

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-211

MEDICAL REVIEW

Follistim®-AQ Cartridge

MEMO

DATE: October 13, 2004
FROM: Audrey Gassman, M.D. (HFD-580)
THROUGH: Daniel Shames, M.D., Division Director (HFD-580)
RE: Medical Officer's review of questions to with regard to one section of the Phase 4 post-marketing commitment – the survey to prescribers regarding the Dose Conversion Chart in the label.
TYPE OF SUBMISSION: Commercial-Sponsor
SPONSOR: Organon, Inc.
375 Mount Pleasant Avenue
West Orange, NJ 07052
DRUG NAME: Follistim®-AQ Cartridge (follistim beta injection)

Background:

The sponsor presented an NDA (21-211) for a new presentation of Follistim® in a liquid formulation that would be used in a pen-injector device (Follistim®-AQ Cartridge). The Approvable Letter (dated 23-Dec-03) to the Sponsor outlined submission of a draft label, a draft patient package insert, and plans for an educational program for patients and prescribers focusing on correct use of the pen injector and the need for careful dose conversion when switching from syringe to pen injector or vice versa. In a follow-up information request letter dated 15-Mar-04, the Division recommended that a survey be proposed for health care providers to evaluate the use of the dose conversion chart when switching from the syringe to the pen or vice versa. Follistim®-AQ Cartridge was approved 23-Mar-04.

The sponsor requested additional guidance with development of the survey on 02-Sep-04 via Email. Consults were obtained from DDMAC and ODS with the following recommendations for the proposed survey:

1. Use of a random sample of participants with an adequate representation from different regions of the United States (i.e. Northern New England, Mid-Atlantic, South, Midwest, and West)
2. Use an adequate sample size so that results are representative
3. Use a cross-sectional research design or longitudinal trend study design
4. Develop a survey instrument that explores, explains or describes use of the Dose Conversion Chart by health care providers.
5. Develop a survey instrument with minimal bias
6. Pilot test the survey instrument
7. Survey questions should be simple and straightforward

Recommendations (continued):

8. The survey may be conducted by paper, on-line, or at a well-attended meeting. However, if you choose to conduct the survey at a meeting, you should not be the primary sponsor of the meeting.
9. Prior to beginning the study, submit for FDA review the a) sampling and recruitment plan, b) study design and proposed data analyses, and c) survey instrument and pilot test results.

Recommended regulatory action: Comments #1 through #9 should be conveyed to the sponsor via a regulatory letter as soon as possible.

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/s/

Audrey Gassman
10/13/04 03:28:30 PM
MEDICAL OFFICER

Daniel A. Shames
10/20/04 04:59:35 PM
MEDICAL OFFICER

Medical Officer's Review of Complete Response to Approvable Action

NDA: 21-211
**Established Drug Name/
Trade Name:** Follistim®-AQ Cartridge (follitropin beta for
injection with a pen-injector device)
Type of Submission: Commercial-Sponsor
Sponsor: Organon, Inc.

Proposed indications in women:

1. Follistim®-AQ Cartridge is indicated for the induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure.
2. Follistim®-AQ Cartridge is also indicated for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology program.

Date of Submission Received: January 23, 2004
Date Review Completed: February 13, 2004
Reviewer: Audrey Gassman, MD

Background:

The sponsor presented an NDA (21-211) for a new presentation of Follistim® in a liquid formulation that would be used in a pen-injector device (Follistim®-AQ Cartridge). The sponsor originally submitted a bioequivalence study (37626) that compared a single dose of 150 IU of the original formulation of Follistim® with a single dose of 150 IU using Follistim®-AQ Cartridge administered with the pen injector for the NDA. The results were non-equivalent. In the NA letter (29-Nov-00), the additional issue raised by the Division was a concern of patient use of the Follistim Pen™. The sponsor submitted two clinical studies (142-001 and 142-002) that addressed the issues of use of the Follistim Pen™ by patients, but did not address the lack of bioequivalence. The sponsor was originally issued an NA letter (23-Jun-03) for the submission, and appealed to the Office Director, and was granted an approvable action by the Deputy Director of ODE III (23-Dec-03).

