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(CHMP)**

DRAFT

GUIDELINE ON FIXED COMBINATION MEDICINAL PRODUCTS

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EXECUTIVE SUMMARY

This guideline covers fixed-combination medicinal products containing two or more active substances. The development of the fixed-combination medicinal products will reflect the intended use (first or second line indication) and the intended indication (one disease or e.g. two closely related diseases like hyperlipidemia and hypertension).

1. INTRODUCTION (background)

Fixed-combination medicinal products have been increasingly used either to improve compliance or to benefit from the added effects of the two medicinal products given together. The proposed combination should always be based on valid therapeutic principles. In addition, it is necessary to assess the potential advantages (e.g. product rapidly effective, higher efficacy or equal efficacy and better safety) in the clinical situation against possible disadvantages (e.g. cumulative toxicity), for each fixed combination product and for each dose of the fixed combination product.

Potential advantages may also include the counteracting by one substance of an adverse reaction produced by another one and the simplification of therapy.

Clinical developments should correspond to each situation/intended claim. In addition, particular attention should be drawn to the doses of each active substance in the fixed combination product. Each dose combination should be carefully justified and clinically relevant (e.g. in cases when each component of the fixed combination has several possible dosages, dosages that have shown benefit on hard clinical outcomes may be preferable for the fixed combination than the dosages effective on surrogate endpoints only).

2. SCOPE

Guideline concerning the scientific requirements for applications according to Article 10b of Directive 2001/83/EC, as amended, so-called 'fixed-combination' medicinal products. The scientific principles applicable to fixed-combination products will also be applied in the assessment of 'combination pack' medicinal products.

Combination packs would only be acceptable in very exceptional cases, when there would be clear public health benefits for the treatment regimen and/or compliance, taking into account the required justifications set-out in section 4.1 of this guideline. Applicants are therefore advised to consult with the relevant National Competent Authority/EMA prior to submission, on the acceptability of the proposed combination pack.

The scientific principles set-out in this guideline are also applicable to a new chemical substance which dissociates in vivo into two well known active substances. A rationale should be given.

3. LEGAL BASIS

In accordance with Article 10b of Directive 2001/83/EC: "In the case of medicinal products containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes, the results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Article 8(3)(i), but it shall not be necessary to provide scientific references relating to each individual active substance".

Chapter 1 section 5.5 of the Notice To applicants¹ provides clarification on the legal dossier requirements for applications for so-called 'fixed combination' medicinal products (see also section «Definitions»).

¹ Notice To Applicants, published by the European Commission Website: <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm>

Applications for fixed-combination medicinal products submitted under Art 10b of Directive 2001/83/EC, should concern individual substances which have been authorised in the EEA via a Community or national procedure. In case of fixed-combination medicinal products containing one or more substances which have not been authorised in the EEA, an application according to art 8.3 of Directive 2001/83/EC should be made.

4. MAIN GUIDELINE TEXT

4.1 Justification

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

4.1.2 For any individual fixed combination it is necessary to assess the potential advantages in the clinical situation against possible disadvantages, in order to determine whether the product meets the requirements of the standards and protocols with respect to efficacy and safety.

Potential advantages of fixed combinations include one of the following:

a) an improvement of the benefit/risk assessment due to :

i. addition or potentiation of therapeutic activities of their substances, which results in:

- a level of efficacy similar to the one achievable by each active substance used alone at higher doses than in combination, but associated with a better safety profile

or

- a level of efficacy above the one achievable by a single substance with an acceptable safety profile.

ii. the counteracting by one substance of an adverse reaction produced by another one.

b) a simplification of therapy

which improves patient compliance.

Disadvantages of fixed combinations include :

i. the fact that even a combination which meets the needs of the average patient is unlikely to be ideally adjusted for the needs of each individual patient;

ii. the addition of the different adverse reactions specific to each substance.

4.1.3 General rules

Combinations, in principle, may not be considered rational if the duration of action of the substances differ significantly. This may not necessarily apply where it can be shown that the combination is clinically valid despite differences in this respect, e.g. if one substance is intended to enhance absorption of the other or where the substances are intended to exert their effects successively.

Each substance of the fixed combination must have documented contribution within the combination.

The inclusion of a substance to counteract an adverse reaction of another substance may be considered justified, but only if the adverse reaction is a serious or a commonly occurring one.

The inclusion of a substance intended to produce unpleasant adverse effects as a means of preventing abuse is undesirable.

Substances having a critical dosage range or a narrow therapeutic index are unlikely to be suitable for inclusion in fixed combinations.

4.2 Indications

The indications claimed for a fixed-combination medicinal product should be such that the presence of each active substance makes a contribution to the claimed effect. The product should be formulated so that the dose and proportion of each substance present is appropriate for the intended use.

An indication must be a well-recognised disease state, modification of a physiological state, dysfunctional state, syndrome or pathological entity. The individual substances of a fixed combination may be intended to relieve simultaneously different symptoms of such a disease state. In this case, it should be a prerequisite that these symptoms regularly occur simultaneously in a clinically relevant intensity and for a relevant period of time. It will not be proper to regard each individual symptom as an indication for the fixed combination, since it may also occur in other diseases and for treating this symptom alone the other substances may be irrelevant.

