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GUIDELINE ON CLINICAL DEVELOPMENT OF FIXED COMBINATION MEDICINAL PRODUCTS

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GUIDELINE ON CLINICAL DEVELOPMENT OF FIXED COMBINATION MEDICINAL PRODUCTS

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EXECUTIVE SUMMARY

This guideline covers fixed combination medicinal products containing two or more active substances, which can be either well-known or not yet authorised in the EU for the intended claim. The development of fixed combination medicinal products will reflect the intended use (first or second line indication in patients inadequately controlled with individual component(s) of the combination) and the intended indication (treatment of one disease or e.g. two closely related diseases such as hyperlipidemia and hypertension, or substitution indication).

1. INTRODUCTION (background)

The proposed combination should always be based on valid therapeutic principles.

Fixed combination medicinal products have been increasingly used to benefit from the added effects of medicinal products given together. 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 of fixed combination products may also include the counteracting by one substance of an adverse reaction produced by another one and the simplification of therapy (improved compliance).

Clinical development 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 when compared with the dosages effective on surrogate endpoints only).

2. DEFINITIONS

The combination of active substances within a single pharmaceutical form of administration is a so-called ‘fixed combination’ medicinal product.

A ‘combination pack’ consists of more than one medicinal product, or more than one pharmaceutical form of the same medicinal product, presented under a single (invented) name and in a single product package (e.g. box, blister pack), where the individual products/forms are intended for simultaneous or sequential administration.

3. SCOPE

This document provides guidance on the clinical strategy to be considered when developing a so-called ‘fixed combination’ medicinal product.

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 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 5 of this guideline. Applicants are therefore advised to consult with the relevant National Competent Authority/EMEA 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 or more well-known active substances. A rationale should be given.

This guideline should be read in conjunction with other relevant therapeutic EU guidelines.

4. 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 Applicants[1] provides clarification on the legal dossier requirements for applications for so-called 'fixed combination' medicinal products.

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. In this case, results of non-clinical tests and clinical trials relating to the individual substances as well as on the combination should be provided, as justified in the non-clinical and clinical overviews, and as supported by scientific advice if appropriate.

5. JUSTIFICATION

Applicants will be required to justify the particular combination of active substances proposed in the intended indication. Fixed combination products will only be considered acceptable if the proposed combination is based on valid therapeutic principles. A scientific advice from National Competent Authorities or the EMEA may be helpful in this respect.

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 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 (serious or commonly occurring) produced by another one.

b) a simplification of therapy by decreasing the number of individual dose units to be taken by the patient, which simplifies therapy and may improve patient compliance. This is also referred to as a "substitution indication". The improvement of patient compliance is considered

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

especially important in situations where it may contribute reducing the incidence of resistance (e.g. HIV products, tuberculosis)

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.

6. GENERAL RULES

As a general rule, the choice of each substance in the fixed combination as well as the whole concept on which the rational for the fixed combination is based have to be fully justified; this can be achieved by taking into account mode(s) of action, pharmacokinetics, and treatment recommendations for a given clinical setting.

Combinations, in principle, may not be considered rational if the duration of action of the substances differs 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 a documented therapeutic 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 not an acceptable reason to develop a fixed combination.

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

6.1 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 or improves the overall benefit risk ratio by mitigating side effects. 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, or two closely related diseases, or a modification of a physiological or dysfunctional state, or a 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 with either component has not demonstrated a satisfactory benefit/risk ratio;
- as a substitution indication, in patients adequately controlled with the individual products given concurrently at the same dose level as in the combination, but as separate tablets.

It should be clearly stated if the claimed indication is first line, second line therapy or a substitution, and the clinical development should be performed accordingly.

6.2 Pharmacodynamic and Pharmacokinetic studies

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

6.2.1 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.

6.2.2 Pharmacokinetic studies

This section covers the pharmacokinetic aspects of fixed combinations for immediate or modified release where applicable.

