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DRAFT

GUIDELINE ON NON-CLINICAL AND CLINICAL DEVELOPMENT OF SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING RECOMBINANT ERYTHROPOIETINS (Revision)

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This guideline replaces the 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 (CHMP/94526/05)

Comments should be provided electronically using this template to BMWP.secretariat@emea.europa.eu

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GUIDELINE ON NON-CLINICAL AND CLINICAL DEVELOPMENT OF SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING RECOMBINANT ERYTHROPOIETINS

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This guideline 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 and the clinical section 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)

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 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 dosages required to achieve the desired response may vary considerably and are highest in the oncology indications. Epoetin can principally be administered intravenously (IV) or subcutaneously (SC).

Recombinant erythropoietins (epoetins) 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 endogenous 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.

The Marketing Authorisation (MA) application dossier of a new recombinant erythropoietin claimed to be similar to a reference product already authorised, shall provide the demonstration of comparable quality, safety and efficacy of the product applied for to a reference product authorised in the EU.

2. SCOPE

This product specific guideline presents the current view of the CHMP on the non-clinical and clinical data requirements for demonstration of comparability of two recombinant human erythropoietin containing medicinal products and should be read in conjunction with the requirements laid down in the EU Pharmaceutical legislation and with other 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 preclinical safety evaluation of biotechnology-derived pharmaceuticals“ (CPMP/ICH/302/95) and the “Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues“ (CHMP/42832/05). Specific guidance on the design and conduct of this study can also be found in the "Note for guidance on repeated dose toxicity" (CPMP/SWP/1042/99). Appropriate toxicokinetic measurements should be performed ("Note for guidance on toxicokinetics: A guidance for assessing systemic exposure in toxicological studies", CPMP/ICH/384/95) as part of the repeat dose toxicity study and include a determination of antibody formation (“Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins”, EMEA/CHMP/BMWP/14327/2006).

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). It is preferable to perform local tolerance testing as part of the described repeat dose toxicity study, if feasible.

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 pharmacokinetic properties of the similar biological medicinal product and the reference product should be compared in single dose crossover studies for the routes of administration applied for, usually including both 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 pharmacokinetic parameters of interest include AUC, 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

Similar clinical efficacy between the similar and the reference product should be demonstrated in adequately powered, randomised, parallel group clinical trials. Since pharmacokinetics and dose requirements usually differ for IV and SC use, similar efficacy between the test and the reference product should be ensured for both routes of administration. This could be achieved by performing separate clinical trials for both routes or by performing one clinical trial for one route and providing adequate bridging data for the other route (see below).

Confirmatory studies should preferably 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 and without major complications (such as severe/chronic infections or bleeding, or aluminium toxicity), expected to relevantly impair the treatment response to epoetin, are therefore recommended as the target study population. Other reasons for anaemia should be excluded. Since epoetin doses necessary to achieve or maintain target haemoglobin levels usually differ in pre-dialysis and dialysis patients, these two populations should not be mixed in the same study.

For demonstration of similar efficacy for both routes of administration it is recommended to perform a 'correction phase' study using SC epoetin (e.g. in a pre-dialysis population) and a 'maintenance phase' study using IV epoetin (e.g. in a haemodialysis population). The combination of such trials is expected to provide a maximum of information with a minimum of clinical trials.

A correction phase study will determine response dynamics and dosing during the anaemia correction phase and is particularly suitable to characterize the safety and immunogenicity profile of the similar biological medicinal product. 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).

A maintenance phase study, on the other hand, may be more sensitive to detect differences in biological activity between the similar and the reference product. 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 a suitable duration of time (e.g. 3 months). Thereafter, study subjects should be randomised to the similar or the reference product, maintaining their pre-randomisation epoetin dosage, dosing regimen and route of administration.

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 titration algorithm should be the same for both treatment groups and be in accordance with current clinical practise.

In the correction phase study 'haemoglobin responder rate' (proportion of patients achieving a prespecified 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) or 'change in haemoglobin' is the preferred primary endpoint. However, 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. Therefore, epoetin dosage should be a co-primary endpoint in both study types.

