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Evaluation of Medicines for Human Use

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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 RECOMBINANT HUMAN SOLUBLE INSULIN

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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/) lays down the non-clinical and clinical requirements for soluble insulin containing 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.

1. INTRODUCTION

The Marketing Authorisation (MA) application dossier of a new recombinant soluble (short acting) human insulin (rh-insulin) 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.

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) 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. 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.

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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 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.

Pharmacodynamic studies

In vitro studies

In order to assess any differences in properties between the similar biological medicinal product and the reference medicinal product, comparative studies such as *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 comparability testing 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 studie*s*

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.

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.

4.2 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. Comprehensive comparative data should be provided on the time-concentration profile (AUC as the primary endpoint and C_{max}, T_{max}, and $T_{1/2}$ as secondary endpoints). 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.

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 comparability of a similar rh-insulin. The double-blind, crossover hyperinsulinaemic euglycaemic clamp study is suitable for this characterisation. Data on comparability regarding glucose infusion rate and serum

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insulin concentrations should be made available. The choice of study population and study duration should be justified.

Plasma glucose levels should be obtained as part of the PK study following subcutaneous administration.

Clinical efficacy studies

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

4 3 CLINICAL SAFETY

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 months, to be completed pre-approval. Data at the end of 12 months could be presented as part of post-marketing commitment. The primary outcome measure should be the incidence of antibodies to the test and reference medicinal 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)

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.

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.

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).
- 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).

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

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