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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

ANNEX TO GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: NON-CLINICAL AND CLINICAL ISSUES

GUIDANCE ON SIMILAR MEDICINAL PRODUCTS CONTAINING RECOMBINANT ERYTHROPOIETINS

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20)
E-mail: mail@emea.eu.int http://www.emea.eu.int

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EXECUTIVE SUMMARY

This Annex to the *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues* (EMEA/CHMP/BMWP/42832/2005) lays down the non-clinical and clinical requirements for erythropoietin containing medicinal products claiming to be similar to another one already marketed.

The non-clinical section addresses the pharmaco-toxicological assessment. The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies as well as the risk management plan. Criteria for extrapolation of clinical data to other indications approved for the reference medicinal product are discussed.

1. INTRODUCTION (background)

The Marketing Authorisation (MA) application dossier of a new recombinant erythropoietins claimed to be similar to a reference product already authorised, shall provide the demonstration of comparability of the product applied for to a reference product authorised in the EU.

Human erythropoietin is a 165 amino acid glycoprotein mainly produced in the kidneys and is responsible for the stimulation of red blood cell production. Erythropoietin for clinical use is produced by recombinant DNA technology (epoetin) using mammalian cells as expression system.

All epoetins in clinical use have a similar amino acid sequence as endogenous erythropoietin but differ in the glycosylation pattern. Glycosylation influences pharmacokinetics and may affect efficacy and safety, particularly immunogenicity. Physico-chemical and biological methods are available for characterisation of the protein.

Epoetin-containing medicinal products are currently indicated for several conditions such as anaemia in patients with chronic renal failure, chemotherapy-induced anaemia in cancer patients, and for increasing the yield of autologous blood from patients in a pre-donation programme. The mechanism of action of epoetin is the same in all currently approved indications but the doses required to achieve the desired response may vary considerably and are highest in the oncology indications. Epoetin can be administered intravenously or subcutaneously.

Recombinant erythropoietins have a relatively wide therapeutic window and are usually well tolerated provided, that the stimulation of bone marrow is controlled by limiting the amount and rate of haemoglobin increase. The rate of haemoglobin increase may vary considerably between patients and is dependent not only on the dose and dosing regimen of epoetin, but also other factors, such as iron stores, baseline haemoglobin and erythropoietin levels, and the presence of concurrent medical conditions such as inflammation.

Exaggerated pharmacodynamic response may result in hypertension and thrombotic complications. Moreover, pure red cell aplasia (PRCA), due to neutralising anti-erythropoietin antibodies, has been observed predominantly in renal anaemia patients treated with subcutaneously administered epoetin. Because antibody-induced PRCA is a very rare event and usually takes months to years of epoetin treatment to develop, such events are unlikely to be identified in pre-authorisation studies. In addition, possible angiogenic and tumour promoting effects of epoetin might be of importance in selected populations.

2. SCOPE

The guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CPMP/42832/05/draft) lays down the general requirements for demonstration of the similar nature of two biological products in terms of safety and efficacy.

This product specific guidance is an Annex to the above guideline and presents the current view of the CHMP on the application of the guideline for demonstration of comparability of two recombinant human erythropoietin containing medicinal products. This Guideline should be read in conjunction with the requirements laid down in the EU Pharmaceutical legislation and with relevant CHMP guidelines (see section 8).

3. LEGAL BASIS

Directive 2001/83/EC, as amended and Part II of the Annex I of Directive 2001/83/EC, as amended.

4. MAIN GUIDELINE TEXT

4.1 NON-CLINICAL STUDIES

Before initiating clinical development, non-clinical studies should be performed. These studies should be comparative in nature and should be designed to detect differences in the pharmaco-toxicological response between the similar biological medicinal product and the reference medicinal product and should not just assess the response *per se*. The approach taken will need to be fully justified in the non-clinical overview.

Pharmacodynamics studies

In vitro studies:

In order to assess any alterations in reactivity between the similar biological medicinal and the reference medicinal product, data from a number of comparative bioassays (e.g. receptor-binding studies, cell proliferation assays), many of which may already be available from quality-related bioassays, should be provided.

In vivo studies:

The erythrogenic effects of the similar biological medicinal product and the reference medicinal product should be quantitatively compared in an appropriate animal assay (e.g. the European Pharmacopoeia polycythaemic and/or normocythaemic mouse assay; data may be already available from quality-related bioassays). Additional information on the erythrogenic activity may be obtained from the described repeat dose toxicity study.

Toxicological studies

Data from at least one repeat dose toxicity study in a relevant species (e.g. rat) should be provided. Study duration should be at least 4 weeks. The study should be performed in accordance with the requirements of the "Note for guidance on repeated dose toxicity" (CPMP/SWP/1042/99) and include appropriate toxicokinetic measurements in accordance with the "Note for guidance on toxicokinetics: A Guidance for assessing systemic exposure in toxicological studies" (CPMP/ICH/384/95). In this context, special emphasis should be laid on the determination of immune responses.

Data on local tolerance in at least one species should be provided in accordance with the "Note for guidance on non-clinical local tolerance testing of medicinal products" (CPMP/SWP/2145/00). If feasible, local tolerance testing can be performed as part of the described repeat dose toxicity study.

Safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not routine requirements for non-clinical testing of similar biological medicinal products containing EPO as active substance.

