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GUIDELINE ON PHARMACEUTICAL FIXED COMBINATION PRODUCTS

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GUIDELINE ON PHARMACEUTICAL FIXED COMBINATION PRODUCTS

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EXECUTIVE SUMMARY

This Guideline outlines the conditions and data requirements for efficacy, safety and residues documentation for veterinary pharmaceutical fixed combination products and should be read in conjunction with current EU/VICH Guidelines.

1. INTRODUCTION (BACKGROUND)

The aim of this guideline is to outline and clarify data requirements for efficacy, safety and residues documentation for veterinary medicinal products, containing 2 or more active substances (so called "fixed combination products"). It is noticed that data on the separate active substances, usually available as a single substance product, are considered as the basis for data on fixed combination products.

2. SCOPE

This Guideline outlines the conditions and data requirements that apply to fixed combination products and should be read in conjunction with current EU/VICH Guidelines (e.g. Good Clinical Practice; Pharmacokinetics, Target Animal Safety).

The objectives of this guideline are:

- to indicate possible advantages and disadvantages, related to the combining of substances into a fixed combination product;
- to provide applicants with information on the data requirements for fixed combination products;

3. LEGAL BASIS

This guideline concerns the application of Part 3 and 4 of Title I of Annex I to Directive 2001/82/EEC as amended in view of the submission of an application for marketing authorisation of a new veterinary pharmaceutical product.

4. JUSTIFICATION OF THE COMBINATION

Applicants will be required to justify the particular combination of active substances proposed. Fixed combination products will be only considered acceptable if the proposed combination is based on valid therapeutic principles.

Any fixed combination product can only be justified, if such a combination offers an advantage over their active substances, when used as single substance products. Fixed combination products cannot be justified for reasons of compensating inadequate diagnosis.

Every active substance in a fixed combination should be indicated for use at the moment of treatment and administered in the correct dose. The mode of action of the combination (e.g. additive/ synergistic) should be documented.

4.1 Interactions

In combining substances into a fixed combination product unintended interactions might occur, leading to a lack of activity and/or adverse effects, an active substance may mask the pharmacological effects of another substance, or may increase the toxic effects of one or more substances present in the fixed combination product. The possibility of interactions, *in vitro* as well as *in vivo* pharmacological interaction, between active substances and/or excipients should always be considered and, if necessary, be investigated, documented and justified in a risk-benefit assessment.

4.2 Indications

The indication(s) claimed for a fixed combination product should be such that each active substance contributes to the overall therapeutic effect of the product. The fixed combination product should be formulated so that the dose and the proportion of each active substance are appropriate to all the recommended uses.

4.3 Potential Advantages

Potential advantages of fixed combinations include one of the following:

4.3.1 Improvement of activity

At the same dose, the therapeutic effect can be improved by synergistic or additive activity.

In case of a synergistic activity, the effect of one substance is influenced and enhanced by another substance (true therapeutic advantage). This can be the consequence of pharmacodynamic and/or pharmacokinetic interaction.

The extent and duration of activity of a substance can be improved by pharmacokinetic interactions, e.g. if bioavailability/distribution is increased or metabolic inactivation or elimination is reduced by another substance. Combination with a substance, which speeds up the action of another substance of the combination or delays its absorption may also be a rationale.

In case of an additive activity, the pharmacodynamic effect of one substance adds to that of another for the same target and in a more or less linear way, without substances interacting. Substances are interchangeable, without affecting the level of effect.

Tolerance can be improved in combination products, because the dose of individual substances with a narrow margin of safety can be reduced, without affecting the total level of efficacy.

Tolerance can also be improved by the addition of a substance, which has been demonstrated to counteract adverse effects produced by another substance. However, this is only justified if the adverse effect is a serious or commonly occurring one.

4.3.2 Broadening of the activity spectrum

Broadening the activity spectrum by combining more than one active substance often relies on the presence of several aetiological factors, which can be diagnosed properly (treatment claims), have been confirmed to occur simultaneously, and are of clinical relevance.

For prevention claims appropriate justification should be provided for the broadening of the activity spectrum.

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 4.3.2), administration as a fixed combination product may offer an advantage in the clinical situation, e.g.

- In fixed combination products the correct quantitative relationship of each active substance has been established ensuring efficacy and accuracy of dosing.

- Fixed combination products may also offer the advantage that possible galenic incompatibility between medicinal products, when used simultaneously as an alternative, can be avoided.

- Fixed combination products can facilitate animal handling (reduction of the total number of tablets/injection sites) as well as owner's compliance.

5. RISK-BENEFIT ASSESSMENT

A risk-benefit assessment addressing safety and efficacy of the combination product should be included in the dossier.

The risk-benefit assessment should determine whether the particular combination of active substances is justified and should assess the potential advantages against the possible disadvantages in the clinical situation, as compared to the use of the single active substances.

A combination of substances with critical dosage ranges or narrow therapeutic indices is unlikely to be suitable in a fixed combination, as it would have a limited range of use and would require precise individual dosing. In particular, such combinations would be unsuitable for certain dose formulations/presentations with limited means of individual dosing e.g. tablets or one-dose presentations.

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.

6. DOSSIER REQUIREMENTS FOR COMBINATION PRODUCTS

6.1 General requirements

6.1.1 New fixed combination products

For any new active substance, when included into a fixed combination product, a full dossier in accordance with Article 12(3) of Directive 2001/82/EC as amended by 2004/28/EC, will be required.

For any active substance(s) already used in authorised veterinary medicinal products but not in a combination product, the results of the safety and residue tests, if necessary, and new preclinical and clinical trials with the combination product shall be provided in accordance with Article 13(b) of Directive 2001/82/EC as amended by 2004/28/EC. It shall not be necessary to provide copies of scientific references to each individual active substance. However, if an applicant, based on animal welfare grounds, chooses to submit relevant pharmacological and toxicological data on each individual active substance, in conjunction with the required user safety, residues, preclinical and clinical studies on the fixed combination product, this will be considered as a suitable justification for omitting such data on the combination product.

