

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-211**

**PHARMACOLOGY REVIEW**

Dequica

**Review and Evaluation of Pharmacology/Toxicology Data**

MAR 24 2000

Key Words: FSH, HRT, ART, ovulation induction

HFD-580/Karen Davis-Bruno; Ph.D.

Submission Date 1/31/00

Review Completion Date: 2/7/00

**NDA 21-211**

**Organon Inc.**; West Orange, NJ

**Drug Name: Follistim-AQ (follitropin beta injection cartridge)**

Code Name: Org 32489 injection 833 IU FSH per ml.

Drug Product: Follitropin beta (rhFSH) at 300IU or 600 IU FSH/cartridge in solution.  
Follitropin beta contains FSH prepared by recombinant DNA technology.

Ingredients	300 IU cartridge	600 IU cartridge	Lyophilized (75, 150, 225 IU)	Function
✓ Follitropin beta (IU)	437	737	75, 150, 225	Active ingredient
✓ Sucrose (mg)				
Sodium citrate (mg)				
Polysorbate 20 (mg)				
Benzyl alcohol (mg)				
L-methionine (mg)				
HCl/NaOH to pH7				
Water for injection (ml)				

Relevant NDAs: NDA 20-582 Organon for Follistim (follitropin beta for injection).

Drug Class: Pituitary gonadotropin

Indication: 1) development of multiple follicles in patients participating in assisted reproductive technology (ART) and 2) induction of ovulation in anovulatory infertile patients where the cause of infertility is functional and not due to primary ovarian failure.

Clinical Dose: Recommended dose is 300 IU (5 IU/kg), up to 600 IU/day has been safely used in ART.

Human Experience: An open label, single center, single dose, cross over study of 150 IU Follistim AQ by pen injector, SC compared to administration of reconstituted Follistim by syringe at the same dose and route (Study 37626). Bioequivalence was established after correction for the actual dose administered. The pen injector administered the correct dose, however reconstituted Follistim in a conventional syringe delivered less than the nominal dose of 150 IU.

The cartridge/pen injector product:

- 1) is considered more convenient than the approved product since it requires less handling
- 2) provides a more accurate and precise method of dosing compared to the conventional syringe, allowing for greater dosing flexibility and more subtle treatment of hyper responders
- 3) patient comfort is improved by the smaller needle and dosing volume
- 4) the cartridge/pen injector facilitates self administration by patients.

Summary: Follistim AQ is essentially identical to the approved product Follistim (follitropin beta for injection) except for the method of delivery. Follistim AQ is an aqueous solution of Follistim placed into a cartridge for injection by a pen injector device. Follistim is lyophilized and reconstituted in water prior to injection. Follistim (follitropin beta; rhFSH) contains FSH prepared by recombinant DNA technology and is reported by the sponsor as almost biochemically and pharmacologically identical to human FSH. Variations in glycosylation (sialylation) result in a spectrum of naturally occurring FSH isoforms with different charge, bioactivity and elimination half life. Considerable clinical experience is available with Follistim, which was approved under NDA 20-582 and other urinary derived human FSH products.

Labeling Review: The label is identical to Follistim and is adequate and acceptable.

Recommendations: Based on the structural and functional similarities of Follistim AQ with natural and approved urinary and recombinant FSH as well as extensive clinical experience regarding the safety and efficacy of these products, approval of NDA 21-211 is recommended for induction of ovulation.

Reviewer/Team Leader Signatures: *Laura Davis-Bruno - 1/11*

Attachment: P/T review of NDA 20-582  
Cc: HFD-580 file/Davis-Bruno/Jordan /Deguia

*A Jordan*  
*3/24/00*

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8-29-1996

NDA 20-582

Organon Inc  
West Orange, NJ

Submission dated: 1-10-1996

Received at CDER: 1-11-1996

Pharmacology Review of original NDA Submission

Drug's established name: Follitropin beta

Code name: Org32489

Dosage form: lyophilized powder in vials for reconstitution

Route of administration: subcutaneous or intramuscular. The sc and im routes of administration are bioequivalent.

