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Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-hFSH)

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Guideline on Non-Clinical and Clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-hFSH)

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1. Executive summary

This guideline lays down the non-clinical and clinical requirements for recombinant human follicle stimulating hormone (r-hFSH)-containing medicinal products claiming to be similar to another one already marketed.

In its non-clinical section, this guideline addresses the pharmaco- toxicological requirements. In the clinical section, guidance is given on suitable pharmacodynamic, pharmacokinetic, efficacy and safety studies for demonstration of comparability of two FSH-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 discussed.

2. Introduction

The marketing authorisation application dossier of a new r-hFSH-containing medicinal product claimed to be similar to a reference medicinal product already authorised in the EU needs to provide the demonstration of comparability of the product applied for to this reference medicinal product.

Follicle stimulating hormone (FSH) is a pituitary glycoprotein hormone that plays a key role in regulating reproductive function in both males and females. FSH is a heterodimeric hormone composed of two linked subunits. The alpha subunit (92 amino acids) is common to other glycoprotein hormones whereas the beta subunit (111 amino acids) is specific. Both subunits contain oligosaccharide structures. As a consequence of carbohydrate variability, different isoforms of hFSH with different sialic acid content exist. Isoforms with a high sialic acid content remain longer in circulation. Physico-chemical and biological methods are available for characterisation of the protein.

Recombinant human FSH (r-hFSH) is used in assisted reproductive technologies (ART) for women to stimulate growth and recruitment of ovarian follicles, and for men to induce and maintain spermatogenesis. It is administered by subcutaneous or, in some cases, intramuscular injections.

The most important side effect of FSH treatment in ovarian stimulation is the occurrence of ovarian hyperstimulation syndrome (OHSS). This possibly life-threatening condition is characterised in its most serious forms by ascites, haemoconcentration, coagulation and electrolyte disorders and extreme ovarian enlargement. High number of follicles recruited and high estradiol levels (released from matured follicles) are risk factors for the development of OHSS.

Immunogenicity of r-hFSH appears to be low and so far, neutralising antibodies have not been reported. Generalised hypersensitivity reactions were observed in 0.2% and <1/10,000 patients treated with two different approved r-hFSH products. Local reactions were observed more frequently (3% and >1/10 of patients treated with two different rhFSH products).

3. Scope

The Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005) lays down the general requirements for demonstration of the similar nature of such biological products in terms of safety and efficacy.

This product class-specific guidance presents the current view of the CHMP on the non-clinical and clinical requirements for demonstration of comparability of two r-hFSH-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 3. Legal Basis).

4. Legal basis and relevant guidelines

- Directive 2001/83/EC, as amended in particular in Directive 2001/83/EC Art 10(4) and 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/BMWP/42832/2005.
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues - EMEA/CHMP/BWP/49348/2005 and EMA/CHMP/BWP/247713/2012
- ICH guideline S 6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998)
- Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins - EMEA/CHMP/BMWP/14327/2006
- Guideline on the investigation of bioequivalence - CPMP/EWP/QWP/1401/98
- Note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals - EMA/CHMP/ICH/731268/1998 (ICH S6)
- Guideline on good pharmacovigilance practices, Module V – Risk management systems (EMA/838713/2011)

5. 4. Non-clinical studies

Non-clinical studies should be performed before initiating clinical development. These studies should be comparative in nature and should be designed to detect differences in the 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.

