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DRAFT

GUIDELINE ON THE NON-CLINICAL DEVELOPMENT OF FIXED COMBINATIONS OF MEDICINAL PRODUCTS

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Disclaimer

This document aims at providing guidance on the development of a non-clinical program for fixed combinations. It is however, without prejudice to the legal basis for submission of a Marketing authorisation application for such product, which should be discussed with the relevant Competent authority on a case-by-case basis.

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EXECUTIVE SUMMARY

When developing a fixed combination the non-clinical program will vary depending on the characteristics of the single components, on the existing non-clinical and clinical experience of their individual and concomitant use as well as the intended clinical use. When there is no experience from use of the combination, even if the individual components are known, bridging studies addressing expected and potential unexpected pharmacodynamic and toxicological interactions are in principle needed. Applicable for any non-clinical combination study, the dose selection should be based on considerations of interspecies differences in pharmacokinetic as well as pharmacodynamics. The aim should be to, as close as possible, mimic the clinical situation, both in terms of systemic exposure of animals to the individual components as well as in relation to pharmacodynamic effects.

1. INTRODUCTION

The rationale for a combination therapy and a fixed combination is often that pharmacological or pharmacokinetic interactions, leading to improved efficacy or safety profiles, compared with the single components. The main aim with the non-clinical studies to support the clinical development of a fixed combination is to characterise potential additive, synergistic, potentiation or antagonistic effects of the compounds when used together and to characterise the pharmacology, pharmacokinetics and toxicology of the combination under development.

2. SCOPE

This document provides guidance on the non-clinical strategies to be considered when developing a fixed combination based on the different data available in order to support the safe human use as well as avoid unnecessary repetition of animal studies. The Guideline may also be considered in situations of development of a combination therapy not involving a fixed combination formulation.

3. LEGAL BASIS

This document should be read in conjunction with Directive 2001/83/EC (as amended).

This guideline does not apply to combined vaccines or to combinations of herbal medicinal products.

4. MAIN GUIDELINE TEXT

4.1 General Consideration

The extent as well as design of non-clinical studies needed to support development of a fixed combination will depend on the available data for the compounds to be combined, as well as the intended clinical use. Several scenarios are possible:

1. A fixed combination of compounds already approved as free combination therapy.
2. A fixed combination of approved compounds not approved as combination therapy.
3. A fixed combination of one or more New Chemical Entities (NCEs) with one or more approved /well know compound.
4. A fixed combination of two or more NCEs

4.2 Planning studies for a fixed combination

When the fixed combination under development includes compounds for which there is sufficiently documented human experience of their individual and combined use, safety studies in animals are in general not required (CPMP/EWP/240/95). However in some situations certain non-clinical testing may still be warranted e.g. when the non-clinical data package does not fulfil the recommendations outlined on the draft Note for Guidance on the Non-Clinical Documentation of Medicinal Products for Mixed Marketing Applications (CPMP/SWP/799/95).

For combination of approved compounds not approved as combination therapy, though the safety and efficacy of the individual substances have been considered adequately documented for approval, some

aspects regarding expected as well as potential unexpected interactions may still need to be addressed (CPMP/EWP/240/95). If pharmacodynamic interactions are the rationale for the combination, such effects should be documented. Relevant non-clinical studies may be part of the proof of principle. Pharmacodynamic data with the combination may also be justified to allow assessment of unexpected/undesirable interactions. Provided that the pharmacokinetics of the single components are adequately characterised in animals, additional non-clinical documentation on pharmacokinetic interactions is generally not needed (CPMP/EWP/240/95). For the safety evaluation of the fixed combination, safety pharmacology and toxicity studies should be considered. The need for (combination) studies will depend on the type of the anticipated interactions between the components and on the range of concentrations and exposures covered in the available studies with the single components. If the systemic exposure expected from the use of the fixed combination is not covered adequately by the existing data, additional studies may be warranted. Additional testing may also be justified if the compounds to be combined target the same organ system(s), or belong to a class of compounds associated with a specific type of toxicity. The toxicological profile of the combination may be studied in non-clinical bridging studies, to support the safe human use and identify potential interactions. In these bridging studies, specific endpoints addressing concerns based on the characteristics (pharmacology, toxicology) of the individual components may be included in addition to the conventional toxicological evaluation. If sufficient systemic exposure can be obtained, identified relevant safety pharmacology endpoints needing to be studied may also be included into the (bridging) toxicity studies. In addition, special and/or mechanistic studies may be warranted, e.g. studies addressing immunotoxicity or dependence, depending on the properties of the individual components in the combination.

