European Medicines Agency
Evaluation of Medicines for Human Use

London, 16 June 2005
EMEA/CHMP/94526/2005

COMMITTEE FOR HUMAN MEDICINAL PRODUCTS (CHMP)

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

GUIDANCE ON BIOSIMILAR MEDICINAL PRODUCTS CONTAINING RECOMBINANT ERYTHROPOIETINS

DISCUSSION AT THE BMWP WORKING PARTY	APRIL 2005 to JUNE 2005
TRANSMISSION TO THE CHMP	JUNE 2005
RELEASE FOR CONSULTATION	JUNE 2005
DEADLINE FOR COMMENTS	OCTOBER 2005

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.eu.int http://www.emea.eu.int
©EMEA 2005 Reproduction and/or distribution of this document is authorised for non commercial purposes only provided the EMEA is acknowledged

1. Introduction

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 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 is a membrane-bound post-translational process which influences pharmacokinetics and may affect efficacy and safety, particularly immunogenicity.

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 and 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 of epoetin but also other factors such as iron stores, baseline haemoglobin, and the presence of concurrent medical conditions.

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 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 difficult to be picked up in pre-authorisation studies.

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 similar nature of two biological products in terms of safety and efficacy.

This product specific guidance as an Annex to the above guideline presents the current view of the CHMP on the application of the guideline for demonstration of comparability of two recombinant human erythropoietin medicinal products. The final set of studies necessary to fulfill non-clinical and clinical requirements for a given medicinal product will be determined by data generated by the comparability exercise itself.

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. Non-clinical studies

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

3.1 Pharmacodynamics studies

In vitro studies:

In order to assess any alterations in reactivity between the similar biological medicinal product and the reference medicinal product, data from a number of comparative bioassays (e.g. receptor-binding

©EMEA 2005

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 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.

3.2 Toxicological studies

Data from at least one repeat dose toxicity study in a relevant species (e.g. rat, dog) should be provided. Study duration should be at least 3 months. 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 (i) pharmacodynamic measurements (i.e. effects on erythrogenic parameters like e.g. haemoglobin level, haematocrit, red blood cell count) and (ii) 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 immunogenic responses.

Data on local tolerance in at least one species should be provided in accordance with the "Note for Guidance for 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 recombinant human erythropoietin as active substance.

4. Clinical studies

4.1 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 primary PK parameter is AUC and the secondary PK parameters are C_{max} and T1/2. Equivalence margins have to be defined a priori and justified, primarily on clinical grounds.

4.2 Pharmacodynamic studies

Reticulocyte count is a relevant pharmacodynamic marker for the activity of epoetin and recommended to be used in comparative pharmacodynamic studies. On the other hand, reticulocyte count is not an established surrogate marker for efficacy of epoetin and therefore no suitable endpoint in clinical trials.

4.3 Clinical efficacy studies

Equivalent therapeutic 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 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 blinded 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.

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

©EMEA 2005

A ‘titration 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 period (at least 3 months). The comparative phase should be at least 12 weeks in order to establish therapeutic equivalence of the similar and the reference product.

The study design for a maintenance study should minimise baseline heterogeneity and carry over effect of previous treatments. It is recommended to include in a maintenance phase study patients optimally titrated on the reference product (stable haemoglobin in the target range on stable epoetin dose and regimen) for at least three month. Thereafter, study subjects should be randomised to the similar or the reference product and followed up for of at least three month. A longer period comparative phase (e.g. 6 month) will be needed if baseline treatment heterogeneity and carry over effects cannot be excluded.

To avoid confounding factors, participating patients in either study should not have been receiving red blood cell transfusions for an appropriate length of time prior to the treatment phase.

In the course of these studies, epoetin doses should be closely titrated to achieve and maintain haemoglobin concentrations. The protocol should clearly pre-define the haemoglobin changes that will demand a change in the dose of epoetin.

Preferably, ‘haemoglobin responder rate’ (proportion of patients achieving a pre-specified haemoglobin target in the ‘titration phase study’) or ‘haemoglobin maintenance rate’ (proportion of patients maintaining haemoglobin levels within a pre-specified range in the ‘maintenance phase’ study) and epoetin dosage should be co-primary endpoints. The fact that epoetin dose is titrated to achieve the desired response reduces the sensitivity of the haemoglobin-targeted endpoints to detect possible differences in the efficacy of the treatment arms. The need of combined end points should therefore be considered but knowing that this reduces the sensitivity of trial. Regardless of the endpoint definition, any relevant difference in the used dose would contradict the assumption of similarity.

