

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-273

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

MEMORANDUM TO THE FILE
NDA 21-273
Ameeta Parekh, Ph.D.
August 22, 2005

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the NDA 21-273 (Follistim AQ, follitropin beta for injection). The original reviews in DFS from Drs. Venkat Jarugula and Dhruba Chatterjee address the relevant issues and provide details of the studies submitted in support of this NDA.

In summary, while Follistim (approved in 1997) is a ~~powder for injection~~ reconstituted before injection, Follistim AQ is formulated as an injectable solution. Bridging studies (in-vitro and in-vivo, see Dr. Jarugula's review) demonstrate that the exposure to follitropin beta from Follistim AQ is expected to be equivalent to that from Follistim. Bioavailability studies for Follistim AQ, per se, were not performed and a waiver was granted based on acceptable bridging information. The label for Follistim AQ provides the pharmacokinetic information derived from Follistim. This has been appropriately clarified in the label. There are no pending issues for OCPB for this NDA.

RECOMMENDATION: NDA 21-273 is acceptable from Clinical Pharmacology and Biopharmaceutics perspective.

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/s/

Ameeta Parekh
8/22/2005 02:01:22 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880) Tracking/Action Sheet for Formal/Informal Consults	
From: Dhruba J. Chatterjee, Ph.D.		To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission	
DATE: 4/25/05	IND No.: Serial No.:	NDA No. 21-273	DATE OF DOCUMENT Nov 22, 2004 (Stamp Date)
NAME OF DRUG Follistim® AQ	PRIORITY CONSIDERATION N/A	DATE OF INFORMAL/FORMAL CONSULT N/A	
NAME OF THE SPONSOR: Organon, Inc.			
TYPE OF SUBMISSION CLINICAL PHARMACOLOGY/BIPHARMACEUTICS RELATED ISSUE			
☐ PRE-IND ☐ ANIMAL to HUMAN SCALING ☐ IN-VITRO METABOLISM ☐ PROTOCOL ☐ PHASE II PROTOCOL ☐ PHASE III PROTOCOL ☐ DOSING REGIMEN CONSULT ☐ PK/PD- POPPK ISSUES ☐ PHASE IV RELATED			
☐ DISSOLUTION/IN-VITRO RELEASE ☐ BIOAVAILABILITY STUDIES ☐ IN-VIVO WAIVER REQUEST ☐ SUPAC RELATED ☐ CMC RELATED ☐ PROGRESS REPORT ☐ SCIENTIFIC INVESTIGATIONS ☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)			
☐ FINAL PRINTED LABELING ☒ LABELING REVISION ☐ CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ ANNUAL REPORTS ☐ FAX SUBMISSION ☐ OTHER (SPECIFY BELOW): <i>Seeking General Guidance</i>			
REVIEW ACTION			
☐ NAI (No action indicated) ☐ E-mail comments to: ☐ Medical ☐ Chemist ☐ Pharm-Tox ☐ Micro ☐ Pharmacometrics ☐ Others (Check as appropriate and attach e-mail)			
☐ Oral communication with Name: [] ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: []			
☒ Formal Review/Memo (attached) ☒ See comments below ☐ See submission cover letter ☐ OTHER (SPECIFY BELOW): []			
REVIEW COMMENT(S)			
☒ NEED TO BE COMMUNICATED TO THE SPONSOR ☐ HAVE BEEN COMMUNICATED TO THE SPONSOR			
COMMENTS/SPECIAL INSTRUCTIONS: The original Follistim® f _____ product (NDA 20-582) was approved by the Agency on 29-Sep-97 for the indications of development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program and induction of ovulation in the anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure. Please refer to the original CPB review by Dr. Gary Barnett, Ph.D., dated Dec 12, 1996 (in the Divisional Action Package for NDA 20-582). The applicant is currently responding to an approvable action pending on this product. In this submission, they are proposing addition of a few lines (lines 68 – 72) within the Clinical Pharmacology section of the label. Based on the original review and the relevance of the study (Study 37601) to the volume and mode of			

injection, in principle, the addition is acceptable to OCPB. However, the following edits (in the proposed text addition) should be incorporated (underlined):

Comments:

The Sponsor should include the above stated information in the package insert.

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/s/

Dhruba Chatterjee
4/26/05 03:12:51 PM
BIOPHARMACEUTICS
OCPB Review of Labeling Revision
After Ameeta's final edits.

Ameeta Parekh
4/26/05 03:53:59 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA: 21-273

Drug: Follistim-AQ

Sponsor: Organon Inc.

Date of Submission: 07/21/00, 10/09/00, 05/11/01

Type of Submission: Original NDA, 3S

Reviewer: Venkateswar R. Jarugula, Ph.D.

