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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 SOMATROPIN

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TABLE OF CONTENTS

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/) lays down the non-clinical and clinical requirements for somatropin-containing medicinal products claiming to be similar to another one already marketed.

The non-clinical section addresses the pharmaco-toxicological assessment. The clinical section addresses 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

The Marketing Authorisation (MA) application dossier of a new recombinant human growth hormone (rhGH, somatropin) claimed to be similar to a reference medicinal product already authorised shall provide the demonstration of comparability of the product applied for to a reference medicinal 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 deamidated 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 currently approved 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, very rarely, 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/) lays down the general requirements for demonstration of the similar nature of two biological products in terms of safety and efficacy.

This product specific guidance is an Annex to the above guideline and 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.

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

Pharmacodynamics studies

In vitro studies:

In order to assess any alterations in reactivity between the similar biological medicinal and the reference medicinal product, data from a number of comparative bioassays (e.g. receptor-binding studies, cell proliferation assays), many of which may already be available from quality-related bioassays, should be provided.

In vivo studies:

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 medicinal product.

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. 2 CLINICAL STUDIES

Pharmacokinetic studies

The relative pharmacokinetic properties of the similar biological medicinal product and the reference medicinal 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 primary pharmacokinetic parameter is AUC and the secondary parameters are C_{max} and $T_{1/2}$. Comparability margins have to be defined a priori and appropriately justified.

Pharmacodynamic studies

Pharmacodynamics should preferably be evaluated as part of the comparative pharmacokinetic study. The selected dose should be in the linear ascending part of the dose-response curve. 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.

Clinical efficacy studies

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

Sensitivity to the effects of somatropin is higher in GH-deficient than non-GH-deficient conditions. Treatment-naïve children with GH deficiency are recommended as the target study population as this provides a sensitive and well-known 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. This may be achieved e.g. by limiting the age/bone age at study entry. 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 or (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. Height standard deviation score is a recommended secondary endpoint. Adjustment for factors known to affect the growth response to somatropin should be considered.

During the comparative phase of the study, standing height should be measured at least 3 times per subject at each 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 approximately at the same time of the day, by the same measuring device and preferably by the same trained observer. These recommendations aim to reduce measurement errors and variability.

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.

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.

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

Comparability margins have to be pre-specified and appropriately justified, primarily on clinical grounds, and serve as the basis for powering the study.

4.3 CLINICAL SAFETY

Data from patients in the efficacy trial(s) are usually sufficient to provide an adequate pre-marketing safety database.

The applicant should provide comparative 12-month immunogenicity data of patients who participated in the efficacy trial(s) with sampling at 3-month intervals and testing 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.

4.4 PHARMACOVIGILANCE PLAN

Within the authorisation procedure the applicant should present a risk management programme / pharmacovigilance plan in accordance with current EU legislation and pharmacovigilance guidelines. 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.

4.5 EXTENSION OF INDICATION

Demonstration of efficacy and safety in GH-deficient children may allow extrapolation to other indications of the reference medicinal product if appropriately justified by the applicant.

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).
- 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)