The need for pharmacokinetic documentation depends on the type of fixed combination, as follows

i) The new fixed combination is a generic of an existing product. In this case the pharmacokinetic bioequivalence following the “NfG on the Investigation of Bioavailability and Bioequivalence” and the “NfG on Modified Release Oral and Transdermal Dosage Forms” is adequate. A BCS (Biopharmaceutics Classification System)-based biowaiver is applicable here for immediate release formulations where all individual components of the fixed combination are considered eligible.

ii) The combination contains known active substances and it is a substitution indication (i.e. use in patients adequately controlled with the individual products given concurrently, at the same dose level as in the combination, but as separate tablets) or the new fixed combination contains known active ingredients that have not been used in combination before. In these cases bioequivalence should be demonstrated between the free combination of the recognised reference formulations of the individual monocomponents and the marketing formulation (fixed combination).

iii) One of the active substances is a new chemical substance. This case should be treated as a New Drug Application and the full characterisation of the pharmacokinetic profile (including interaction studies and studies in special populations and patients) is recommended to be made using the combination (and not only with just the new mono-component). This may be especially important if the rationale of the fixed combination is based on an interaction (such as for ritonavir boosted protease inhibitors).

For the latter two cases (ii and iii), the applicant should in general evaluate to what extent the various substances affect each others respective pharmacokinetic patterns (interaction) based either on previous knowledge or on experimental evidence. In some cases, a pharmacokinetic interaction (i.e. combination with a metabolism inhibitor) constitutes the rationale of the fixed combination. These interactions should normally be studied in healthy volunteers.

If the application covers several strengths, then demonstration of bioequivalence study with only one strength may be acceptable. Biowaiver for an additional strength may be applicable when the conditions for this as detailed in the guideline on bioequivalence are fulfilled for all individual active substances.

If the SPC recommends taking each component in fasting or fed states then one bioequivalence study is adequate according to SPC recommended condition. But comparative studies in the fasted and fed state are necessary for fixed modified release drugs following the recommendations in the NfG on Bioequivalence and NfG on Modified Release Drugs.

6.3 Efficacy and Safety

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 from the simultaneous use 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 or one active substance is a new chemical entity), 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). A full dossier will be needed for a new chemical entity in the fixed combination, and on the individual substances as appropriate. Existing experience with the substances will also be taken into account.

6.4 Dosage strengths and treatment regimen

The proposed dosage regimen must be justified.

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

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. The multilevel factorial design may be used.

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.

In the case that the doses used in the fixed combination are identical to the doses used in the broad clinical setting and safety data generated with these doses are available, demonstration of comparability in the PK properties might be sufficient.

6.5 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 whenever feasible. Comparative clinical studies of the fixed combination versus reference treatment might be necessary in order to put into perspective the improvement obtained with the fixed combination.

For the first line therapy indication (in patients previously receiving neither of the substances), the acceptance of such an indication (and corresponding development) for a fixed combination product will depend on recommendations for treatment and clinical practice in each therapeutic field.

For the second line therapy indication, a trial in non-responders or patients insufficiently controlled with optimally dosed monotherapy, is recommended; patients should be randomized to a fixed combination versus optimal monotherapy and active comparator.

In both cases, the development of a fixed combination should follow specific disease-related guidelines in the choice study design (severity of the disease at baseline, primary and secondary efficacy endpoints, study duration, comparators).

For a substitution indication (for patients adequately controlled with a stable doses of monocomponents), comparative pharmacokinetic data and (in some cases) pharmacodynamic data (e.g. different administration time) are generally considered sufficient.

These situations mostly cover one disease.

6.6 Safety aspects

In principle, the safety considerations as per the corresponding notes for guidance on clinical development of medicinal products in the treatment of the targeted disease/diseases should be met.

To what extent such safety information should be provided “ex novo” for the submitted dossier will depend on the available information for each of the components at the proposed doses given as either monotherapy or as a free combination. For pure substitution indications in case of FDC containing active substances with a wide therapeutic experience in the claimed indication at the proposed dosing schedule an abridged safety database from available experience may be considered. Otherwise, a self-standing database tailored to the claimed indication should be provided. In any case, the rationale supporting abridging available safety data to the final formulation should be adequately justified on the basis of the following considerations (see also under pharmacokinetics and efficacy sections):

1. Degree of knowledge of the active substances in the indication claimed. As stated above, any FDC containing a new chemical substance should be considered as a new chemical substance itself, and therefore be supported by a full dossier.

2. Proposed dosing schedule. Changes in dosage and/or posology regimen of any of the components that may lead to tolerability differences, specially linked to the switch from individual tablets to a FDC, should be adequately addressed.

3. Potential for PK and/or PD interactions leading to safety concerns.

4. Existing recommendations on specific safety issues (e.g. special populations, cardiac repolarisation and need for a TQT study)

In the case of fixed combinations intended for long term use, the amount of safety data to provide should follow recommendations given in specific disease-related guidelines. 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.

REFERENCES

- Directive 2001/83/EC, as amended.

- The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 1 on ‘Marketing authorisation’.