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**COMMITTEE ON HERBAL MEDICINAL PRODUCTS
(HMPC)**

FINAL

**GUIDELINE ON THE CLINICAL ASSESSMENT OF FIXED COMBINATIONS OF
HERBAL SUBSTANCES / HERBAL PREPARATIONS**

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1. INTRODUCTION

Fixed combinations of herbal medicinal products are in widespread use in Phytotherapy. A rational assessment of well-established and of traditional fixed-combination products must be based on clear criteria that guarantee consumer safety and appropriate indications. Such criteria contribute to the rational use of herbal fixed combinations by consumers, patients and health professionals. They are one tool to protect consumers or patients from fraudulent products, misleading claims and risks associated with the use of unjustified combinations of herbal substances/preparations.

2. SCOPE

This guideline is intended to provide guidance to applicants on how to structure the clinical documentation of herbal fixed-combination products. It provides advice to assessors for an assessment of the clinical safety and efficacy. Different criteria may apply to chemically defined substances¹.

This guideline should be read in conjunction with other EMEA guidance documents, especially guidance on the assessment of preclinical safety and clinical safety / efficacy.

3. LEGAL BASIS

For well-established herbal medicinal products reference is made to Directive 2001/83/EC, as amended, especially to its Annex 1, Part I Module 4 (4.2.1), Module 5 (5.2.h) and to Part II (5). These provisions have to be read in conjunction with Part II (1) of the Annex that clarifies that the tests and trials required for new combination products may be replaced by bibliographic data under the conditions set out by the Annex.

For traditional herbal medicinal products all provisions of Chapter 2a of Directive 2001/83/EC are applicable. For fixed combinations, the provisions of Article 16a (2), 16c (1) a (iv), 16c (2) and 16e (1) d are of particular relevance.

4. GENERAL CONSIDERATIONS

The extent of the data required in the case of those fixed combinations which correspond closely to combinations which are already in widespread use², provided these are thoroughly and reliably documented, will differ from 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 should be submitted. Provided that the respective bibliographic data on the fixed combination and on its ingredients are thoroughly and reliably documented, this analysis may be sufficient for the justification of the efficacy and safety of the fixed combination and could facilitate the selection of doses for each substance and the proposed dose range of the fixed combination.
- b) When the fixed combination does not meet the criteria to be considered as well-established or traditional, the data needed are similar to those required for a new product. Existing experience with the active substances should be taken into account. (Art. 10b of Directive 2001/83/EC)

Applicants will be required to justify the rationale of the particular combination of active substances (herbal substances/herbal preparations) proposed.

Well-established fixed combination products will only be considered acceptable if the proposed combination is based on scientifically valid therapeutic principles.

¹ Note for guidance on fixed combination medicinal products (CPMP/EWP/240/95), adopted April 1996

² Even if the quantitative composition of usually combined substances (herbal substance or herbal preparations) has been adjusted to reflect the current scientific knowledge, the combination itself still may be classified as well-established, if the applicant justifies that the modifications will not alter the safety-profile of the product.

Traditional fixed combination products must be plausible within the relevant system of traditional medicine.

For both types of herbal medicinal products, the function of each constituent of the herbal medicinal product must be clarified, taking into account the indication of the combination, the profile of the active substance and its dosage / concentration. For well-established herbal medicinal products, such clarification may result from different types of data, such as comparative clinical studies, epidemiological studies, bibliographic data on single ingredients together with pharmacological data etc.

It must be clearly stated by the applicant if a constituent of the fixed combination has to be considered as an active substance or as an excipient, e.g. to improve the taste or to influence physical properties of the product. This decision will have important consequences for the data requirements in all parts of the documentation and for the assessment of the quality, the non-clinical and the clinical part of the dossier.

For any individual fixed combination it is necessary to assess the potential advantages in the therapeutic situation against possible disadvantages, in order to determine whether the product meets the requirements with respect to efficacy or plausible traditional use and to safety:

Well-established herbal medicinal products:

Potential advantages of fixed combinations may include one of the following:

a) An improvement of the benefit/risk ratio due to:

The addition or potentiation of therapeutic activities of the active 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.

The counteracting by one substance of an adverse reaction produced by another one.

b) A simplification of therapy

A fixed combination of active substances may be acceptable if it achieves a similar level of efficacy to the one achievable by each active substance used alone at higher doses than in combination but improves patient compliance (e.g. simplification of posology, improvement of taste etc.).