Strength: 75 IU or 150 IU FSH activity

Type of dosage form: Administered after reconstitution with \_\_\_\_\_ sodium chloride, USP. Each vial of Org 32489 contains 75 IU or 150 IU of FSH activity, plus \_\_\_\_\_ sucrose, NF; \_\_\_\_\_ sodium citrate dihydrate, USP; \_\_\_\_\_ polysorbate 20, NF, and hydrochloric acid, NF and/or sodium hydroxide, NF to adjust the pH in a sterile lyophilized form. The pH of the reconstituted preparation is approx 7.0.

Anticipated human dose: 300 IU (5 IU/kg). It was stated that up to 600 IU/day has been safely used in ART and a maximum of 300 IU for ovulation induction.

Proposed indications for use: 1) Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program and 2) induction of ovulation in the anovulatory infertile patients in whom the cause of infertility is functional and is not due to primary ovarian failure.

These proposed indications are consistent with those approved for

urinary gonadotropins preparations.

Related DMFs:

Related IND: It was stated that follitropin beta was not investigated clinically under an IND and all clinical studies were conducted outside of the United States.

Follitropin beta (rhFSH) is a drug substance containing follicle stimulating hormone (FSH) prepared by recombinant DNA technology and is stated to be biochemically and pharmacologically almost identical to human FSH.

FSH has a dimeric structure and contains 2 glycoprotein subunits (alpha and beta). Both the 92 amino acid alpha-chain and 111 amino acid beta-chain have 2 N-linked oligosaccharide chains presented as complex heterogeneous structures. Variations in glycoprotein pattern (in the degree of sialylation) result in a spectrum of naturally-occurring FSH isoforms with different charge, bioactivity and elimination half-life.

Recombinant human FSH is produced by CHO cells transfected with a plasmid containing the 2 subunits DNA sequences encoding human FSH. As a result, biologically active recombinant human FSH is produced and secreted. Structural and conformational analysis showed that the amino acid sequence and the tertiary structure are identical to those of natural human FSH. Also the carbohydrate chain structures of the recFSH are very similar to those reported for natural hFSH. Small structural difference observed do not affect the degree of charge heterogeneity, receptor binding affinity and the in vivo and in vitro bioactivities of recFSH relative to natural hFSH.

Org32489 compared to urine-extracted human gonadotropins has the following advantages:

1. Org 32489 was more effective than FSH based on number of follicle developed, oocyte recovery, number of ampules used and duration of treatment;
2. Org 32489 has very little intrinsic LH bioactivity and is considered devoid of LH activity;

3. It caused minimal irritation at the site of injection following sc or im injection;
4. Org32489 has a high biochemical purity and high in vivo specific bioactivity; and
5. The manufacturing process excludes the potential presence of human derived proteins or microbiological contaminants as compared to urine-extracted human FSH products.

Preclinical pharmacology and toxicology:

Preclinical development of Org 32489 was discussed with the sponsor in a pre-IND meeting on February 8, 1990. As a results of this meeting and further discussion internally regarding preclinical safety issues, it was concluded that there is considerable clinical experience with exogenous administration of this drug and as such there are no preclinical safety concerns with FSH per se and that subtle differences in glycosylation would not be expected to render the molecule toxic. Therefore sponsor was informed on March 7, 1990 that Pharmacology's requirement for toxicology testing are minimal which would consist of an acute (single dose) iv study in rats and a test of physiological function (cardiovascular and respiratory parameters) in dogs. A study in monkeys comparing the antigenicity of rhFSH to uhFSH would be useful (prior to any human exposure) but is not mandatory. FSH antibodies should be monitored in clinical trials. Furthermore, there is no requirement for 4 or 13 week toxicology studies, reproductive studies or mutagenicity studies.

However, since the sponsor has conducted and included many more toxicology studies than requied by Pharmacology, these are reviewed and only summarized (with details in appended sponsor's tables taken from the submission) as follows:

The sponsor has conducted pharmacological, toxicological and pharmacokinetics studies with Org 32489. Primary pharmacological studies were conducted to determine the isohormone profile, receptor binding affinity, in vitro bioactivity, and in vivo bioactivity in rats and dogs.