SYNOPSIS

Follistim-AQ is a new formulation of an already approved Follistim (follitropin beta for injection, NDA 20-582). The currently approved product, Follistim, is a freeze dried cake to be administered after reconstitution with water for injection and is available as 75 IU and 150 IU vials. Follistim-AQ, the subject of current application, is formulated as an injectable solution of 75, 150, ~~300~~ IU follitropin beta per 0.5 ml in a glass vial to be administered with a syringe.

The main difference between the approved formulation and the current proposed formulation is in the concentration of follitropin beta. The approved product according to the label results in the concentration range of 75 IU/ml to 300 IU/ml where as the proposed Follistim-AQ has from 75 IU/0.5 ml to 300 IU/0.5 ml (i.e., 150 IU/ml to 600 IU/ml). Since, the increase in concentration in the proposed formulation may affect the bioavailability, the sponsor submitted a biowaiver request based on an existing bioequivalence study between the lyophilized cake and cartridge formulation injected by a pen injector (submitted in NDA 21-211). In this bioequivalence (BE) study, it was shown that the concentration of follitropin in the range of 150 IU/ml to 833 IU/ml did not affect the bioavailability (refer to the attached Clinical Pharmacology and Biopharmaceutics review of NDA 21211). Since the maximum concentration of current formulation is 600 IU/ml, the BE study would support this concentration.

However, it was noted in the BE study that the handling of lyophilized cake during the injection process resulted in dose losses. The sponsor was therefore requested to provide information regarding the comparison of dose losses in handling the cake versus the solution. The information submitted in the current NDA shows that the volume/dose losses during the injection are similar between the cake and the solution formulations.

The BE study, that is the basis for waiver of bioequivalence study for the current NDA was conducted following subcutaneous administration. So, the sponsor was requested to

provide information to show that subcutaneous equivalence can be extrapolated to intramuscular administration. The information submitted by the sponsor showed that Follistim was bioequivalent when administered by SC and IM routes at 150 IU/ml concentration given in 1 ml as well as 2 ml total injection volumes. A safety and efficacy study in the original NDA also showed comparable safety and efficacy between SC and IM routes. Based on this information, the bioequivalence via SC route can be extrapolated to IM route of administration.

The Clinical Pharmacology and Biopharmaceutics section and the Drug Interactions section of the draft labeling are identical to the current approved labeling and thus are acceptable.

RECOMMENDATION

The human pharmacokinetics and biopharmaceutics section of NDA 21-273 is acceptable from the Clinical Pharmacology and Biopharmaceutics perspective.

Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Ph.D., Team Leader _____

FT signed by Ameeta Parekh, Ph.D., Team Leader _____

CPB briefing attendees: Drs. Hank Malinowski, John Hunt, Ameeta Parekh, Ridgely Bennett, Dornette Spell-lesane and Venkat Jarugula.

cc: NDA 21-273, HFD-580 (Bennette, Deguiaie), HFD-870 (Malinowski, Parekh, Jarugula), CDR (B. Murphy for Drug).

**Appears This Way
On Original**

SUMMARY

How is the new formulation different from the approved Follistim?

Composition of Follistim (cake) and Follistim-AQ (Solution):

Ingredient	Follistim (Cake)	Follistim-AQ (Solution)
recFSH	75 or 150 IU	75, 150, <del> </del>
Sucrose, NF	25 mg	25 mg
Sodium citrate Dihydrate, USP	7.35 mg	7.35 mg
Polysorbate 20, NF	0.1 mg	0.1 mg
L-Methionine, USP	-----	0.25 mg
HCl/NaOH	Trace*	Trace*
Water	Trace	qs to 0.5 ml
For injection		

*to adjust pH between 6.9-7.1

The solution formulation has L-methionine as additional ingredient, apparently to improve the stability of FSH in solution. The solution formulation is available in 0.5 ml volume, whereas the approved Follistim is reconstituted in before injection. Therefore, for any given dose, final concentration of active drug in injection is doubled in the proposed formulation when compared to the approved formulation.

Is the new formulation bioequivalent to the approved Follistim?

Since the concentration of active ingredient is doubled with the new formulation, sponsor requested a biowaiver based an earlier bioequivalence study that was submitted to NDA 21211. In this study it was shown that the bioavailability of FSH was not influenced by the concentration in the range of 150 IU/ml to 833 IU/ml of FSH. Since this concentration range includes the maximum concentration of the proposed solution formulation (600 IU/ml), the results of the cited BE study can be extrapolated to the current solution formulation. Therefore, sponsor's request for waiver of a bioequivalence study for the solution formulation is acceptable.

Since the BE study supporting the waiver request for the solution formulation has revealed that there were some losses in dose during the handling and preparation of the injection for cake formulation, sponsor was requested to provide comparative data regarding the loss of dose during handling and injection preparation for the two formulations (cake Vs solution).