Interactions between active substances and/or excipients in the fixed combination product may, however, need to be further investigated in pharmacological/toxicological studies using the final formulation, depending on the type and level of interaction.

6.1.2 Combination products that meet the criteria for well established use

In the case of combination products containing active substances used in authorised veterinary medicinal combination products, appropriate scientific literature shall be provided to demonstrate safety and efficacy in the target species according to Article 13a (1) of Directive 2001/82/EEC as amended.

6.1.3 Combination products that meet the criteria for generic application

If a combination product meets the criteria for a generic product, the rules for generics in Article 13 of Directive 2001/82/EEC as amended apply.

Depending on the pharmaceutical formulation (e.g. differences in excipients) and route of administration, data on residue depletion, where applicable, and on tolerance in the target animal species (e.g. local irritation) may be required.

6.2 Specific Requirements

6.2.1 Part 3: Specific requirements for safety and residues documentation

It is necessary to provide pharmacological data for the combination in order to demonstrate the mode of action and to investigate the possibility of interactions. Any omissions must be justified.

It may also be necessary to provide toxicological data for the combination if there are interactions between the active substances and/or excipients or a possibility of masking toxicity. In all cases where there is a synergistic effect, more detailed toxicological data will be required.

User, environmental and consumer safety of a fixed combination product must be demonstrated. The safety of a combination product should be compared with that of the active substances, when used as single substance products.

User safety studies relating directly to effects on the person administering the product, or any other persons exposed during treatment and after treatment (e.g. children handling animals after treatment), such as skin and eye irritation, sensitisation and inhalation studies, should always be carried out with the final formulation. Therefore, in cases where user safety studies are required, they would be conducted using the fixed combination product and would be part of the dossier. Guidance on user safety studies and user safety assessment is given in the CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-FINAL).

Environmental Impact Assessment should be targeted at the effects of the combination product. If scientifically justified, data in accordance to VICH phase I and phase II guidelines might be provided for the individual substances only.

For food producing animals the withdrawal periods must be established to ensure consumer safety.

Residues depletion studies for foodstuffs (according to species) must be conducted with the fixed combination/final formulation in accordance with appropriate guidance to establish withdrawal periods. The residues of the pharmacologically active substances and any significant metabolite(s) in the fixed combination product that remain in the animal's body or are excreted in milk, eggs or honey, must be demonstrated by appropriate investigations.

In the case of injectable products (intramuscular or subcutaneous) intended for food producing animals, demonstration of residues depletion at injection sites must be submitted.

6.2.2 Part 4: Specific requirements for preclinical and clinical documentation

Both the efficacy and target animal safety of a fixed combination product should be investigated in the animal species for which the combination product is intended.

Preclinical data

It is necessary to provide preclinical data (pharmacokinetic and/or pharmacodynamic) for the combination product to demonstrate its mode of action (e.g. additive/synergistic), investigate possible interactions or clearly establish that interactions do not occur.

In case that pharmacokinetic interactions constitute the rationale for the fixed combination, these interactions should be studied in healthy animals of the target species.

Dose-finding

The proposed dosage regime must be justified. If the pharmacological data have clearly demonstrated no interactions between the active substances, justification for the dose selection can be based on data for each individual active substance.

Where the potential advantage of the combination product is based on synergistic or additive activity, several dose combinations for each substance might have to be tested to establish the optimal quantitative relationship between the individual substances in the fixed combination product.

Tolerance

Target animal safety testing should include an untreated control or, in the case where an improved tolerance is the rationale for the fixed combination, a reference treatment.

Clinical data

Dose confirmation and clinical field studies should always be carried out with the final formulation.

The efficacy and target animal safety of the combination product should be compared with that of the active substances, when used as single substance products.

Resistance

For fixed combinations of antimicrobials or antiparasitics an assessment of the potential for the development of resistance will be necessary.

Exceptions

If one active substance has no inherent therapeutic effect, but just enhances or complements the activity of the other one (e.g. beta-lactams and beta-lactamase inhibitors), the efficacy of the combination product should be compared with that of the main active substance, when used alone as a single substance product. It should be demonstrated that the active substance without direct therapeutic efficacy produces the expected effect (e.g. the fixed combination must show a superiority over the main component when given alone).

For fixed combination products of vitamins, oligoelements and minerals, it may be difficult to establish the interest of each active substance. Therefore, such combinations are accepted as being effective and safe if the indications claimed are restricted to deficiency diseases where treatment by a fixed combination is justified and the maximum doses do not exceed internationally and scientifically accepted limits. This exemption is possible for fixed combination products containing solely vitamins, oligoelements and/or minerals (e.g. combinations of vitamins and antibiotics are not covered by the exemption).

A fixed combination of electrolytes and nutrients may also be exempted from the requirements of this guideline. In fact, any experimental evidence comparing the separate activities of each of these substances is irrelevant as the combination of different components in a solution for fluid therapy is justified by the parallel losses and imbalances quantified in the animal suffering from dehydration (see also the note for guidance *Veterinary Medicinal Products for Fluid Therapy in Case of Diarrhoea*).

This does not apply for fixed combination of electrolytes, indicated for the use in case of e.g. milk fever or grass tetany. In this case the single substances do have to comply to the conventional criteria for fixed combination products.

7. COMBINATION PACKS

The principles applicable to fixed combination products will also be applied in the assessment of preparations, consisting of different medicinal products in combination packs, in which the components of the combination pack are intended for simultaneous or sequential administration and for one therapeutic purpose.