary product use because of re-infestation, depending on the epidemiology of the concerned parasitic disease, this may also be viewed as promotional and rather relevant to case-by-case assessment.

- The current guideline states that suspected cases of resistance should be further investigated using appropriate tests (e.g. FECRT - Faecal Egg Count Reduction Test). This recommendation is still appropriate but could be completed by advice to investigate the underlying resistance mechanism, where a suitable method is available and where this is relevant to treatment.

  Adapted advice could also be elaborated in relation to suspected cases of resistance in ectoparasites, depending on the availability of reliable test methods.

- 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.

Amounts to be administered, administration route

- The current advice in SPC sections 4.4 and 4.9 for careful weighing and administration technique in order to avoid underdosing might be collated in a same section, 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 the administration of long-acting formulations.

- Parasiticides are often used for routine prophylaxis during extended periods of time, i.e. with continuous re-treatments. Based on the general notion that increased exposure increases the risk for resistance development, the recommended treatment frequency should be carefully

considered, and recommendations to limit and/or guide such repeated use should be contemplated.

In the context of the treatment of existing infections, it should be ensured that adequate user instructions are given regarding the need for several administrations (possibly based on follow-up examinations).

- In line with the specific indications of combination products, it is considered adequate to recommend the use of narrow spectrum products as soon as the use of a combination or broad-spectrum product can no longer be justified by the presence of mixed infections or risk thereof. An appropriate standard wording and/or section could be sought, while avoiding redundancies where possible.

Pharmacodynamic properties

- In line with the Guideline on the SPC for pharmaceutical veterinary medicinal products (Notice to Applicants, Volume 6C), information on resistance should be included in SPC section 5.1. The information required to populate this section (e.g. prevalence, mechanisms and genetics, reported side- and cross-resistance), and the type and amount of supporting data, might be specified for antiparasitic 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.

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.

Other points

- It should be considered whether to make specific recommendations regarding the conditions of use of multi-active products (i.e. products containing a combination of substances with different mechanisms of action but targeting the same parasite species).
- It will also be useful to define in which SPC section, and under which form, efficacy claims against parasites with acquired resistance to other active substance classes may be included. Notably, resistance is evolving and there is always a possibility that multiple resistance emerges involving also the active substance under assessment.

4. Recommendation

In light of the above, the Committee for Medicinal Products for Veterinary Use (CVMP) recommends that the Efficacy Working Party reviews and revises as necessary the existing guideline in order to clarify some aspects that are currently not adequately addressed.

It is recommended to also include veterinary medicinal products acting against other parasites than helminths in the scope of the guideline.

Furthermore, the scope should be extended to other target species than ruminants and horses.

5. Proposed timetable

7 December 2017	Concept paper adopted by CVMP for release for consultation
31 March 2018	Deadline for comments from interested parties
22 April 2021	Revised concept paper released for consultation
31 May 2021	Deadline for comments from interested parties
July 2021	Adoption of the draft revised guideline by CVMP for release for consultation
September 2021	Expected end of consultation
December 2021	Expected date for adoption by CVMP and publication of the revised guideline

6. Resource requirements for preparation

Revision of the guideline will involve one EWP-V rapporteur and two co-rapporteurs. Preparation of the draft revised guideline will require discussion at approximately 2 EWP-V plenary meetings.

Drafting group (virtual) meetings 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, EU Regulatory authorities involved in the assessment of marketing authorisation applications for veterinary medicinal products, scientific associations and professional bodies concerned with the use of antiparasitics and with antiparasitic resistance.

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 (EMA/CVMP/EWP/573536/2013)

Draft CVMP Reflection paper on resistance in ectoparasites (EMA/CVMP/EWP/310225/2014)

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

Guideline on the summary of product characteristics for pharmaceutical veterinary medicinal products, Notice to Applicants, Volume 6C

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC