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Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins

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This is a technical update to reflect current best practise with regard to implementation of 3Rs approaches and it is not intended as a full revision of this guideline (only section 4 is affected). These changes are considered to be minor and uncontroversial and consequently a consultation phase was considered unnecessary.

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Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins

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Executive summary

The main aim of the guideline is to address the non-clinical and clinical requirements for recombinant human erythropoietin (epoetin)-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 and termed epoetin.

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 including 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).

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-epoetin antibodies has been observed, predominantly in renal anaemia patients treated with subcutaneously administered epoetin. Because antibody-induced PRCA usually is a very rare event taking 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 epoetin 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.

In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and Directive 2010/63/EU on protection of animals used for scientific purposes, the 3R principles (replacement, reduction and refinement) should be applied to development of medicinal products.

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 epoetin-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. Non-clinical studies

As regards non-clinical development, a stepwise approach should be applied to evaluate the similarity of the biosimilar and reference medicinal product.

Non-clinical studies should be performed before initiating clinical trials. In vitro studies should be conducted first and a decision then made as to the extent of what, if any, in vivo work will be required. General guidance on the stepwise approach is provided in the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues". The approach taken will need to be fully justified in the non-clinical overview.

In vitro studies

In order to compare differences in biological activity between the similar and the reference medicinal product, data from comparative bioassays should be provided, including receptor-binding studies and functional assays (e.g. cell proliferation assays in human cell lines). Wherever possible, analytical methods should be standardised and validated according to relevant guidelines.

In vivo studies

Generally, comparative in vivo studies in animals are not recommended. Potency measurement of the erythrogenic effects of the similar biological medicinal product may already be available from quality-related bioassays (e.g. the European Pharmacopoeia normocythaemic mouse assay).

Measurement of pharmacokinetic and pharmacodynamic parameters is expected to be included in clinical studies and similar studies in animals are usually not expected to contribute additional relevant information to the biosimilarity exercise. Such studies as well as toxicological studies should only be considered in specific cases, as explained in the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues."

5. Clinical studies

5. 1 Pharmacokinetic (PK) 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, Cmax and T1/2 or CL/F. Equivalence margins have to be defined a priori and appropriately justified. Differences in T1/2 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.

5.2 Pharmacodynamic (PD) 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 not a suitable endpoint in clinical trials.

5.3 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 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.

The following sections present different options and recommendations on how to demonstrate similar efficacy of two epoetin-containing medicinal products. A sponsor may choose from these options or modify them but should always provide sound scientific justification for the approach taken.

Demonstration of efficacy for both routes of administration

a) Similar efficacy for both routes of administration may be demonstrated by performing two separate clinical trials.

The combination of 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) would be expected to provide a maximum of information on the biosimilar epoetin.

A correction phase study will determine response dynamics and dosing during the anaemia correction phase and is particularly suitable to characterize the safety profile related to the pharmacodynamics of the similar biological medicinal product. It should include treatment naïve patients or previously treated patients after a suitably long epoetin-free and red blood cell transfusion-free period (e.g. 3 months). In case of pre-treatment with long-acting erythropoesis stimulating agents (such as pegylated epoetin), the treatment-free phase may need to be longer.

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, although experience suggests that

correction phase studies are also likely to be sufficiently discriminatory. 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 (usually at least 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.

Alternatively, both the SC and the IV study may be performed in the maintenance setting if appropriately justified.

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.

Data for calculation of the primary efficacy endpoints should be collected during an appropriate evaluation period. A 4-week evaluation period from study month 5 to 6 in both the correction phase as well as the maintenance phase study has been found suitable 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 change from baseline in haemoglobin is used as the primary endpoint, an equivalence margin of ± 0.5 g/dL is recommended. Transfusion requirements should be included as an important secondary endpoint.

b) Another 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 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 clinical trial using SC epoetin and to provide PK/PD bridging data for the IV route.

In this case, patients included in a SC study should be treated with test or reference ideally for a total of 12 months to obtain 12-month comparative immunogenicity data (see section 5.4 below). At this point patients on the reference medicinal product should be switched to the test product and all patients followed, e.g. for another 6 months, to increase the safety and immunogenicity database of

the similar medicinal product. Otherwise, regarding the design, enrolled population and endpoints of the clinical trial, the same considerations apply as stated in subsection a) above.

Demonstration of efficacy for one route of administration

If only one route of administration is intended to be applied for, a single dose PK/PD study and either a correction phase or a maintenance phase study for the desired route should be performed. Regarding the design, enrolled population and endpoints of the clinical trial, the same considerations apply as stated in subsection a) above.

The lack of data in the other route of administration will be clearly reflected in the SmPC.

5.4 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 at least 12-month 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). In the absence of standardized assays, concomitant immunogenicity data on the reference medicinal product are required for proper interpretation of results. The comparative phase should preferably cover the complete 12 month assessment period. For shorter comparative phases, 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 (low affinity antibodies, especially IgM class) and late (high affinity antibodies) 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 markedly 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.

6. 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 and tumour-promoting potential.

7. Extrapolation 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.

8. References

- 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 local tolerance testing of medicinal products (CPMP/SWP/2145/00).
- ICH M3(R2) "Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals" (CPMP/ICH/286/95).
- Note for Guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95)
- 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)