Pharmacodynamic studies

in vitro

In order to evaluate potential differences in pharmacodynamic properties between the biosimilar and the reference medicinal product, comparative *in vitro* bioassays for receptor affinity and activation should be performed (such data may already be available from bioassays submitted as part of the quality dossier). Two principal approaches exist for this purpose. First, primary granulosa cells or sertoli cells can be used. Second, permanently cultured cells (e.g. CHO) stably transfected with the human FSH receptor may be constructed. The advantage of the first approach is that the FSH receptor is investigated in its natural context. A drawback is that the number of cells is limited which in turn limits the number of replicates and the number of different r-hFSH concentrations that can be tested to obtain reliable concentration-response-relationships. The second approach, although providing enough material, relies on an artificial construct (transfected cells). Appropriate sensitivity of the assay used for comparability testing to detect potential differences should be demonstrated and experiments should be based on a sufficient number of dilutions per curve to characterise the whole concentration-response relationship. Binding studies including on-off-kinetics should be provided as well as measures

of receptor activation i.e. plasminogen activator production (only in the classical granulosa cell assay) or intracellular cAMP accumulation. Other endpoints are conceivable (e.g. reporter gene activation). The Applicant should justify the approach taken.

in vivo

FSH is a highly glycosylated protein and in vitro studies may not fully reflect the more complex situation in vivo. Hence, to qualify any potential differences between the biosimilar FSH and the reference product, the need for additional comparative in vivo studies should be considered.

Currently, the potency of r-hFSH-containing products is evaluated by calibration against an international standard (or an internal reference standard calibrated against the international standard; Steelman-Pohley assay). As the in vivo potency of both the biosimilar and the reference product may be evaluated in such a way, the number of different assays performed may be reduced by a study design in which the biosimilar and the reference medicinal product are compared and simultaneously calibrated against the reference standard. This reduces inter-assay variation and is more economical with regard to reagents and animals used. The Steelman-Pohley assay is only expected to establish biological activity but not to reveal small differences in potency between reference product and biosimilar. If feasible, an evaluation of safety endpoints, e.g. body weight and local tolerance, could be included within the framework of the in vivo pharmacodynamic studies.

If a different bioassay – for example an ex vivo assay such as whole follicle culture or primary granulosa cell culture - is used to compare pleiotropic effects of FSH in a natural tissue environment, this should be justified. Such an approach would further reduce the number of animals needed, circumvent inter-animal variability and would give the possibility for multiple pharmacodynamic readouts.

Toxicological studies

Generally, separate repeated dose toxicity studies are not required. In specific cases, e.g. when novel or less well studied excipients are introduced, the need for additional toxicology studies should be considered.

Safety pharmacology and reproduction toxicology studies are not required for non-clinical testing of similar biological medicinal products containing r-hFSH as active substance. Studies on local tolerance are not required, unless excipients are introduced for which there is no or only little experience with the intended route of administration. If other *in vivo* studies are performed, evaluation of local tolerance may be evaluated as part of these studies.

5. 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 cross-over study using subcutaneous injections. With respect to the general study design, the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) should be taken into account. Healthy female volunteers are considered appropriate. Suppression of endogenous FSH production with a GnRH agonist or a combined oral contraceptive is recommended. The dose of r-hFSH should be justified, taking into account that a dose in the linear part of the dose response curve is suitable to detect potential differences in the pharmacokinetic profiles of the biosimilar and the reference medicinal product. The pharmacokinetic parameters of interest are AUC, C_{max}, t_{max}, $t_{1/2}$ and clearance. For the primary endpoints AUC and C_{max}, the 90% confidence interval of the ratio test/reference should lie within 80%

to 125%, the conventional acceptance range for bioequivalence, unless otherwise justified. For the other parameters descriptive statistics would be appropriate. Separate pharmacology studies for intramuscular use, if applicable, are not required.

Pharmacodynamic studies

PD parameters should be investigated as part of the phase III trial.

Clinical efficacy

Clinical comparability regarding efficacy between the similar and the reference biological medicinal product should be demonstrated in an adequately powered, randomised, parallel group clinical trial.

The recommended model for the demonstration of comparability of the test and the reference product is the stimulation of multifollicular development in patients undergoing superovulation for ART such as in vitro fertilisation (IVF), gamete intrafallopian transfer (GIFT) or zygote intrafallopian transfer (ZIFT). The first treatment cycle should be used for comparison of efficacy.

Double-blind trials are recommended. If the performance of a double-blind trial is not feasible, blinded assessment of study outcomes that might be particularly affected by subjective factors, such as ultrasound examinations and parameters of oocyte/embryo quality, should be carried out. The r-hFSH dose should be fixed for the first 5 days of stimulation. A GnRH agonist or GnRH antagonist protocol can be used.

“Number of oocytes retrieved” is the recommended primary endpoint. Equivalent efficacy between the test product and the reference product should be demonstrated and equivalence margins prospectively defined and justified. It should be taken into account that over-stimulation as well as understimulation can result in cycle cancellation and a number of zero oocytes retrieved (primary endpoint). Thus, the data should be presented in such a way that a detailed comparison of the reasons for cancellation of ART cycles is possible.

As an alternative possibility, demonstration of non-inferiority for “ongoing pregnancy rate at least 10 weeks after embryo transfer” is also an acceptable primary endpoint. In the latter case, “number of oocytes retrieved” should be included as co-primary endpoint with an appropriate equivalence margin, or as the most important secondary endpoint.

With regard to secondary endpoints, the following issues should be taken into account:

- If number of oocytes is chosen as the primary endpoint, ongoing pregnancy rate after at least 10 weeks after embryo transfer should be evaluated as secondary endpoint.
- In ART cycles, the dose of FSH has to be adjusted based on ovarian response which might obscure product-specific differences. Thus, dose adjustments and possible differences between the dosages of the similar biological product and the reference product should be carefully considered. Secondary endpoints covering this issue, such as total dose of r-hFSH required, number of days of r-hFSH stimulation and percentage of patients with need to increase or lower the dose of r-hFSH, should be investigated. Major differences with regard to dose requirements between the similar biological product and the reference product would not be in accordance with the concept of biosimilarity.
- Parameters supporting comparable pharmacodynamic properties of the similar biological product and the reference product should be investigated. The respective endpoints should include number and size distribution of follicles during treatment and at the day of ovulation induction. A further endpoint covering the initial PD effect of r-hFSH on the ovary could be the number of follicles after

5 days of FSH stimulation (before dose adjustments). In addition, serum levels of inhibin-B, estradiol, luteinizing hormone and progesterone should be measured.

- Markers of oocyte/embryo quality should be included. Number of good quality oocytes/embryos should be documented.

Clinical safety

Data from the efficacy trial will usually be sufficient to characterise the adverse event profile of the biosimilar product.

An adverse reaction of special interest is ovarian hyperstimulation syndrome (OHSS). All events of OHSS should be carefully recorded, using a grading system (mild, moderate, severe) and also distinguishing between early and late onset OHSS.

Immunogenicity of a therapeutic protein is more likely when given intermittently than continuously and the subcutaneous route of administration is more immunogenic than the intravenous one. Both of these factors may apply to r-hFSH as women may receive more than one ART cycle. Therefore, immunogenicity data should be provided on all women included in the efficacy trial and also on women exposed for more than one ART cycle. Immunogenicity testing should continue up to three months after r-hFSH treatment using validated antibody assays of adequate sensitivity and specificity. The potential impact of FSH-antibodies, if detected, on efficacy and/or safety should be assessed and the necessity for further characterisation, e.g. with regard to their neutralising potential, considered.

6. Pharmacovigilance

Within the authorisation procedure the applicant should present a risk management plan in accordance with current EU legislation and pharmacovigilance guidelines. The RMP of the biosimilar should take into account identified and potential risks associated with the use of the reference product and, if applicable, safety in indications licensed for the reference product that are claimed based on extrapolation. In addition, it should be discussed in detail how these safety concerns will be addressed in post-marketing follow-up.

7. Extrapolation of indication

Demonstration of similar efficacy and safety of the test compared to the reference product for stimulation of multifollicular development in patients undergoing superovulation for ART will allow extrapolation to other therapeutic indications approved for the reference product.