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Committee for Medicinal Products for Veterinary Use (CVMP)

Questions and answers on the CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005)

Question 1:

The current CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005) seems to include a contradiction. In section 4 (Justification of the combination), subsection 4.3 (Potential advantages) states that potential advantages include:

- Improvement of activity (4.3.1)
- Broadening of activity spectrum (4.3.2)
- Use of a combination product versus combined use of single substances (4.3.3)

In section 4.3.3, it is stated that "...If simultaneous administration of more than one pharmacologically active substance is justified for therapeutical reasons (4.3.1 and 4.3.2), administration as a fixed combination product may offer an advantage in the clinical situation, e.g..."

a) In the third option (4.3.3), both other options (1 and 2) have to be fulfilled (as stated in brackets in the first sentence) or would it be one or the other (i.e. should the "and" be replaced by "or")?

b) It is considered misleading that the first sentence under section 4.3 requires to show one (out of three) option to justify a fixed dose combination, although option 4.3.3 requires demonstration of at least one of the other 2 justifications too.

Answer:

a) The word “and” in brackets should be interpreted as “and/or”, meaning that at least one of the two options should be fulfilled.

The text in the guideline should therefore be amended/understood as:

4.3.3 Use of a combination product versus combined use of single substances

“If simultaneous administration of more than one pharmacologically active substance is justified for therapeutical reasons (4.3.1 and/or 4.3.2), administration as a fixed combination product may additionally offer an advantage in the clinical situation, e.g.…”

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b) The third potential benefit should normally only be an additional benefit, not a stand-alone benefit; i.e. a fixed combination product should be justified by at least one of the two other potential benefits (improvement of activity and/or broadening of activity spectrum).

Although for certain fixed combination products, ease of administration (and by implication, improved compliance) may be an additional benefit, it is not normally a pivotal justification for the combination. However, under specific and well-defined circumstances (described below, and referred to as a 'substitution indication') it may be permissible as the sole justification for a fixed combination.

It is recognised that for animals which are stable on multiple medications commonly prescribed together for long-term administration(e.g. treatment of cardiac insufficiency), a fixed combination product which contains recognised combinations of active substances at established dose ratios may provide simplification of treatment by substituting monosubstance products for the combination product. Due to the 'substitution' nature of this justification, it is only applicable where the active substances have already been separately authorised in monovalent formulations. Interchangeability with these monosubstance products must be demonstrated in order to ensure that dose adjustment involving the monosubstance products remains feasible. Antimicrobial and antiparasitic active substances fall outside the scope of this justification.

Question 2:

What factors should be considered for justification for a fixed combination product with mixed ectoparasiticide and endoparasiticide indications?

Answer:

It is fully acknowledged that there can be strong justification for the inclusion of combinations of active substances in a veterinary medicinal product, and the potential advantages of such products are recognised. Examples of these benefits compared to the use of two mono-substances alone can include characterisation of interactions (or confirmation of their absence) and description of accurate withdrawal periods in the context of food producing animals.

However, as experience of assessing fixed combination parasiticide products has grown it has become evident that the benefit risk assessment for such products can be very complex. The goal of this question and answer document is therefore to highlight the concerns which have arisen and to provide recommendations to industry on how these should be addressed.

The CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005) sets out overarching principles to be taken into consideration when judging whether a fixed combination presentation can be justified compared with administration of the separate products containing the individual active substances. The principles behind potential advantages of fixed combinations are reviewed below.

Synergistic activity: pharmacokinetic or pharmacodynamic interaction resulting in improved efficacy greater than the sum of the effects of the active substances. This should result in a clinically relevant benefit (e.g. stronger effect or longer duration); this may result in a lower dose of one or both active substances.

Additive activity: the pharmacodynamic action of one active substance adds in a more or less linear way to the pharmacodynamic effect of another, meaning that the therapeutic effect can be increased without a corresponding increase in dose-related adverse effects. The suitability of this justification will usually rest on the safety profiles of the proposed active substances in the combination.

Counteraction of serious or commonly occurring adverse effects: the property of one active substance to counteract an adverse effect caused by another active substance in the combination. Where this relates to a lack of expected efficacy including the management of resistant pathogens/parasites, the acceptability of a combination will be evaluated on a case by case basis.

Broadening of spectrum of activity for treatment claims: this is appropriate where the indication involves several aetiological factors which are known to occur concurrently in individual animals of the target species in Europe.