The approvable letter included the following four requests to the Sponsor:

1. Draft professional labeling
2. A safety update on the global marketing experience for Follistim AQ Cartridge
3. Draft patient package insert
4. Plans for an educational program for patients and prescribers focusing on correct use of the pen-injector and of the need for careful dose conversion when switching from the syringe to the pen or vice versa.

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/s/

Audrey Gassman
3/23/04 08:19:10 AM
MEDICAL OFFICER

Daniel A. Shames
3/23/04 09:58:52 AM
MEDICAL OFFICER

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 § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 10, 2004

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Achana Reddy, M.P.H., Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Follistim AQ
Cartridge (follitropin beta injection), NDA 21-211

The patient labeling which follows represents the revised risk communication materials of the PPI and *Instructions for Use* for Follistim AQ Cartridge (follitropin beta injection), NDA 21-211. The Division of Surveillance, Research, and Communication Support (DSRCS) reviewed the labeling from a patient comprehension perspective. The Division of Medication Errors and Technical Support (DMETS) reviewed the *Instructions for Use* in an attempt to focus on safety issues to prevent possible medication errors. DMETS comments do not address any safety concerns with the carton labeling or container labels for this product. These issues will be forwarded to the Review Division in a separate consult from DMETS.

These revisions are based on labeling submitted February 26, 2004.

Comments

We also have the following comments and recommendations:

1. All patient materials should be written at a 6th to 8th grade reading comprehension level. The reading ease score should be 60% or greater which corresponds with an 8th grade reading level. Approximately 50% of the U.S. adult population functions at a lower literacy level and

reads below an 8th grade reading level. The proposed PPI has a Flesch-Kincaid Reading Level of 10.7 and a Flesch Reading Ease of 48.8%. To improve these scores, and enhance comprehension to a broader population, including those with lower literacy, we recommend simplifying language, shortening sentences, and removing unnecessary information throughout this document.

2. Remove all promotional material per DDMAC guidelines, e.g., The sponsor states "_____"

_____ A comprehension study with an adequate study methodology that produces results that can support conclusions would be required. The study would need to include an adequate number of patients with lower literacy levels.

3. DMETS continues to recommend that the name "Follistim Pen" be revised to "Follistim AQ Pen" on all labels and labeling.

Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division

Please let us know if you have any questions.

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/s/

Jeanine Best
3/10/04 01:06:42 PM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
3/10/04 01:18:41 PM
MEDICAL OFFICER

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 § 552(b)(4) Trade Secret / Confidential

 X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Follistim® AQ Cartridge

MEMO

DATE: March 2, 2004
FROM: Audrey Gassman, M.D. (HFD-580)
THROUGH: Daniel Shames, M.D., Division Director (HFD-580)
RE: Medical Officer's review of response to labeling comments

TYPE OF SUBMISSION: Commercial-Sponsor
SPONSOR: Organon, Inc.
375 Mount Pleasant Avenue
West Orange, NJ 07052

Drug Name: Follistim®-AQ Cartridge (follistim beta injection)
Date of Submission: February 27, 2004
Date Review Completed: March 2, 2004

Background:

The sponsor presented an NDA (21-211) for a new presentation of Follistim® in a liquid formulation that would be used in a pen-injector device (Follistim®-AQ Cartridge). The sponsor originally submitted a bioequivalence study (37626) that compared a single dose of 150 IU of the original formulation of Follistim® with a single dose of 150 IU using Follistim®-AQ Cartridge administered with the pen injector for the NDA. The results were non-equivalent. In the NA letter (29-Nov-00), the additional issue raised by the Division was a concern of patient use of the Follistim Pen™. The sponsor submitted two clinical studies (142-001 and 142-002) that addressed the issues of use of the Follistim Pen™ by patients, but did not address the lack of bioequivalence. The sponsor was originally issued an NA letter (23-Jun-03) for the submission, and appealed to the Office Director, and was granted an approvable action by the Deputy Director of ODE III (23-Dec-03).