The primary efficacy endpoints should preferably be assessed after 5 to 6 months in both the correction phase as well as the maintenance phase study in order to avoid potential carry-over effects

from baseline treatment and allow full assessment of potential differences in both endpoints in the presence of stabilised haemoglobin levels and epoetin dosages. If the primary efficacy assessment is performed at an earlier time point the applicant will need to demonstrate that potential differences in efficacy have been fully captured.

Equivalence margins for both co-primary endpoints should be pre-specified and appropriately justified and should serve as the basis for powering the studies. If haemoglobin is used as primary endpoint, an equivalence margin of ± 0.5 g/dL is recommended. Transfusion requirements should be included as an important secondary endpoint.

An alternative approach to demonstrate similar efficacy for both routes of administration would be to show comparable efficacy for one route of administration in a comparative clinical trial and provide comparative single dose and multiple dose PK/PD bridging data in an epoetin-sensitive population (e.g. healthy volunteers) for the other route of administration. The primary efficacy endpoint in the clinical trial should preferably be assessed after 5-6 months. The multiple dose PK/PD study should be at least 4 weeks in duration using a fixed epoetin dosage within the therapeutic range and change in haemoglobin as primary PD endpoint.

Since comparative immunogenicity data will always be required for SC use, if applied for, the most reasonable approach in this alternative scenario would be to perform a correction phase study using SC epoetin and to provide PK/PD bridging data for the IV route.

In this case, patients included in a SC correction phase study as described above should be treated with test or reference ideally for a total of 12 months to obtain 12-month comparative immunogenicity data (see section 4.3 below). At this point patients on the reference medicinal product should be switched to the test product and all patients followed for another e.g. 6 months to increase the safety and immunogenicity database of the similar medicinal product.

If only one route of administration is applied for, a single dose PK/PD study and either a correction phase or a maintenance phase study as described above should be performed. The choice of study design should take into account the most likely use in clinical practice and a.m. considerations regarding safety and immunogenicity assessment. Therefore, a correction phase study may be most appropriate in case of intended SC use and a maintenance phase study for IV use.

4.3 Clinical safety

Comparative safety data from the efficacy trials are usually sufficient to provide an adequate pre-marketing safety database. Adverse events of specific interest include hypertension/aggravation of hypertension and thromboembolic events.

The applicant should submit preferably12-month comparative immunogenicity data pre-authorisation. Principles of immunogenicity assessment are laid down in the "Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins" (EMEA/CHMP/BMWP/14327/2006). Concomitant immunogenicity data on the reference medicinal product are important for proper interpretation of results. If the comparative phase of the immunogenicity assessment is less than 12 months the applicant will need to provide sound argument that this does not increase the uncertainty about the immunogenic potential of the biosimilar epoetin.

The use of a validated, highly sensitive antibody assay, able to detect both early and late immune responses, is mandatory. Detected antibodies need to be further characterized including their neutralising potential. Retention samples for both correction phase and maintenance phase studies are recommended.

Due to their rarity, neutralising antibodies or even PRCA are unlikely to be captured pre-marketing and, if occurring, would constitute a major safety concern. Although, the relevance of binding, non-neutralizing antibodies is not clear, a relevantly increased frequency of such antibodies for the test product would elicit a safety concern and contradict the assumption of biosimilarity.

Since the SC route of administration is usually more immunogenic than the IV route and patients with renal anaemia constitute the population at risk for developing anti-epoetin antibody induced PRCA, the immunogenicity database should include a sufficient number of SC treated patients with renal anaemia, unless SC use in this population is not applied for.

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.

The risk management plan should particularly focus on rare serious adverse events such as immune mediated PRCA.

4.5 Extension of indication

Since the mechanism of action of epoetin is the same for all currently approved indications and there is only one known epoetin receptor, demonstration of efficacy and safety in renal anaemia will allow extrapolation to other indications of the reference medicinal product with the same route of administration.

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).
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CPMP/42832/05).
- 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).
- Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006)