For NCEs developed to be used in a fixed combination or for combined therapy, different possibilities can be envisaged. One approach may be to undertake a complete non-clinical development program with the NCE, together with additional bridging studies taking the considerations outlined in this document into account. Another approach may be to perform a more extensive non-clinical development program with the combination, together with a limited set of studies with the NCE alone. In each situation, reference to relevant guidance documents should be made.

4.2.1 Dose Selection

It is desirable that the non-clinical studies are designed in such a way that the exposure of animals to the compounds under evaluation reflects the anticipated human situation. Deviations from the clinical dose ratios may be necessary if there are marked interspecies differences in the pharmacokinetic or pharmacodynamic profiles of the compounds. In such a case, adjustment of the dose ratios may be needed to allow appropriate exposure and to avoid irrelevant pharmacodynamic effects in animals masking effects that are relevant for the human safety assessment.

4.2.2 General toxicity studies

For a fixed combination containing approved compounds indicated for long term use where experience of concomitant use is lacking, a 3-month repeat dose toxicity study in one appropriate species, supported by toxicokinetic data is generally recommended. The need for studies of longer duration or in an additional species will depend on the effects observed with the combination compared with those induced by the individual components, and on the anticipated pharmacodynamic and/or pharmacokinetic interactions. In cases with «complicated» pharmacodynamic and/or safety profiles, or if there is limited clinical experience with any of the components further studies may be warranted. On the other hand, a study of shorter duration may also be justified when the intended clinical use is of short duration. Depending on the pharmacological and toxicological profiles of the individual components, collection of data on specific endpoints in addition to the standard parameters monitored in such studies may be recommended. It is advisable that study designs should be as close as possible to those available for the single components, and it is recommended that parallel groups treated with the individual components are included in the bridging studies.

4.2.3 Genotoxicity:

For fixed combination of non-genotoxic substances, genotoxicity studies with the combination are not needed. If there are concerns regarding genotoxicity for one substance in the combination, further evaluation of e.g. the possibility of a potentiation of the identified effect may be needed. The rationale for addressing such situation should be assessed on a case-by-case basis taking the available knowledge of the substances into consideration.

4.2.4 Carcinogenicity

The carcinogenic potential of a combination should be addressed on the basis of existing information for the individual components. If the fixed combination contains compounds assessed as non-carcinogenic, carcinogenicity studies with the combination would not be needed. If there is any concern related to one included compound, the risk of the concern increasing due to interactions with the additional component, should be carefully assessed. If possible and meaningful, it is advisable to include relevant endpoints eg. for cell proliferation the bridging repeated dose toxicity study(ies), to obtain further data to address any concern identified. As for general toxicity testing, the importance of including parallel groups treated with the individual components is stressed.

If the combination contains one NCE, the ideal situation would be to include additional animal groups treated with the combination into the carcinogenicity study(ies) for the NCE. Deviations from this approach may be acceptable and should be considered on a case-by-case basis. A similar approach as outlined above would apply.

4.2.5 Reproductive Toxicity Studies

When the single components have been adequately tested, and the reproductive/developmental toxicity profiles of these compounds are sufficiently characterised, additional studies with the combination may not be warranted. However, the decision will depend on the nature and properties of the individual components and of their potential interactions.

5. REFERENCES

- CPMP/EWP/240/95: Note for Guidance of Fixed Combination Medicinal Products.
- CPMP/SWP/799/95: Draft Note for Guidance on the Non -Clinical Documentation for Mixed Marketing Authorisation Applications
- CPMP/ICH/286/95 (ICH-M3): Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
- CPMP/ICH/300/95 (ICH-S4A): Note for guidance on Duration of Chronic Toxicity Testing in Animals (Rodent and non Rodent Toxicity Testing)
- Note for Guidance on single dose toxicity Eudralex vol. 3B3BS1A