The Approvable Letter (dated 23-Dec-03) to the Sponsor outlined submission of the following four items to proceed with the approval of Follistim®-AQ Cartridge:

1. Draft professional labeling
2. A safety update on the global marketing experience for Follistim®-AQ Cartridge
3. Draft patient package insert
4. Plans for an educational program for patients and prescribers focusing on correct use of the pen-injector and of the need for careful dose conversion when switching from the syringe to the pen or vice versa.

The Sponsor submitted a complete response to the Approvable letter on 22-Jan-04. The submission was reviewed and a teleconference was held with the Sponsor on 19-Feb-04.

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_____ § 552(b)(4) Trade Secret / Confidential

0 § 552(b)(4) Draft Labeling

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/s/

Audrey Gassman
3/2/04 09:41:10 AM
MEDICAL OFFICER

Daniel A. Shames
3/2/04 06:33:12 PM
MEDICAL OFFICER

**Follistim®-AQ Cartridge
Team Leader Review**

NDA: 21-211
(Class 2 resubmission)

Drug: Follistim®-AQ Cartridge (Follitropin beta for injection)

Indication:

1. Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program.
2. Induction of ovulation in the anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure.

Dosage/Form/Strength: Sterile, clear, colorless aqueous solution filled into ready-for-use disposable cartridges intended to fit Becton-Dickinson Pen \surd for adjustable administration. 833 IU FSH per ml in either 300 IU or 600 IU cartridges.

Applicant: Organon, Inc
Receipt Date: December 24, 2002
Review Completed: June 20, 2003
Date of Memorandum: June 23, 2003

Background and Regulatory History

Follistim® was approved by the Agency on September 29, 1997 for the indications of development of multiple follicles (controlled ovarian stimulation) in ovulatory patients participating in an Assisted Reproductive Technology (ART) 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. Follistim® is a freeze-dried cake formulation for reconstitution with water for injection. On March 18, 1999, the Sponsor, Organon, met with the Agency in a pre-NDA guidance meeting to discuss a completed bioequivalence study of Follistim® vs. a new pharmaceutical presentation, Follistim®-AQ Cartridge. A bioequivalence study was proposed to support the NDA submission for the new formulation. No clinical trials were proposed or conducted. The completed bioequivalence study compared a single dose of 150 IU of Follistim® (2-vials of 75 IU dissolved in _____ diluent) administered subcutaneously with a syringe to a single dose of 150 IU of Follistim®-AQ Cartridge administered subcutaneously with a Becton Dickinson (BD) Pen \surd injector. The results were non-equivalent; the pen injector dose had a higher bioavailability. To address the non-equivalence of the dosage forms, the Sponsor was presented with the option of conducting another bioequivalence study after adjusting the dose of the BD Pen \surd injector to match the dose delivered with the reconstituted freeze-dried cake formulation. It was also discussed that the labeling for Follistim®-AQ Cartridge with the BD Pen \surd injector should clearly address the delivery volume. Finally, because a significant safety

risk could exist for patients switching from the cake formulation of Follistim® to Follistim®-AQ delivered via the BD Pen → injector, the Sponsor was asked to address this with a justification for the use of either product. Following acceptable justifications for the use of either product, the proposed labeling would then allow the physician to decide the choice of product, dose and mode of administration. It was decided at the pre-NDA meeting that the bioequivalence issues should be resolved before the NDA application was submitted.

