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European Medicines Agency
Evaluation of Medicines for Human Use

London, 16 May 2005
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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 SIMILAR MEDICINAL PRODUCTS CONTAINING RECOMBINANT HUMAN INSULIN

DISCUSSION AT THE BMWP WORKING PARTY	FEBRUARY 2005 to MARCH 2005
TRANSMISSION TO CHMP	MAY 2005
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Note:

Any comments to this Guideline should be sent to the EMEA BMWP Secretariat by e-mail: Denisa.dechiara@emea.eu.int or by fax: +44 20 74 18 86 13 by the end of October 2005

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1. Introduction

The Marketing Authorisation (MA) application dossier of a new recombinant short acting human insulin (rh-insulin) 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 insulin for therapeutic use is a non-glycosylated, disulphide-bonded heterodimer of 51 amino acids. There is extensive experience with the production of insulin for therapeutic use from animal sources, in the form of semisynthetic insulin, and through different recombinant techniques. Physico-chemical and biological methods are available to characterise the primary, secondary and tertiary structures of the recombinant insulin molecule, as well as its receptor affinity and biological activity *in vitro* and *in vivo*. Current quality guidelines on comparability provide information on the characterisation and analysis of similar biological medicinal product and its comparator. For rh-insulin, attention should be given to product related substances/impurities and process related impurities, and in particular to desamido forms and other forms that may derive from the expression vector or arise from the conversion steps removing the C-peptide and regenerating the three-dimensional structure.

The effects of insulin are mediated predominantly via stimulation of the insulin receptor but insulin is also a weak natural ligand of the insulin-like growth factor-1 (IGF-1) receptor.

The same receptors are known to be involved in the mechanism of action relevant for the currently approved therapeutic indications of rh-insulins.

Antibodies to rh-insulin occur frequently, mainly as cross-reacting antibodies. These have been rarely described to have major consequences for efficacy or safety. The potential for development of product/impurity-specific antibodies needs to be evaluated. Rh-insulin 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/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 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 insulin-containing 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 VI).

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 product and the reference product and should not just assess the response *per se*. The approach taken will need to be fully justified in the non-clinical overview.

3.1 Pharmacodynamic studies

In vitro studies

In order to assess any differences in properties between the similar biological medicinal product and the reference product, comparative studies with *in vitro* bioassays for affinity, insulin- and IGF-1-receptor binding assays, as well as tests for intrinsic activity should be performed. Partly, such data may already be available from bioassays that were used to measure potency in the evaluation of physico-chemical characteristics. It is important that assays used for equivalence are demonstrated to have appropriate sensitivity to detect minute differences and that experiments are based on a sufficient number of dilutions per curve to characterise the whole concentration-response relationship.

In vivo studies

Comparative study(ies) of pharmacodynamic effects would not be anticipated to be sensitive enough to detect any non-equivalence not identified by *in vitro* assays, and are normally not required as part of the comparability exercise.

3.2. 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.

Other routine toxicological studies are not required for rh-insulins developed as similar biological medicinal products.

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 a single dose crossover study using subcutaneous administration. Comprehensive comparative data should be provided on the time-concentration profile (including C_{max}, T_{max}, AUC and half-life). Studies should be performed preferably in patients with type1 diabetes. Factors contributing to PK variability *e.g.* insulin dose and site of injection / thickness of subcutaneous fat should be taken into account.

4.2 Pharmacodynamic studies

The clinical activity of an insulin preparation is determined by its time-effect profile of hypoglycaemic response, which incorporates components of pharmacodynamics and pharmacokinetics. Pharmacodynamic data are of primary importance to demonstrate therapeutic equivalence of a similar rh-insulin. The double-blind, crossover hyperinsulinaemic euglycaemic clamp model is considered suitable for this characterisation. Data on comparability regarding glucose infusion rate and serum free insulin concentrations should be made available. The choice of study population and study duration should be justified.

4.3 Clinical efficacy studies

Provided that equivalence can be concluded from PK and PD data, there is no anticipated need for efficacy studies on intermediary or clinical variables.

5. Clinical safety

5.1 Immunogenicity

The safety concerns with a similar rh-insulin relate mainly to the potential for immunogenicity. The issue of immunogenicity can only be settled through clinical trials of sufficient duration, *i.e.* at least 12 months using subcutaneous administration. The comparative phase of this study should be at least 6 month. The primary outcome measure should be the frequency of antibodies to the test and reference product.

