European Medicines Agency
Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP) CONCEPT PAPER

SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING RECOMBINANT HUMAN ERYTHROPOIETIN

ANNEX TO THE GUIDELINE FOR THE DEVELOPMENT OF SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY DERIVED PROTEINS AS ACTIVE SUBSTANCE - (NON) CLINICAL ISSUES

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Note:

Any comments to this Concept Paper should be sent to the EMEA Comparability Working Party Secretariat (Fax: +44 20 74 18 86 13 or E-mail: susana.soobhujhun@emea.eu.int) by end of January 2005

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I Introduction

An applicant may choose to develop a new recombinant human erythropoietin (rh-erythropoietin) containing medicinal product claimed to be "similar" (biological) to an original, rh-erythropoietin-containing medicinal product (reference product), which has been granted a marketing authorisation in the Community.

The guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance - non-clinical and clinical issues - lays down the general requirements for demonstration of similar nature of two biological products with respect of safety and efficacy in terms of safety and efficacy. A product class-specific guidance as Annex to the above guideline will lay down specific requirements for the demonstration of comparability of two rh-erythropoietin - containing medicinal products with respect to safety and efficacy.

This guideline should be read in conjunction with the requirements laid down in the EU Pharmaceutical legislation and other relevant CHMP guidelines (see section VI).

II Problem statement

Human erythropoietin is a 165 amino acid protein. The biological activity is strongly dependent on the glycosilation pattern. The characterisation of the protein structure is based on physico-chemical, and biological methods.

For rh-erythropoietin attention should be given to product-related substances/impurities in particular to the glycosylation profile and process-related impurities.

Recombinant rh-erythropoietin is usually well tolerated provided that the stimulation of bone marrow is controlled by limiting the amount and rate of haemoglobin increase. Failure to control the bone marrow response may result in hypertension and thrombotic complications.

Pure red cell aplasia (PRCA), in association with neutralising antibodies to native rh-erythropoietin, has been observed in patients treated with recombinant rh-erythropoietin and predominantly in patients with chronic renal failure treated with epoietin alfa.

III Discussion

The guideline will address the requirements in terms of pre-clinical and clinical data necessary to ensure that a new biosimilar medicinal product has a comparable safety and efficacy as the reference medicinal product.

The main topics addressed in the guideline are the following:

Pre-clinical requirements

While a complete set of routine toxicological studies is not required for epoietins developed as similar biological products, recommendations will be given to the choice of appropriate species and model to be used to study safety pharmacology and to compare the pharmacodynamic effects of the test and the reference products as well as for the need for toxicological studies.

Clinical requirements

Guidance will be given on the following critical points:

Pharmacokinetics

- Design of pharmacokinetic studies

Pharmacodynamics

- Design of pharmacodynamic studies, including choice and relevance of pharmacodynamic markers

Efficacy

The effect of the new product should be compared to the reference product in randomised clinical trials that are sensitive to potential differences between the two medicinal products.

The efficacy guidance will address methodological considerations, including:

- Selection of the most relevant patient population/therapeutic indication
- Design and recommended primary and secondary clinical endpoints in efficacy studies
- Clinical endpoints,
- Dosing strategy
- Duration of the studies
- Extrapolation of clinical data to relevant patients 'populations.

Safety

Guidance will be provided on the following itms:

- Extent of the safety database
- Requirements for long term immunogenicity data
- Requirements for a validated antibody assay with acceptable sensitivity
- Requirements for a Pre-licensing pharmacovigilance plan.
- Recommendations for collection and storage of plasma/serum samples in patients for whom a switch in epoietin product is planned.

IV Recommendations

It is proposed to draft an Annex to the guideline on comparability of biological medicinal products containing biotechnology-derived proteins as active substance–(non) clinical issues- regarding recombinant human rh-erythropoietin containing products.

V Timetable

It is anticipated that an Annex to the Guideline on comparability of biological medicinal products containing biotechnology derived proteins as active substance–(non) clinical issues will be available 6 month after adoption of the concept paper and will be released 3 month for external consultation, before finalisation within 6 month.

VI References

- Directive 2001/83/EC, as amended
- Part II of the Annex I of Directive 2001/83/EC, as amended
- CHMP/437/04 Guideline on similar biological medicinal products
- ICH topic S6 - Note for guidance on Pre-clinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (CPMP/ICH/302/95)
- ICH topic E9 statistical principles for clinical trials – Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96)
- ICH topic E10 - Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96)
- Points to consider on switching between superiority and non-inferiority (CPMP/EWP/482/99)