Fixed combination medicinal products may be indicated in different situations:

- in first line therapy, for patients receiving previously neither of the substances
- in second line therapy, when monotherapy has not demonstrated a satisfactory benefit/risk ratio.

The applicant should clearly state if the claimed indication is first line, second line therapy or other uses and the clinical development should be performed accordingly.

4.3 Pharmacodynamic and Pharmacokinetic studies

The possibility of interactions between the substances should always be considered. The applicant should submit data either to establish that such interactions do not occur or that they are clearly recognized and defined.

4.3.1 Pharmacodynamic studies

Frequently, the addition or the potentiation of the pharmacodynamic effects of the various substances may constitute the rationale of the fixed combination.

In this case several dose combinations for each substance might have to be tested and the concentration-response information can help to select the fixed combination leading to a satisfactory response.

4.3.2 Pharmacokinetic studies

In general, the applicant must demonstrate that the various substances do not affect each others respective pharmacokinetic patterns.

In some cases, however, a pharmacokinetic interaction (i.e. combination with a metabolism inhibitor) constitutes the rationale of the fixed combination.

These interactions should be studied in healthy volunteers but also in patients if the disease modifies the pharmacokinetics of one substance and in high risk subgroups (elderly, patients with renal failure or hepatic impairment).

4.4 Efficacy and Safety

Applications for fixed-combination medicinal products submitted under Art 10b of Directive 2001/83/EC, should concern individual substances which have been authorised in the EEA via a Community or national procedure. Full safety and efficacy data in relation to the fixed-combination should be provided. Inclusion of data on the individual substances is in principle not required.

However, information on the individual substances may be included in the application in particular when the applicant justifies any absence of specific data on the combination.

It is permissible to distinguish between the extent of the studies required in the case of those fixed combinations which correspond closely to combinations which are already in widespread use provided these are thoroughly and reliably documented, and those studies required in the case of those combinations which are essentially new :

- a) When the fixed combination corresponds closely to combinations that are already in widespread use, a well founded bibliographical data analysis could be submitted. Provided that the respective data are thoroughly and reliably documented, this analysis may be helpful in reducing the amount of clinical trials to be performed and could facilitate the selection of doses for each substance and the proposed dose range of the fixed combination.
- b) When the fixed combination is essentially new (active substances not usually combined or unusual quantitative composition of usually combined substances), the data needed are similar to a new chemical entity in the situation where the fixed combination is to be proposed (first line or second line therapy). Existing experience with the substances should be taken into account.

4.4.1 Composition and dosage regimen

The proposed dosage regimen must be justified.

The dosage of each substance within the fixed combination must be such as the combination is safe and effective for a significant population subgroup and the benefit/risk assessment of the fixed combination is equal or exceeds the one of each of its substances taken alone.

The multilevel factorial design may be used but other confirmatory strategies exist to prove that the combination is superior to its substances. Descriptive tools such as response-surface methods may be useful (see guideline ICH E4 Dose response information to support drug registration).

In some cases, studies have to be specifically designed to determine the minimal effective dose and usual effective dose of the fixed combination. Multiple dose-effect studies may be required.

Where substances are intended to relieve simultaneously different symptoms or to prevent different diseases, selected doses of each substance are often those commonly used for the treatment of each symptom or the prevention of each disease.

4.4.2 Therapeutic trials

Confirmatory clinical trials are necessary to prove efficacy, preferably by parallel group comparisons in which the fixed combination is compared to its individual substances. Inclusion of a placebo group is recommended when feasible.

Comparative clinical studies of the fixed combination versus reference treatment might be necessary.

4.4.3 Safety aspects

Safety studies in animal should, as a general rule, have been performed with the active substances of the fixed combination in the proportion present in the product. Such studies may not be required where all the substances have been extensively and safely used in humans in identical or very similar combinations for a long period and the safety of such combinations is well documented.

In the case of combinations for long term use (see guideline ICH E1 Population Exposure: The Extent of Population Exposure to Assess Clinical Safety), safety data on 300-600 patients for six months or longer will be required. The absence of such data should be justified by the applicant.

Where there are grounds to expect that a fixed-combination product may be substantially more harmful or give rise to much more frequent adverse effects than any individual substances given alone, the applicant should provide evidence that this does not occur in therapeutic use, or that the advantages of the combination e.g. increased efficacy, outweigh such disadvantages.

DEFINITIONS

The combination of active substances within a single pharmaceutical form of administration is a so-called 'fixed combination'.

A 'combination pack' consist of more than one medicinal product, or more than one pharmaceutical form of the same medicinal product, presented under a single (invented) name, where the individual products/forms are intended for simultaneous or sequential administration.

REFERENCES (scientific and / or legal)

- Directive 2001/83/EC, as amended – Article 10b
- The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 1 on "Marketing authorisation"
- ICH E1 Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95) <http://www.emea.europa.eu/pdfs/human/ich/037595en.pdf>
- ICH E4 Dose response information to support drug registration (CPMP/ICH/378/95) <http://www.emea.europa.eu/pdfs/human/ich/037895en.pdf>