In response to this request, an in vitro study was conducted to determine the dose losses. Comparative losses for the two formulations during handling and preparation of injection are given in the following table:

Comparison of injectable volume/dose for Cake Vs Solution

	Injectable Vol	Injectable FSH activity
Cake (4X75 IU/ 1ml)		
Mean	1.07 ml	285 IU
SD	0.04	24
RSD (%)	3.5	8.4
Solution (1X300 IU/0.5 ml)		
Mean	0.49 ml	296 IU
SD	0.01	20
RSD	1.96	6.9

Based on these results, the mean injectable FSH (based on immunoassay method) from Follistim cake (when 4 cakes of 75 IU were reconstituted in 1 ml) was 285 IU and the mean injectable FSH for the solution formulation (with 1 X300 IU per 0.5 ml) was 296 IU.

The mean injectable FSH activity (as measured by radio immunoassay method) from solution formulation compared to Follistim cake was 104%, with a 95% confidence interval of 99% - 109%. The difference in mean injectable FSH activities between the two formulations was found to be statistically insignificant. Therefore, based on these results, it can be concluded that the two formulations will result in similar doses being injected into the body.

Based on the BE study submitted in NDA 21211 and the *in vitro* results reported in the current NDA, sponsor's request for waiver of a BE study for solution formulation is acceptable.

An open label, randomized group-comparative multicenter study was conducted to compare the efficacy and safety of Follistim AQ solution with the approved Follistim freeze-dried cake formulation (both administered subcutaneously) for the induction of ovulation in clomiphene-resistant subjects with chronic anovulation WHO group II). A total 126 subjects (64 on cake formulation and 62 on solution formulation) were enrolled and completed the study. Sponsor concluded that both approved Follistim and Follistim-AQ are equally safe when used to stimulate follicles in women undergoing treatment with FSH. Follistim-AQ has a higher efficiency in terms of less time to ovulation and less total dose required to achieve the same endpoints (please refer to the medical officer's review for more details on safety and efficacy results of this clinical study).

Extrapolation of bioequivalence from subcutaneous (SC) route to intramuscular (IM) route.

The referenced bioequivalence study was conducted by subcutaneous administration. Sponsor sought approval of solution formulation for both SC and IM routes. So, the sponsor was requested to provide information that supports the equivalence between SC and IM routes in terms of the bioavailability and the influence of concentration of the active ingredient.

In response, to substantiate the bioequivalence of SC and IM routes as a function of dose and concentration of active ingredient in the injection fluid, sponsor submitted the synopses of the following studies that were previously submitted in the original NDA 20-582 (Follistim):

1. Study 37614: This study showed that the subcutaneous and intramuscular routes were bioequivalent in terms of AUC when 300 IU were administered in 2 ml volume (conc. of 150 IU/ml). However, C_{max} for SC administration is about 21% lower (with 90% CI: 72%-101%) than IM administration.
2. Study 37624: In this study, it was found that subcutaneous and intramuscular routes were bioequivalent when 150 IU (cake) were administered in 1 ml volume (conc. of 150 IU/ml). Dose proportionality was also observed over the dose range of 75 to 225 IU/ml administered subcutaneously.
3. A pharmacokinetic study in dogs (SDGRR 3756). This study showed that SC and IM routes were bioequivalent when 25 IU/0.1ml/kg FSH was administered. (conc. of 250 IU/ml).
4. Study 37613: This is an open-label, randomized, group-comparative, multi-center study to assess the tolerance, safety and efficacy of FSH administered subcutaneously as compared with the intramuscular route in infertile women undergoing in vitro fertilization and embryo transfer. The treatment started with either 150 or 225 IU for the first 4 days of treatment. From Day 5 the treatment was individualized. The number of subjects treated with Follistim was 77 for IM and 118 for the SC route. The conclusions of this study were: There were no clinically relevant differences in efficacy between SC and IM routes with respect to the number of oocytes retrieved and ongoing pregnancy rates (based on a non-confirmatory analysis). There was also no significant difference in terms of safety and tolerability of Follistim administered SC Vs IM routes.

According to the above information, Follistim is shown to be bioequivalent following administration via SC and IM routes both by means of pharmacokinetic studies and a safety and efficacy study. So, the bioequivalence of the two formulations (cake Vs solution) by SC route can be extrapolated to IM route.

ATTACHMENT I

(Synopsis of Clinical Pharmacology and Biopharmaceutics Review of NDA 21211)

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Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	21-211
Drug:	Follistim –AQ (follitropin beta injection) Cartridge
Sponsor:	Organon Inc
Date of Submission:	01-31-00, 03-30-00, 10-31-00, and 11-06-00
Type of Submission:	Original NDA
Reviewer:	Venkateswar R. Jarugula, Ph.D.

