EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on similar biological medicinal products containing recombinant follicle stimulation hormone

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Comments should be provided using this template. The completed comments form should be sent to BMWP.secretariat@ema.europa.eu

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7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. INTRODUCTION

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.

Recombinant human FSH (rhFSH) is used in fertilization medicine for women, and for men to induce and maintain spermatogenesis.

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 with respect to safety and efficacy. A product class-specific guidance will lay down specific requirements for the demonstration of comparability of rhFSH-containing medicinal products with respect to safety and efficacy.

This guideline should be read in conjunction with the requirements laid down in the EU Pharmaceutical legislation and other relevant CHMP guidelines.

2. PROBLEM STATEMENT

Currently, two rhFSH-containing medicinal products are authorised in the EU: follitropin alfa and follitropin beta.

Follitropin alfa is approved for the following therapeutic indications:

- Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomiphene citrate.
- Stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer (GIFT) and zygote intra-fallopian transfer (ZIFT).
- In association with a luteinising hormone (LH) preparation for the stimulation of follicular development in women with severe LH and FSH deficiency.
- In men for the stimulation of spermatogenesis who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotrophin (hCG) therapy.

Follitropin alfa is approved for subcutaneous administration.

Follitropin beta is approved for essentially the same therapeutic indications, with the exception of the stimulation of follicular development in women with severe LH and FSH deficiency. Follitropin beta can be administered subcutaneously or intramuscularly.

Safety issues associated with rhFSH include local and generalised hypersensitivity reactions, ovarian hyperstimulation syndrome, an increased risk of ectopic pregnancies and multiple gestation in pregnancies after induction of ovulation with gonadotropic preparations and a possibly slightly higher risk of congenital malformations in women undergoing ART.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

The guideline will address the requirements for non clinical and clinical data necessary to ensure that a new rhFSH product claimed to be similar to an already licensed EU reference product has a comparable safety and efficacy within the remits of current best practice.

The main topics addressed in the guideline are the following:

Non clinical requirements

While a complete set of routine non clinical studies is not required for a rhFSH developed as a similar biological product, recommendations will be given on the choice of appropriate species and models to be used for comparison of the pharmacodynamic effects of the test and the reference product as well as for the requirements for toxicological studies.

Clinical requirements

Guidance will be given on the following critical points:

- Design of pharmacokinetic studies
- Pharmacodynamic studies, including choice and relevance of pharmacodynamic endpoints
- Efficacy
    - Selection of the most relevant/sensitive patient population(s)/therapeutic indication(s) to establish biosimilarity
    - Recommended primary and secondary clinical endpoints
    - Pharmacodynamic markers as possible surrogates for efficacy
    - Duration of the comparative phase
- Safety
    - Extent of the safety database
    - Requirements for pre-approval safety evaluation
    - Requirements for immunogenicity testing
    - Requirements for a pharmacovigilance/ risk management plan at the time of MAA
- Recommendation for extrapolation of efficacy and safety data obtained in one therapeutic indication to other indications approved for the reference product.

4. RECOMMENDATION

It is proposed to draft a product-specific guideline on non-clinical and clinical requirements for rh FSH-containing products claimed to be similar to an already licensed reference product.

5. PROPOSED TIMETABLE

Release for external consultation: March 2010

Deadline for external comments: 11 June 2010

6. RESOURCE REQUIREMENTS FOR PREPARATION

The BMWP experts will develop the guideline. At least 2 formal meetings of the drafting group will be required in the margins of the working party meetings.

7. IMPACT ASSESSMENT (ANTICIPATED)

Guidance on the investigation and assessment of biosimilar rhFSH-containing products will ensure a more rational and consistent development and assessment of these products by industry and regulators.

8. INTERESTED PARTIES

Competent authorities of the member states, and pharmaceutical industry.

CHMP and its working parties EWP, SWP and BWP.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

- 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: Quality Issues (EMEA/CHMP/BWP/49348/2005)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005)
- ICH topic S6 - Note for guidance on Pre-clinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (CPMP/ICH/302/95)
- ICH topic E9 statistical principles for clinical trials – Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96) CHMP/BMWP/7241/2006 Page 4/4 _EMEA 2006
- ICH topic E10 - Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96)
- Points to consider on switching between superiority and non-inferiority (CPMP/EWP/482/99)