4.2 Clinical studies

Pharmacokinetic studies

The relative pharmacokinetic properties of the similar biological medicinal product and the reference product should be determined in single dose crossover studies using subcutaneous and intravenous administration. Healthy volunteers are considered an appropriate study population. The selected dose should be in the sensitive part of the dose-response curve. The primary pharmacokinetic parameter is AUC and the secondary pharmacokinetic parameters are C_{max} and $T_{1/2}$ or CL/F. Equivalence margins have to be defined a priori and appropriately justified. Differences in $T_{1/2}$ for the IV and the SC route of administration and the dose dependence of clearance of epoetin should be taken into account when designing the studies.

Pharmacodynamic studies

Pharmacodynamics should preferably be evaluated as part of the comparative pharmacokinetic studies. The selected dose should be in the linear ascending part of the dose-response curve. In single dose studies, reticulocyte count is the most relevant and therefore recommended pharmacodynamic marker for assessment of the activity of epoetin. On the other hand, reticulocyte count is not an established surrogate marker for efficacy of epoetin and therefore no suitable endpoint in clinical trials.

Clinical efficacy studies

Comparable clinical efficacy between the similar and the reference product should be demonstrated in at least two adequately powered, randomised, parallel group clinical trials.

Confirmatory studies should be double-blind to avoid bias. If this is not possible, at minimum the person(s) involved in decision-making (e.g. dose adjustment) should be effectively masked to treatment allocation.

Sensitivity to the effects of epoetin is higher in erythropoietin-deficient than non erythropoietin-deficient conditions and is also dependent on the responsiveness of the bone marrow. Patients with renal anaemia are therefore recommended as the target study population as this would provide the most sensitive model. Other reasons for anaemia should be excluded.

The clinical trials should include a ‘correction phase’ study during anaemia correction and a ‘maintenance phase’ study in patients on epoetin maintenance therapy.

A correction phase study is important to determine response dynamics and dosing during the anaemia correction phase. It should only include treatment naïve patients or previously treated patients after a suitably long epoetin-free and transfusion-free period (e.g. 3 months). It is recommended that the comparative phase be 6 months in order to establish comparable clinical efficacy of the test and the reference product in patients with stabilised haemoglobin levels and epoetin dose. Shorter study duration should be justified.

The study design for a maintenance phase study should minimise baseline heterogeneity and carry over effects of previous treatments. Patients included in a maintenance phase study should be optimally titrated on the reference product (stable haemoglobin in the target range on stable epoetin dose and regimen without transfusions) for three month. Thereafter, study subjects should be randomised to the similar or the reference product and followed up for at least three and ideally 6 months to avoid carry over effects.

In the course of both studies, epoetin doses should be closely titrated to achieve (correction phase study) or maintain (maintenance phase study) target haemoglobin concentrations. The protocol should

clearly pre-define the dose adjustment algorithm. Haemoglobin target range and titration schedule should be in accordance with current clinical practise.

In the correction phase study 'haemoglobin responder rate' (proportion of patients achieving a pre-specified haemoglobin target) or 'change in haemoglobin' is the preferred primary endpoint. In the maintenance phase study 'haemoglobin maintenance rate' (proportion of patients maintaining haemoglobin levels within a pre-specified range without transfusion) or 'change in haemoglobin' is the preferred primary endpoint. Epoetin dosage should be a co-primary endpoint in both studies. The fact that epoetin dose is titrated to achieve the desired response reduces the sensitivity of the haemoglobin-related endpoints to detect possible differences in the efficacy of the treatment arms.

Equivalence margins for both co-primary endpoints have to be pre-specified and appropriately justified and serve as the basis for powering the studies.

Transfusion requirements should be included as an important secondary endpoint.

Since epoetin doses necessary to achieve target haemoglobin levels differ in pre-dialysis and dialysis patients, these two populations should not be mixed in the same study.

Clinical comparability has to be demonstrated for both routes of administration. This is best achieved by performing separate studies, e.g. a correction phase study in a pre-dialysis population using SC epoetin and a maintenance phase study in a haemodialysis population using IV epoetin.

4.3 CLINICAL SAFETY

Comparative safety data from the efficacy trials are sufficient to provide an adequate pre-marketing safety database.

The applicant should provide at least 12-month comparative immunogenicity data pre-authorisation. Retention samples for both correction phase and maintenance phase studies are recommended. For detection of anti-epoetin antibodies, a validated, highly sensitive assay should be used.

4.4 PHARMACOVIGILANCE PLAN

Within the authorisation procedure the applicant should present a risk management programme/ pharmacovigilance plan in accordance with current EU legislation and pharmacovigilance guidelines. In order to further study the safety profile of the similar biological medicinal product, particularly rare serious adverse events such as immune mediated PRCA, safety data should be collected from a cohort of patients representing all approved therapeutic indications.

4.5 EXTENSION OF INDICATION

Demonstration of efficacy and safety in renal anaemia may allow extrapolation to other indications of the reference medicinal product if appropriately justified by the applicant.

REFERENCES (scientific and / or legal)

- Directive 2001/83/EC, as amended.
- Part II of the Annex I of Directive 2001/83/EC, as amended.
- Guideline on similar biological medicinal products (CHMP/437/04/draft).
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CPMP/42832/05/draft).

- Note for guidance on repeated dose toxicity (CPMP/SWP/1042/99).
- Note for guidance on toxicokinetics: A Guidance for assessing systemic exposure in toxicological studies (CPMP/ICH/384/95).
- Note for guidance on non-clinical locale tolerance testing of medicinal products (CPMP/SWP/2145/00).
- Guideline on risk management systems for medicinal products for human use (EMEA/CHMP 96286/2005).
- Note for Guidance on Good Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95).
- ICH Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03 - Final approval by CHMP on PHV).