SYNOPSIS

Follistim-AQ (follitropin beta injection) cartridge is a new pharmaceutical presentation of the approved Follistim (follitropin beta for injection), NDA 20-582. The approved product is formulated as a freeze-dried cake; to be administered after reconstitution with water and is available in 75 IU and 150 IU vials. Follistim-AQ cartridge, the product of current NDA, is an injectable aqueous solution of 300 IU and 600 IU follitropin beta (FSH) in a glass/ [redacted] rubber multidose cartridge, to be administered with a pen-injector device.

According to the sponsor, a multi-dose ready to use product is considered to be more convenient than the approved product since its use requires less handling and it provides a more accurate and precise method of dosing as compared to the conventional syringe.

The concentration of follitropin beta in Follistim-AQ cartridge (833 IU/ml) is higher than that in the reconstituted approved Follistim (75-300 IU/ml). Since absorption from the injection site may be influenced by the concentration of the drug and injection volume, sponsor conducted a bioequivalence study with Follistim-AQ cartridge Vs Follistim reconstituted product. This was an open-label, single-center, single-dose, crossover study in 22 female subjects comparing the bioavailability of a single dose of Follistim-AQ (150 IU) with reconstituted Follistim (150 IU). In this study, Follistim-AQ resulted in 20% higher AUC than the approved Follistim and the two formulations were found to be not bioequivalent. However, in the same study, it was found that the conventional syringe, due to filling, removing excess air and the dead volume of the syringe, actually delivered on average 16% lower than the nominal dose of 150 IU FSH, whereas pen-injector was assumed to accurately deliver the dose (150 IU) to which it was set. Consequently, pen-injector dosing was higher than the conventional syringe.

Since the conventional syringe delivered [redacted] lower than the nominal dose, sponsor analyzed the pharmacokinetic data by dose correction. The formulations were shown to be bioequivalent following dose correction of the PK parameters, AUC and Cmax.

The fact that the two products were shown bioequivalent following dose correction to account for losses from conventional syringe indicates that the difference in concentration does not influence the bioavailability in the concentration range tested. However, if used without this dose adjustment, the pen-injector would result in about 20% higher bioavailability than the Follistim reconstituted product that has been tested in clinical trials and has been in use for its indication since approval.

Sponsor stated that the higher bioavailability of pen-injector does not affect the safety and efficacy of Follistim. However, no data was provided to support this statement. Before filing the NDA, sponsor was informed by the clinical division that there was no data to conclude that higher bioavailability of pen-injector does affect the safety and efficacy of this product. In response, sponsor proposed some changes in the dosing and administration section by including a conversion table showing doses of the conventional injection with the corresponding settings for the pen-injector to deliver equivalent doses. In the conversion table, the setting of pen injector was reduced (by approximately 18%) to match the actual dose delivered by conventional syringe. However, the conversion table appears to be confusing to be used appropriately by the patients who are going to self-administer the drug product. This issue is currently under review the clinical review division.

Sponsor has submitted in vitro measurements that estimate the drug loss during reconstitution of lyophilized cake and injection to NDA 21-273. Although this data were submitted to different NDA, it is relevant for this NDA as well. The estimated dose loss determined for Follistim lyophilized cake varied from [REDACTED] among in vitro measurements in different studies. This variability could be due to different technical persons performing the reconstitution, and also due to differences in methods of measurements. The estimate reported in the BE study of the current NDA is the highest and conservative. Since the therapy of Follistim is dose titrated based on efficacy (follicle growth is monitored by ultrasound), sponsor's proposal to adjust the pen-injector by the highest (conservative) estimate of all the in vitro measurements appears to be appropriate.

The accuracy and precision of the pen-injector device should be evaluated by the devices expert reviewer.

In conclusion, the results of the bioequivalence study showed that pen-injector device provided approximately 20% higher bioavailability than the Follistim reconstituted product. The two products as administered were not shown to be bioequivalent. However, the two products were shown to be bioequivalent when corrected for the dose loss during injection of lyophilized cake. Sponsor proposed to adjust the pen-injector setting in order to deliver a dose that matches the dose delivered by syringe.

RECOMMENDATION

The NDA is acceptable from Clinical Pharmacology and Biopharmaceutics perspective.

Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Ph.D., Team Leader _____

FT signed by Ameeta Parekh, Ph.D., Team Leader _____

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Venkateswar Jarugula
5/16/01 10:30:32 AM
BIOPHARMACEUTICS
Original NDA review

Ameeta Parekh
5/16/01 12:22:29 PM
BIOPHARMACEUTICS
I concur