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AD HOC WORKING GROUP ON HERBAL MEDICINAL PRODUCTS

Note for Guidance on  
Fixed Combinations of Herbal Medicinal Products with Long-Term  
Marketing Experience - Guidance to Facilitate Mutual Recognition and  
Use of Bibliographic Data

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The ad hoc Working Group on Herbal Medicinal Products prepared the following Note for guidance on fixed-combinations.

*The views presented in this document are those of the HMPWP, which has been created as a forum for exchange of experience in the field of herbal medicinal products. This document is released for the purposes of transparency and has no legal force with respect to Directive 2001/83/EC.*

# **Fixed Combinations of Herbal Medicinal Products with Long-Term Marketing Experience - Guidance to Facilitate Mutual Recognition and Use of Bibliographic Data**

## **INTRODUCTION**

Fixed combinations of herbal medicinal products are in widespread use in Phytotherapy. This Note for guidance is intended to contribute to a rational assessment of the safety and efficacy of such fixed combinations, therefore guaranteeing the availability of such rational fixed combinations to consumers and medical doctors.

Note for guidance concerning the application of section C.6 Part 4 of the Annex to Directive 91/507/EEC as amended, with a view to the submission of an application for a marketing authorisation for a well-established herbal medicinal product. This guideline should be read in conjunction with current EU guidelines.

## **1. JUSTIFICATION**

Applicants will be required to justify the particular combination of active substances (herbal drugs/herbal drug preparations) proposed. Fixed combination products will only be considered acceptable if the proposed combination is based on valid therapeutic principles.

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 and safety.

### **1.1 Potential advantages of fixed combinations include one of the following:**

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

- i. the 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**

A fixed combination of active substances is 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 organoleptic properties).

### **1.2 Possible 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.

### **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 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.

## **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.

## **3. PHARMACODYNAMIC AND PHARMACOKINETIC DATA**

The possibility of interactions between the active substances should always be considered and discussed in the expert report. When data on interactions are available, they have to be submitted with the dossier and discussed by the expert.

### **3.1 Pharmacodynamic data**

The expert report should address the question of the addition or the potentiation of the pharmacodynamic effects of the various active substances (herbal drug/herbal drug preparation) as far as data are available.

### **3.2 Pharmacokinetic data**

The expert report should address the question of the various pharmacokinetic parameters of each active substance (herbal drug/herbal drug preparation) as far as data are available.

## 4. SAFETY AND EFFICACY

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<sup>1</sup>, 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 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 helpful in reducing the amount of clinical trials to be performed<sup>2</sup> 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, unusual quantitative composition of usually combined substances or one substance entirely new), the data needed are similar to a new chemical entity in the situation where the fixed combination is to be proposed. Existing experience with the substances should be taken into account.

### 4.1 Safety aspects

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 active 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.

This should be read in conjunction with the draft Note for guidance on the non-clinical testing of herbal drug preparations with long-term marketing experience - guidance to facilitate mutual recognition and use of bibliographic data (EMEA/HMPWG/11/99).

### 4.2 Therapeutic data

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

This should be read in conjunction with the draft Points to consider on the evidence of safety and efficacy required for well-established herbal medicinal products in bibliographic applications (EMEA/HMPWG/23/99).

### 4.3 Composition and dosage regimen

The proposed dosage regimen must be justified in the clinical expert report.

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

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<sup>1</sup> Even if the quantitative composition of usually combined substances (herbal drug or herbal drug preparations) has been adjusted to reflect the current scientific knowledge, the combination itself still may be classified as well known.

<sup>2</sup> In some cases this analysis may be sufficient for the justification of the efficacy and safety of the fixed combination of the herbal medicinal products.