European Medicines Agency
Evaluation of Medicines for Human Use

London, 22 February 2006
EMEA/CHMP/BMWP/31329/2005

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 GRANULOCYTE-COLONY STIMULATING FACTOR

DRAFT AGREED BY BMWP WORKING PARTY	February 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	June 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	October 2005
AGREED BY BMWP WORKING PARTY	January 2006
ADOPTION BY CHMP	22 February 2006
DATE FOR COMING INTO EFFECT	1 June 2006

KEYWORDS	G-CSF, recombinant, similar biological medicinal products, comparability, non-clinical studies, clinical studies

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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/CPMP/42832/05/) provides guidance for demonstration of comparability of two recombinant granulocyte colony-stimulating factor-containing medicinal products.

In its non-clinical section, this Annex addresses the need for appropriate pharmacodynamic and toxicological studies. In the clinical section, guidance is given on suitable pharmacodynamic, pharmacokinetic, efficacy and safety studies for demonstration of comparability of two rG-CSF-containing medicinal products as well as on specific risk management measures. Criteria for extrapolation of clinical data to other indications approved for the reference medicinal product are also discussed.

1. INTRODUCTION

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

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. 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 pharmaco-toxicological response between the similar biological medicinal product 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.

Pharmacodynamic studies

In vitro studies:

At the receptor level, comparability of test and reference medicinal product should be demonstrated in appropriate *in vitro* cell based bioassays or 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:

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

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 investigation of immune responses to the products.

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.

4.2. CLINICAL STUDIES

Pharmacokinetic studies

The pharmacokinetic properties of the similar biological medicinal product and the reference medicinal product should be compared 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 are applicable.

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 medicinal 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 comparability range should be justified.

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 between these conditions.

The recommended clinical model for the demonstration of comparability of the test and the reference medicinal product is the prophylaxis of severe neutropenia after cytotoxic chemotherapy in a homogenous patient group (e.g. tumour type, previous and planned chemotherapy as well as disease stage). This model requires a chemotherapy regimen that is known to induce a severe neutropenia in patients. A two-arm comparability study is sufficient in chemotherapy models with known frequency and duration of severe neutropenia. If other chemotherapy regimens are used, a three arms trial, including placebo, may be needed. The sponsor must justify the comparability delta for the primary efficacy variable, the duration of severe neutropenia (ANC below 0.5 x 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.

Demonstration of the clinical comparability in the chemotherapy-induced neutropenia model will allow the extrapolation of the results to the other indications of the reference medicinal 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 comparability margins.

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/).

4.3 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. Attention should be paid to immunogenicity and potential rare serious adverse events, especially in patients undergoing chronic administration. Lack of efficacy should also be monitored, especially in individuals undergoing haematopoietic progenitor cell mobilisation.

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).
- 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).
- 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)