The plans for these trials should take into account:

Justification of study population including history of previous insulin exposure

Definitions of pre-specified analyses of the immunogenicity data with respect to effects on clinical findings (glycaemic control, insulin dose requirements, local and systemic allergic reactions)

5.2 Local reactions

If any concern is raised through non-clinical and short-term clinical studies outlined above, additional evaluation of local tolerability may be needed pre-marketing. Otherwise, such reactions should be monitored and recorded within immunogenicity trials.

6. Pharmacovigilance plan

Within the authorisation procedure the applicant should present a pharmacovigilance plan / risk management programme in accordance with current EU legislation and pharmacovigilance guidelines. This should take into account risks identified during product development and potential risks, especially as regards immunogenicity, and should detail how these issues will be addressed in post-marketing follow-up.

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

- Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus (CPMP/EWP/1080/02).

European Medicines Agency
Evaluation of Medicines for Human Use

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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 SIMILAR MEDICINAL PRODUCTS CONTAINING SOMATROPIN

DISCUSSION AT THE BMWP WORKING PARTY	FEBRUARY 2005 to MARCH 2005
TRANSMISSION TO THE CHMP	MAY 2005
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Note:

Any comments to this Guideline should be sent to the EMEA BMWP Secretariat by e-mail:

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1. Introduction

The Marketing Authorisation (MA) application dossier of a new recombinant human growth hormone (rh-GH, somatropin) 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.

The principal bioactive human growth hormone (hGH) is a single chain non-glycosylated 191 amino acid, 22 kD polypeptide produced in the anterior pituitary gland. Growth hormone for clinical use has an identical amino acid sequence and is produced by recombinant technology using E. coli, mammalian cells or yeast cells as expression system. The structure and biological activity of somatropin can be characterised by appropriate physico-chemical and biological methods. Several techniques and bioassays are available to characterise both the active substance and product-related substances/impurities such as deaminated and oxidized forms and aggregates.

Growth hormone has potent anabolic, lipolytic and anti-insulin effects (acute insulin-like effect). The effects of GH are mediated both directly (e.g. on adipocytes and hepatocytes) and indirectly via stimulation of insulin-like growth factors (principally IGF-1). Somatropin-containing medicinal products are currently licensed for normalising or improving linear growth and/or body composition in GH-deficient and certain non GH-deficient states. The same receptors are thought to be involved in all therapeutic indications of rhGHs.

Somatropin has a wide therapeutic window in children during the growth phase whereas adults may be more sensitive for certain adverse effects. Antibodies to somatropin have been described, including neutralising antibodies. Problems have been associated with the purity and stability of the formulations. Somatropin is administered subcutaneously; 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/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 somatropin-containing 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 VI).

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 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.

3.1 Pharmacodynamics studies

In vitro studies:

In order to assess any alterations in reactivity between the similar biological medicinal and the reference 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:

An appropriate *in vivo* rodent model (e.g. the weight-gain assay and/or the tibia growth assay in immature hypophysectomized rats; data may already be available from quality-related bioassays) should be used to quantitatively compare the pharmacodynamic activity of the similar biological medicinal and the reference product.

3.2 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 rhGH 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 a single dose crossover study using subcutaneous administration. Healthy volunteers are considered appropriate but suppression of endogenous GH production e.g. with a somatostatin analogue should be considered. The relevant pharmacokinetic parameters are AUC and $t_{1/2}$. Equivalence margins have to be defined a priori and justified, primarily on clinical grounds.

4.2 Pharmacodynamic studies

IGF-1 is the preferred pharmacodynamic marker for the activity of somatropin and is recommended to be used in comparative pharmacodynamic studies. In addition, other markers such as IGFBP-3 may be used. On the other hand, due to the lack of a clear relationship between serum IGF-1 levels and growth response, IGF-1 is not a suitable surrogate marker for the efficacy of a somatropin in clinical trials.

4.3 Clinical efficacy studies

Equivalent therapeutic efficacy between the similar biological medicinal product and the reference product should be demonstrated in at least one adequately powered, randomised, parallel group, confirmatory clinical trial. Clinical studies should be preferably double-blind to avoid bias. If this is not possible, at minimum the person performing height measurements should be masked to treatment allocation.

