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POINTS TO CONSIDER ON THE CLINICAL REQUIREMENTS OF MODIFIED RELEASE PRODUCTS SUBMITTED AS A LINE EXTENSION OF AN EXISTING MARKETING AUTHORISATION

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POINTS TO CONSIDER ON THE CLINICAL REQUIREMENTS OF MODIFIED RELEASE PRODUCTS SUBMITTED AS A LINE EXTENSION OF AN EXISTING MARKETING AUTHRISATION

This note are intended to provide a guidance for the evaluation of Modified Release Products as a line extension of an existing marketing authorisation. This Note should be read in conjunction with Directive 2001/83/EC, as amended, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- Note For Guidance on Quality of Modified Release Products:A.Oral Dosage Forms; B. and Transdermal Dosage Forms; Section I (Quality). (CPM/QWP/604/06)
- Note For Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (PharmacoKinetic and Clinical Evaluation). (CPMP/EWP/280/96)
- Points to Consider on Switching between Superiority and Non-inferiority (CPMP/EWP/482/99)
- Topic E10. Step 4 Note for Guidance on Choice of Control Group for Clinical Trials (CPMP/ICH/364/96)

This note addresses the situation when a clinical trial is considered necessary and more specifically design issues like demonstrating non-inferiority and/or equivalence.

INTRODUCTION

The development of modified-release preparations have a clinical rationale as it may reduce dose related side effects, improve efficacy and add to compliance to drug therapy.

Modified release products may be developed to reduced dose frequency which adds to convenience of use which in turn may facilitate compliance. Another rationale for developing modified release preparations is to smoothen the peaks of the plasma concentration curves in order to prevent peak concentration related adverse events.

Rarely a modified release preparation has been developed solely in order to mimic a TID or QID dosage schedule. In these cases the modified release preparation should be bioequivalent with the immediate release formulation given in dose schedule that is imitated.

In general modified-release formulations are not bioequivalent to their immediate release form. Consequently it might be difficult to assess whether the benefit/risk of the modified release is comparable to the corresponding doses of the immediately release form. Depending on the clinical setting additional clinical data will be required. See NfG concerning modified released products.

I. Principles

As a principle, additional comparative clinical data are needed for modified release products developed as a line extension of an existing marketing authorisation UNLESS a justification for not doing so is given and accepted.

As this is a line extension and therefore the efficacy and safety of the immediate release product is known, the major issue would be to demonstrate that the new formulation is as effective as the existing one. Additionally the benefits of the new formulation should be shown or justified.

Whether these pharmacodynamic / clinical studie(s) should show equivalence or non-inferiority as compared to the standard formulation depends on the direction of the effect or safety issue at stake. In case efficacy and safety are closely related (e.g. anti-arrhythmic agents) equivalence studies are needed for showing that the effect studied remains within the equivalence margins. If an effect is bi-directional (e.g. thrombolytics, insulines) equivalence trials are needed as well. If an effect is unidirectional a demonstration of non-inferiority might be sufficient.

The type of studies that are required depends on whether appropriate, dynamic endpoints can be defined, whether the relationship between the dynamic markers and clinical efficacy is known, whether assay sensitivity is guaranteed and whether a non-inferiority margin or equivalence margins can be defined.

Such equivalence and non-inferiority studies may include a placebo arm besides the immediate and modified release preparation. A placebo arm is mandatory if assay sensitivity of the trial cannot be guaranteed (see ICH E10).

In addition**,** equivalence margins or non-inferiority margins have to defined and justified irrespective whether the endpoint is based on, pharmacodynamic measurement or clinical variable.

If for a modified release product an indication is claimed different from that of the immediate release formulation a clinical development plan in accordance with existing guidelines or the state of art is required.

II. Requirements

In principle, additional comparative clinical data are needed for modified release products developed as a line extension of an existing marketing authorisation.

The rationale for the development of a modified release product, the existence of a plasma concentration- effect relationship and the condition studied determines the extend of these clinical data.

An applicant should justify the clinical development plan of a modified release product i.e.:

Justify the rationale of the modified release product.

Justify in case an equivalence or non-inferiority study is performed, the choice of equivalence studies versus non-inferiority study, the lack of a placebo arm, the choice of equivalence margins for the endpoints chosen and the choice of the endpoints itself in the light of this rationale.

Justify the absence of a comparative study e.g. provide evidence of a well-established plasma concentration effect relationship (with respect to efficacy, safety or both) in the light of this rationale.