The results of these studies demonstrated that Org 32489 when

compared to Metrodin contained approx 2-fold higher percentage of relatively acidic isohormones and 2-fold lower percentage of relatively basic isohormones. These differences in isohormone composition ~~was~~ attributed for lower Cmax and AUC for Org 32489 ~~because basic isohormones are clearly more~~. Org 32489 was comparable to FSH preparations from urinary sources in regards to receptor binding affinity and in vitro aromatase induction in Sertoli and granulosa cells. In vivo it was capable of inducing follicular growth comparable to Metrodin and thus small differences in oligosaccharide side chains of Org 32489 do not affect its bioactivity.

The effects of Org 32489 on CVS and on the regulatory functions of autonomic nervous system were investigated in conscious rabbits and anesthetized Beagle dogs. No biologically significant effects on these functions were reported. Also no significant hemodynamic effects were observed.

The toxic effects of Org 32489 were determined in rats and dogs using both single and multiple dosing regimens. Special toxicity studies included determination of local tolerance. The genotoxicity was assessed using 2 in vitro systems.

Pk after single and multiple dose administration was determined in rats and dogs and compared to 2 urinary preparation i.e. Metrodin and Humegon. Studies were conducted to determine the effect of isohormone profile on PK in comparison to Metrodin.

Results of these toxicology studies demonstrated that both single and multiple dosing produced no significant toxicologic effects, even when dogs were administered 10 times and rats 100 times the anticipated maximal daily human dose. Effects observed were pharmacological effects of Org 32489, primarily ovarian stimulation and hormonal effects.

As far local tolerance no treatment effects were seen after iv or im administration.

Org 32489 was not mutagenic in Ames test and did not produce an increase in chromosomal aberrations in an in vitro assay using human lymphocytes.

Details of the pharmacology, toxicology and PK studies are provided in the data tables appended.

Clinical studies: The sponsor has conducted 17 studies with Org 32489 which include clinical pharmacology studies, controlled clinical studies, uncontrolled compassionate use study and other studies.

Results from a pivotal, randomized, assessor-blind, group comparative multicenter safety and efficacy study of Org 32489 in 981 infertile women treated for in vitro fertilization with Org 32489 or Metrodin after pituitary suppression with GnRH agonist showed that Org 32489 was sig better in total number and number of mature oocytes recovered. Maximum serum E2 before hCG was higher, total number of vials used and duration of treatment length was lower. Also ongoing pregnancy rate/attempt and per transfer were slightly higher.

In another single study in 89 infertile women treated with Org 32489 or Humegon without pituitary suppression with GnRH agonist, showed no significant differences between 2 treatments.

Results of an other randomized, assessor-blind, group comparative, multicenter safety and efficacy study of Org 32489 in 172 chronic anovulatory women who failed to ovulate and/or conceive during clomiphene citrate treatment showed that Org 32489 and Metrodin (Serono Laboratories) were equally effective in cumulative ovulation and pregnancy rates.

Treatment did not induce formation of anti-FSH antibodies.

Foreign marketing of Org 32489: The sponsor has listed 11 EU countries and 5 non-EU countries where registration is pending. It has been approved in New Zealand and Switzerland but has not been marketed.

Labeling: is adequate and conforms to Metrodin labeling.

Summary: The pharmacology and toxicology of Org 32489 (rhFSH) is similar to the marketed urinary derived human FSH (uhFSH) which has a very safe and effective record based on its extensive

therapeutic use.

Org 32489 (rhFSH) is proposed for similar therapeutic indications as for Metrodin and as such poses no toxicity concerns.

Recommendations: Based on structural and functional similarity of Org 32489 (rhFSH) with natural FSH as well as its similarity to marketed human urinary FSH, along with extensive clinical experience of their effective and safe therapeutic use, Pharmacology considers it safe and recommends approval of NDA 20-582 for the proposed indications.

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Original NDA 20-582  
HFD-345  
HFD-580  
HFD-580/A. Jordan  
HFD-580/K. Raheja, 8-29-1996, N20582.ori