Transfusion requirement should be included as secondary endpoint.

Due to different epoetin doses necessary to achieve target haemoglobin level in pre-dialysis and dialysis patients, these two populations should be investigated in separate studies.

Therapeutic equivalence has to be demonstrated for both routes of administration. This is best achieved by performing separate studies (e.g. a ‘titration phase’ s.c. study in a pre-dialysis population and a ‘maintenance phase’ i.v. study in a haemodialysis population).

5. Clinical safety

Safety data from at least 300 patients treated with the similar biological medicinal product in the efficacy trials is considered sufficient to provide an adequate pre-marketing safety database and to exclude excessive immunogenicity.

The applicant should provide at least 12-month immunogenicity data in patients treated with the similar biological medicinal product. In this respect, retention samples for both ‘titration’ and ‘maintenance’ studies are recommended. For detection of anti-epoetin antibodies, a validated, highly sensitive assay should be used.

6. Pharmacovigilance plan

The sponsor has to present a pharmacovigilance plan to address immunogenicity and potential rare serious adverse events. Special attention should be paid on the possibility of antibody-induced PRCA and immune-related adverse events.

For those indications where higher epoetin doses are required additional safety data should be generated.

©EMEA 2005

7. Extension of indication

Appropriate demonstration of efficacy and safety in the most sensitive clinical model (renal failure), may allow extension to other indications of the reference product if the mode of action is the same and if appropriately justified by current scientific knowledge.

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/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 local tolerance testing of medicinal products (CPMP/SWP/2145/00).

©EMEA 2005

European Medicines Agency
Evaluation of Medicines for Human Use

London, 16 June 2005
EMEA/CHMP/31329/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

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

GUIDANCE ON BIOSIMILAR MEDICINAL PRODUCTS CONTAINING RECOMBINANT GRANULOCYTE-COLONY STIMULATING FACTOR

DISCUSSION AT THE BMWP WORKING PARTY	FEBRUARY 2005
TRANSMISSION TO CHMP	JUNE 2005
RELEASE FOR CONSULTATION	JUNE 2005
DEADLINE FOR COMMENTS	OCTOBER 2005

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 8613
E-mail: mail@emea.eu.int http://www.emea.eu.int
©EMEA 2004 Reproduction and/or distribution of this document is authorised for non commercial purposes only provided the EMEA is acknowledged

1. Introduction

The marketing authorisation application dossier of a new recombinant Granulocyte Colony-stimulating Factor (rG-CSF) claimed to be similar to a reference product already authorised in the EU shall provide the demonstration of comparability of the product applied for to this reference product.

Human G-CSF is a single polypeptide chain protein of 174 amino acids with *O*-glycosylation at one threonine residue. Recombinant G-CSFs produced in *E. coli* (filgrastim) and in CHO (lenograstim) are in clinical use. Compared to the human and to the mammalian cell culture derived G-CSF, the *E. coli* protein has an additional amino-terminal methionine and no glycosylation. The rG-CSF protein contains one free cysteinyl residue and two disulphide bonds. Physico-chemical and biological methods are available for characterisation of the protein.

Effects of G-CSF on the target cells are mediated through its transmembrane receptor that forms homo-oligomeric complexes upon ligand binding. Several isoforms of the G-CSF receptor arising from alternative RNA splicing leading to differences in the intracytoplasmic sequences have been isolated. One soluble isoform is known. However, the extracellular, ligand-binding domains of the known isoforms are identical. Consequently, the effects of rG-CSF are mediated via a single affinity class of receptors.

Antibodies to the currently marketed E. coli derived rG-CSF occur infrequently. These have not been described to have major consequences for efficacy or safety. RG-CSF is administered subcutaneously or intravenously. Possible patient-related risk factors of immune response are unknown.

2. Scope

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

This product-specific guidance is an annex to the above-mentioned guideline. It presents the current view of the CHMP on the application of the main guideline for demonstration of comparability of two rG-CSF-containing medicinal products. The final set of studies necessary to fulfil non-clinical and clinical requirements for a given medicinal product will be determined by data generated by the comparability exercise itself.