Potential disadvantages of fixed combinations may include:

- a) 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;
- b) The addition of the different adverse reactions specific to each substance.

Combinations 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.

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 commonly occurring one.

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

Traditional herbal medicinal products

Similar considerations will be, in principle, applicable to traditional herbal medicinal products. It should be noted, however, that the requirements relating to efficacy will be reduced to the level of plausibility, whereas considerations related to safety will become more critical in an overall benefit/risk-assessment, because scientific evidence on efficacy is not available for traditional herbal medicinal products.

Where there are grounds to expect that a well-established or a traditional fixed-combination product may be substantially more harmful or give rise to much more frequent adverse effects than any individual active substances given alone, the applicant must provide clinical evidence that this does not occur in therapeutic use. Such evidence may include epidemiological or post-marketing studies and data. In the case of well-established herbal medicinal products the applicant may submit clinical evidence that the advantages of the combination, e.g. increased efficacy outweigh such disadvantages.

5. INDICATIONS

5.1 Well-established herbal medicinal products

The efficacy and the clinical safety of the fixed combination must be evident from clinical trials or from bibliographic data submitted by the applicant.

The indications claimed for a fixed-combination product must be such that the presence of each active substance makes a contribution to the claimed effect. The product should be formulated in such a way that the dose and proportion of each active substance 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 must 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 acceptable 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.

5.2. Traditional herbal medicinal products

Similar considerations will be applicable to traditional herbal medicinal products. The traditional use of the product or of a corresponding product has to be substantiated. If reference is made to a particular traditional system of therapy, this should be expressed in the wording of the indication.

If vitamins and/or minerals are part of a traditional herbal combination product, their action has to be ancillary to the herbal active ingredient(s) regarding the specific indication(s). In general, the presence of vitamins/minerals will not modify the indication of the fixed combination. An ancillary action must be made plausible, e.g. by providing bibliographic or expert evidence of the traditional use of these substances in the respective traditional indication.

6. COMPOSITION AND DOSAGE REGIMEN

The proposed dosage of the fixed combination and the contribution of each active substance must be justified in the clinical overview / expert report.

6.1 Well-established herbal medicinal products

The dosage of each active 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 active substances taken alone.

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

Where active substances have an additive action, the dosage of each active substance has to be reduced, as compared to the single use of the substance. It should be noted, however, that in such a situation the reduction of the dose will not result in a linear decrease of the effect and that small amounts of active substances, e.g. less than 10% of the single dose, are very unlikely to contribute to the overall effect of the combination product.

6.2 Traditional herbal medicinal products

The dosage of each active substance must be such that a contribution to the traditional use is plausible. The assessment of “plausibility” will take into account the extent of traditional use of the combination, traditional posology of the individual active constituents and, as far as applicable, specific views of the relevant system of traditional medicine.

Vitamins and minerals may be part of a traditional herbal medicinal product. For the definition of the terms “vitamin” and “mineral” reference is made to Annex I and II of the Directive 2002/46/EC. If vitamins/minerals are part of a combination, the posology must be such that their action is “ancillary” as compared to the action of herbal active substance(s). Taking into account the pharmacodynamic profile of typical traditional herbal substances / preparations, dosages of vitamins/minerals that correspond to currently accepted Recommended Daily Allowance (RDA)-values will be considered to be appropriate, unless justified. Dosages of vitamins/minerals that exceed the upper safe limits established by other scientific committees of the Community as applicable will not be acceptable for traditional herbal medicinal products.

7. PHARMACOKINETIC AND PHARMACODYNAMIC DATA

7.1. Well-established herbal medicinal products.

In applications for marketing authorization, the possibility of pharmacodynamic interactions between the active substances must be considered and discussed in the clinical overview. When data on pharmacokinetic interactions between the active substances are available, they have to be submitted and discussed by the expert.

7.2. Traditional herbal medicinal products

For traditional herbal medicinal products, the profile of traditional use of each constituent and of the combination should be addressed in the expert report. Pharmacodynamic and/or pharmacokinetic data would only be required, if such interactions, e.g. potentiation of the action of constituents, are claimed by the applicant or referred to in the expert report. In case of safety concerns, additional data might be required.