Broadening of spectrum of activity for prevention claims: the guideline currently recommends that if a fixed combination is intended to be used for prevention claims, the combination must be appropriately justified. This category is seen most commonly with products indicated for prevention of parasite infestations, for example the combination of flea and heartworm prevention in geographical areas where risk of infestation by both parasites exists.

Justification of fixed combination products which have mixed treatment and prevention ectoparasiticide /endoparasiticide indications is more complex. Frequently such combinations will not have synergistic or additive efficacy, so the justification may rely solely on the fact that the spectrum of activity, i.e. the number of parasite species which can be treated or prevented, is extended. Under these circumstances the benefits must be carefully explored and balanced against the risks. For fixed combination products containing more than two active substances, the benefits and risks should not only be considered against monosubstance products, but also against combinations consisting of fewer active substances than the proposed formulation.

For example and to illustrate the above, a potential justification might be as follows: for prevention of mixed infestations which are recognised as occurring together (e.g. known regional epidemiological risk of co-infestation) where the dose for each indication is fixed and the timing of treatment can be justified for each target parasite on epidemiological grounds (sensitivity of parasite stage, period of infestation, prevalence of mixed infestations etc). Appropriate and responsible administration of pharmacological active substances to animals includes giving the correct dose at the correct dosage interval for the authorised indication. This principle underpins the statement in the CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005): “Each substance of a fixed combination must have documented contribution within the combination. It should be clear that superfluous administration of a substance in a fixed combination product, when administered to animals, is considered inappropriate, even if the substance is considered as safe on the basis of target animal tolerance data and when used as indicated.” In line with this principle, if the product is for repeated use, the treatment interval for each indication should be approximately the same. A fixed combination product will not be accepted if the treatment intervals for indications differ substantially.

Taking the above considerations into account, the true size of the target population (animals infested with or at risk of infestation by a spectrum of target parasites which requires simultaneous treatment with every active substance in the combination) will frequently decrease as the number of active substances increases. Therefore, the clinical relevance of the product should be supported by ensuring that this target population is accurately represented in field studies conducted to support the efficacy of the fixed combination. This can be accomplished through careful description of inclusion and exclusion criteria and should be done even when the efficacy endpoints in an individual study do not relate to all the active substances (e.g. when multiple target parasites make it unfeasible for all to be evaluated in a single field study, bearing in mind the recommendation that a confirmatory field study should “only address a limited number of questions” (Guideline on statistical principles for veterinary medicinal products, pharmaceuticals; (EMA/CVMP/EWP/81976/2010)).

Applicants should also consider the potential for going against the spirit of the 3Rs principles in case of multicomponent combinations. Are the benefits to the target population sufficient to justify additional experimental animal studies required for a combination product e.g. interaction studies, which would not be required for monovalent products?

Potential disadvantages of fixed combination products which must be taken into consideration and balanced by benefits brought by the product:

- Potential for unnecessary/superfluous administration of one or more active substances if a combination product is used in preference to monovalent products for convenience. (N.B. the fixed combination guideline states that fixed combination products cannot be justified for reasons of compensating inadequate diagnosis.) This potential for misuse of a fixed combination product may also be more likely if a novel active substance is authorised for the first time in a fixed combination and is unavailable as a mono product. Therefore, with the exception of an active substance which lacks clinically relevant efficacy or an acceptable safety profile except in combination with another, initial authorisation of a novel active substance as a monosubstance veterinary medicinal product is encouraged.
- Potential for superfluous use to increase risk for development of resistance.
- Multiplicative increase in risk of adverse reactions and interactions between active substances with each additional active component.
- Size of the true target population (i.e. animals for which the benefit risk balance of the combination is favourable) is likely to decrease with increasing number of active substances due to restrictions on administering only when all are genuinely indicated.

The above points will be taken into consideration during assessment of applications. Applicants should clearly justify the existence of the target population and show that they have taken into account responsible use principles regarding minimising the risk of development of resistance. Where justifications are accepted, SPC warnings and other statements will still be required, as necessary, in order to accurately describe the appropriate use of the product. It should be noted that the greater the number of active substances and the wider the range of indications, the more restrictive the dosing recommendations are likely to be and the stronger the safety warnings are likely to be in order to discourage misuse (for reasons of convenience) of the product.