This Guideline should be read in conjunction with the requirements laid down in the EU Pharmaceutical legislation and with relevant CHMP guidelines (see section 7).

3. Non-clinical studies

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

3.1 Pharmacodynamics studies

In vitro studies:

At the receptor level, comparability of test and reference medicinal product should be demonstrated in appropriate *in vitro* receptor-binding assays. Such data may already be available from bioassays that were used to measure potency in the evaluation of biological characteristics in module 3. It is important that assays used for comparability will have appropriate sensitivity to detect differences and that experiments are based on a sufficient number of dilutions per curve to fully characterise the concentration-response relationship.

In vivo studies:

©EMEA 2004

In vivo rodent models, neutropenic and non-neutropenic, should be used to compare the pharmacodynamic effects of the test and the reference medicinal product.

3.2 Toxicological studies

Data from at least one repeat dose toxicity study in a relevant species should be provided. Study duration should be at least 28 days. 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 (i) pharmacodynamic measurements and (ii) 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 immunogenic responses.

Data on local tolerance in at least one species should be provided in accordance with the "Note for Guidance for 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 recombinant G-CSF as active substance.

4. Clinical studies

4.1 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. The primary PK parameter is AUC and the secondary PK parameters are C_{max} and T1/2. The general principles for demonstration of bioequivalence should apply.

4.2 Pharmacodynamic studies

The absolute neutrophil count (ANC) is the relevant pharmacodynamic marker for the activity of r-G-CSF. The pharmacodynamic effect of the test and the reference products should be compared in healthy volunteers. The selected dose should be in the linear ascending part of the dose-response curve. Studies at more than one dose level may be useful. The $CD34^+$ cell count should be reported as a secondary PD endpoint. The equivalence range should be justified.

4.3 Clinical efficacy studies

rG-CSF can be used for several purposes such as:

- Reduction in the duration of neutropenia after cancer chemotherapy or myeloablative therapy followed by bone marrow transplantation.
- Mobilisation of peripheral blood progenitor cells (PBPCs);
- For treatment of severe congenital, cyclic, or idiopathic neutropenia
- Treatment of persistent neutropenia in patients with advanced human immunodeficiency virus (HIV) infection

The posology varies in these conditions.

The recommended clinical model for the demonstration of comparability of the test and the reference product is the prophylaxis of severe neutropenia after cytotoxic chemotherapy in a homogenous patient group. This model requires a chemotherapy regimen that is known to induce a severe neutropenia in patients. A two-arm therapeutic equivalence study is sufficient in chemotherapy models with known frequency of severe neutropenia where reference product is indicated. If other chemotherapy regimens are used, a three arms trial, including placebo, may be needed. The sponsor must justify the equivalence delta for the primary efficacy variable, the duration of severe neutropenia (ANC below 0.5×10^9/l). The incidence of febrile neutropenia, infections and the cumulative r-G-CSF dose are secondary variables. The main emphasis is on the first chemotherapy cycle.

©EMEA 2004

Demonstration of the equivalence in the chemotherapy-induced neutropenia model will allow the extrapolation of the results to the other indications of the reference product if the mechanism of action is the same.

Alternative models, including pharmacodynamic studies in healthy volunteers, may be pursued for the demonstration of comparability if justified. In such cases, the sponsor should seek for scientific advice for study design and duration, choice of doses, efficacy / pharmacodynamic endpoints, and equivalence margins.

5. Clinical safety

Safety data should be collected from a cohort of patients after repeated dosing preferably in a comparative clinical trial. The total exposure should correspond to the exposure of a conventional chemotherapeutic treatment course with several cycles. The total follow up of patients should be at least 6 months. The number of patients should be sufficient for the evaluation of the adverse effect profile, including bone pain and laboratory abnormalities. Immunogenicity data should be collected according to the principles described in the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (EMEA/CPMP/42832/05/draft).

6. Pharmacovigilance plan

The sponsor has to present a pharmacovigilance plan to address immunogenicity and potential rare serious adverse events. Special attention should be paid on immunological adverse events in patients with chronic administration.

7. 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/CHMP/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 local tolerance testing of medicinal products (CPMP/SWP/2145/00).

©EMEA 2004