EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Question and answer on the CVMP guideline on the SPC for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005)

Question 1: What does CVMP mean by "treatment and prevention"? (Section 4.2 - Indications for use)

Answer:

A number of antimicrobial products for food producing species have indications containing the expression "For treatment and prevention of …". The word "prevention" in English is open to a wide range of interpretations and it may also be translated in a number of different ways into other European languages, leading to subtle but important differences in the indications for use in the SPCs for the same product in different countries/languages. In order to clarify the meaning of this term in the context of SPCs for antimicrobial veterinary medicinal products, the CVMP provides the following clarification.

The term "For treatment and prevention of …" should only be read *in combination* and does not include routine preventive use in healthy animals where the bacterial disease has not been established in the group/flocks at the time of treatment. The word "prevention" in combination with "treatment" in any new assessments of antimicrobial veterinary medicinal products will be replaced by the word "metaphylaxis" (i.e. treatment and metaphylaxis), to allow for a separate definition and use of a prevention claim as outlined below.

In the context of the phrase "for treatment and prevention" (now: "treatment and metaphylaxis")":

- The term "treatment" refers to the treatment of an individual animal, or a group of animals showing clinical signs of an infectious disease.
- The term "metaphylaxis", refers to the administration of the product at the same time to a group of clinically healthy (but presumably infected) in-contact animals, to prevent them from developing clinical signs, and to prevent further spread of the disease. The presence of the disease in the group/flock must be established before the product is used. A metaphylaxis claim will always have to be combined with a treatment claim.

In new assessments, "prevention" as a single and separate claim, will refer to the administration of an antimicrobial veterinary medicinal product to an individual healthy animal to prevent infection. Such a

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claim will only be considered in those situations where the risk for infection is very high and the consequences are severe. Prevention claims are not expected to be common and will be carefully scrutinized to ensure that the intended use complies with responsible use principles. The need for prevention must be fully justified for each target species and indication.

Question 2: What are “suitable pack sizes” for antimicrobials?

Answer:

In general, any veterinary medicinal product (VMP) should be made available in a suitable pack size to ensure the appropriate treatment of the intended target animal(s). For antimicrobial VMPs, adequate pack size(s) should be chosen with particular care as an additional consideration to support their prudent use.

A suitable number of different pack sizes may have to be supplied to allow dosing of individual animals of different sizes, or different numbers of animals within a group. A reasonable balance has to be identified between the need for different pack sizes to allow correct dosing without a significant amount of leftovers, and the practical and economic difficulties that could be connected to the supply of many different packages.

Legal basis:

Specific reference to pack sizes in the veterinary legislation is spare:

Annex I of Directive 2001/82/EC (as amended by 2009/9/EC; Art I, Part 2 A4 of Development pharmaceutics) states that “*An explanation shall be provided with regard to the choice of composition, constituents, immediate packaging, possible further packaging, outer packaging if relevant, the intended function of the excipients in the finished product and the method of manufacture of the finished product. This explanation shall be supported by scientific data on development pharmaceutics. ….*” Although the pack size is not specifically included in this paragraph of the Directive, the information regarding the choice of packaging is not limited to the type of material, but would also include considerations on e.g. the number of units in one pack or the fill volume of multidose or single dose vials.

Furthermore, reference to pack sizes is made in the Variation Regulation, in regard to a change in the pack size of the finished product (variation B.II.e.5). Conditions for such a change include that the new pack size should be consistent with the approved posology and treatment duration, and that the remaining presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the SPC.

Pursuant to Article 67 of Directive 2001/82/EC, as amended, *“Member States shall take all necessary measures to ensure that, in the case of medicinal products supplied only on prescription, the quantity prescribed and supplied shall be restricted to the minimum amount required for the treatment or therapy concerned.”* This fully applies to antibiotics, since they are supplied only on prescription within the EU.

Justification for the pack sizes

Any pack size(s) for an application for marketing authorisation should be justified, taking into account the risks that might arise from inadequate pack sizes (e.g. safety concerns in case of too large packs, or efficacy concerns for too small pack sizes). It is particularly important that appropriate pack size(s)

is (are) available for VMPs that may be administered by the farmers/animal owners. Such products are mainly formulations for oral administrations, but in some Member States injectable products can also be administered by the animal owner under the responsibility of a veterinarian. If the pack size is too large in regard to the animal(s) to be treated and/or the recommended treatment period, leftovers may be misused, e.g. by prolonging the treatment period or by administration to other animals without veterinary support.

It is fully acknowledged that establishing the appropriate pack size is very difficult. Several factors e.g. species, herd sizes and husbandry practices affect what can be regarded as an appropriate pack size, and these factors can vary to a great extent both within and among Member States. Notwithstanding these difficulties, some basic principles on how to determine an appropriate pack size are given in this document. The principles for determining a suitable pack size differs substantially between the situation when only one animal is to be treated, or when group treatment is applied. For this reason, advice is given separately for packages intended for individual treatment and for group treatment.

Individual treatment

For products intended for individual treatment, the dosage, treatment duration, and the average bodyweight of the animal species for which it is indicated will define the minimum amount required for one treatment course. As a basic requirement, one package should be available which is not larger than necessary to allow the full course of the treatment of one single animal of average size. When the total amount needed to complete a full course of treatment varies considerably due to e.g. different sizes of the animals, dosages or duration of administration, different pack sizes should be made available.

Any additional pack size which is larger than necessary to treat one single animal would have to be carefully justified. In case of multi-dose packages, e.g. vials for injectables intended to be used by a veterinarian to treat several animals, the amount of VMP per vial would have to be justified taking into in account of the disease and species to be treated. In some EU countries, the veterinarian may provide vials to the animal owner to complete a treatment episode. The size of the multi-dose vial would have to be adapted taking into in account of such use to ensure that it would not result in substantial amounts of left-overs.

Group treatment

The definition of appropriate pack size(s) for products intended for group treatment, would have to include an estimation of the average number and weight of the animals that will be concomitantly treated for the particular disease, within the intended area(s)/country(ies). Since these parameters vary considerably among Member States and between diseases, acceptable figures cannot be given in this document.

As a general rule, and in account of what is mentioned above one pack size should be made available that contains not more than the amount necessary to complete one treatment course in a mean size group of animals of an average body weight with the lowest recommended dose and shortest treatment duration. If the size of a group of the target population varies considerably within or between Member States, several pack sizes might need to be made available.

When a product is intended for use in more than one target species or different indications with significantly different recommended dosages and duration of administration, different pack sizes should be made available. Any pack size which differs from the one ensuring the minimum amount necessary - established according to the principles above - should be carefully justified by the applicant.

Individual and group treatment

If a product is intended for both group and individual treatment, ideally two pack sizes should be made available. One should allow the full course of one treatment of one single animal, with the smallest recommended dose and duration of treatment. The other pack size should cover the full course of one treatment of a group of animals according to the principles outlined under “Group treatment”. Any pack size which differs from the ones ensuring the minimum amount required - established according to the principles above - should be carefully justified by the applicant.

Overall conclusions:

A minimum pack size that would allow the completion of one treatment course in an individual animal or in a mean size group of the target animals, of an average body weight with the lowest recommended dose and shortest treatment duration should always be supplied.

A justification for the pack sizes presented in connection to an application for marketing authorisation should always be provided, in particular any pack size(s) which differs from the one ensuring the minimum amount necessary.

Livestock, herd sizes and diseases can vary across Member States, and Member States might therefore decide to apply individual measures in regard to the distribution/supply of certain pack size(s) in their country (subject to national legislation/implementation of Art. 67 of Directive 2001/82/EC, as amended).