CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-582

PHARMACOLOGY REVIEW(S)

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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 dosae form: Administered afer reconstitution with 0.45% sodium chloride, USP. Each vial of Org 32489 contains 75 IU or 150 IU of FSH activity, plus 25.0 mg sucrose, NF; 7.35 mg sodium citrate dihydrate, USP; 0.10 mg 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 prepartion is approx 7.0.

Anticipated human dose: 300 IU (5 IU/kg). It was stated that up to 600 IU/day has been safety 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 acidic isohormones. These differences in isohormone composition ~~was~~ attributed ~~for~~ lower Cmax and AUC for Org 32489 ~~becuase bsic 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 signicificant 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 an 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.

Teatment 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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