Sensitivity to the effects of somatropin is higher in GH-deficient that non-GH-deficient conditions. Treatment-naïve children with GH deficiency are therefore recommended as the target study population as this would provide the most sensitive model. Study subjects should be pre-pubertal before and during the comparative phase of the trial to avoid interference of the pubertal growth spurt with the treatment effect. It is important that the study groups are thoroughly balanced for baseline characteristics, as this will affect the sensitivity of the trial and the accuracy of the endpoints.

Change in height velocity standard deviation score from baseline to the pre-specified end of the comparative phase of the trial is the recommended primary efficacy endpoint while change in height standard deviation score and change in height velocity are recommended secondary endpoints.

For this purpose, standing height should be measured at least 3 times per subject and time point and the results averaged for analyses. The use of a validated measuring device is mandatory. Consecutive height measurements should be standardised and performed at the same time of the day, by the same observer and the same measuring device. For the determination of reliable baseline growth rates, it is important that also height measurements during the pre-treatment phase are obtained in a standardised manner using a validated measuring device.

Equivalence margins have to be justified, primarily on clinical grounds, taking into account assay sensitivity of the proposed trial. Due to significant variability in short-term growth, seasonal variability in growth and measurement errors inherent in short-term growth measurements, the recommended duration of the comparative phase is at least 6 months and may have to be up to 12 months.

Longer observation periods are particularly advisable if studies are performed in less sensitive models, e.g. in children with reduced growth potential due to advanced age or bone age.

Calculation of pre-treatment growth rate should be based on observation periods of no less than 6 and no more than 18 months.

5. Clinical safety

Data from patients in the efficacy trials usually comprise an adequate pre-marketing safety database to assess the adverse event profile and detect excessive immunogenicity. The applicant should provide comparative immunogenicity data of patients who participated in the efficacy trials for 12 months at 3-month intervals, using validated assays of adequate specificity and sensitivity. In addition, adequate blood tests including IGF-1, IGFBP-3, fasting insulin and blood glucose should be performed.

The clinical impact of antibodies, if present, should be assessed.

6. Pharmacovigilance plan

Within the authorisation procedure the applicant should present a pharmacovigilance plan/ risk management programme in accordance with current EU legislation and pharmacovigilance guidelines. This should take into account risks identified during product

development and potential risks, especially as regards immunogenicity, and should detail how these issues will be addressed in post-marketing follow-up.

7. Extension of indication

Appropriate demonstration of efficacy and safety in one indication 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/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).

European Medicines Agency
Evaluation of Medicines for Human Use

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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

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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:

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 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 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).

European Medicines Agency
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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

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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

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.

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.

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).

SANDOZ

資料8

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Sandoz Welcomes CHMP Positive Opinion on Omnitrope

Holzkirchen, Germany, January 27, 2006 – Sandoz welcomes the positive opinion issued by the European Medicines Agency's Committee on Medicinal Products for Human Use (CHMP) regarding the company's recombinant human growth hormone Omnitrope.

"The positive CHMP opinion for Omnitrope is an important step on the way to make this medicine available for patients who need it," said Dr. Andreas Rummelt, CEO Sandoz. "Omnitrope will contribute to cost savings in the Health Care systems and we are confident that the European Commission will now grant marketing authorization."

In June 2003, the CPMP (as the Committee was named at that time) recommended that the European Commission grant Marketing Authorization for Omnitrope, but the Commission refused the Marketing Authorization on legal grounds related to the selected approval pathway. Sandoz submitted a second application in July 2004, based on a recommendation from the European Medicines Agency (EMEA) and the Commission. This application followed the new Annex to Directive 2001/83/EC as amended and published with directive 2003/63/EC, which provided a pathway for these products.

Australia's Therapeutic Goods Administration approved Omnitrope in September 2004 for treatment of growth disorders in children. The product was launched in Australia in November 2005.

In the U.S., the Food and Drug Administration notified Sandoz in August 2004, that it was unable to reach a decision on whether to approve the company's application for Omnitrope. In September 2005, Sandoz filed a lawsuit against the US Food and Drug Administration, seeking a ruling on its pending application. That lawsuit is still pending.

"With Omnitrope's positive status in Europe, we now hope the FDA will finally move in granting a marketing authorization for the US, acknowledging the sound science that supports this product," said Rummelt. "We are determined to make high-quality and cost-effective biosimilar products like Omnitrope available for patients and healthcare providers worldwide."