The NDA for Follistim®-AQ Cartridge was submitted on January 28, 2000. A teleconference between the Agency and the Sponsor was held on March 22, 2000. In this teleconference, the Deputy Division Director reiterated to the Sponsor the discussion points of the March 18, 1999 meeting (as presented in the previous paragraph). The Sponsor was told that the safety and efficacy of the BD Pen → injector must be linked to Follistim® by establishing bioequivalence. The Sponsor was presented with alternatives to conducting another pharmacokinetics trial to establish bioequivalence and these are as follows:

1. Adjust the dose of the pen-injector to match the dose delivered by the syringe and label the product in a way to convey bioequivalence to the more familiar dose. This scenario would require that the B D Pen→ injector device be recalibrated to facilitate the ease and use by patients and physicians. Under this scenario, the bioequivalence study requirement would be waived.
2. Generate clinical trial data with the new formulation and the pen-injector to show that the higher bioavailability of the dose delivered with the pen-injector was both safe and effective.
3. Change the concentration of drug while maintaining the same administration volume. Stability data would be required with this new formulation.

The Sponsor was clearly told that the Division did not accept the Sponsor's position that the higher bioavailability of the dose delivered with the BD Pen → injector is of no clinical concern. Subsequent to this meeting it was determined that the higher bioavailability of the dose delivered by the BD Pen → injector would be a review issue rather than a filing issue and the NDA was filed on March 31, 2000. No clinical trial data was submitted. In support of the NDA application for Follistim®-AQ Cartridge, Organon submitted only the bioequivalence study comparing it to Follistim®. The bioequivalence study showed that the two were not bioequivalent. The pen injector had a higher bioavailability (20% high Cmax and AUC). The Sponsor argued that the difference could be accounted for by the fact that the BD Pen → injector device provides a more accurate and precise method of dosing as compared to the conventional syringe.

In addition to the bioequivalence study, the Sponsor submitted results from an in vitro study wherein the conventional use syringe was weighed before and after the administration of Follistim. It was determined that the conventional syringe delivered a → lower amount than the nominal dose. On March 29, 2000, the Sponsor submitted a proposal to the Agency for a conversion table to translate the dosing units of Follistim® to that for Follistim-AQ that is to be given with the pen-injector. This proposed conversion table utilized an 18% correction factor derived in the bioavailability study (which the Sponsor used to support bioequivalence of the drug product). This approach was acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

The Sponsor argued that the conversion table would be important only in the instance where one is switching within a cycle from one formulation to the other. The clinical reviewers felt that the Sponsor's argument overlooked the consideration of starting dose which is frequently planned based on the previous cycle (s) for the patient who is undergoing a repeat cycle of Ovulation and

Induction or in vitro fertilization (IVF). Further the conversion table submitted by the Sponsor provided for a calculated correction based on data from the bioavailability study and it was noted that not every subject in the bioavailability study demonstrated a 20% higher bioavailability of the BD Pen —injector delivered dose than the syringe-delivered dose. The reviewers felt that universal application of this 18% correction factor would result in some subjects being given a lower dose than necessary.

The clinical team found the manual to be unduly cumbersome and potentially difficult and unsafe for patients to follow.

The Follistim®-AQ Cartridges and BD Pen —injector device consists of 15 parts and requires the patient handling and assembly before a dose can be administered. The device requires that the patient be able to set the pen to a numerical indicator as well as discern audible clicks in order to deliver the correct dose. The device allows for the selection of up to 54 different dosages. The conversion table submitted by the Sponsor lists the approximate equivalent for the cake formulation delivered via conventional syringe for only 5 of these possible doses. The review of the BD Pen —injector device by the Center for Devices and Radiological Health-Division (CDRH) of Dental, Infection Control and General Hospital Devices did not support the high accuracy of the BD Pen —injector as represented by the Sponsor. The CDRH review concluded that a determination of the safety and efficacy of the device could not be made from the information provided in the NDA.

There were also approvability issues from a Chemistry, Manufacturing and Controls point of view. The pre-filled cartridge is manufactured by Vetter Pharma-Fertigung GrmGH & Co. KG; packaged and tested by Organon, Ltd. (Ireland) and Organon, Inc. (West Orange, NJ); and secondary packaging was to be done by Organon Inc. (Allentown, PA). Organon, Inc. is not in compliance with cGMP. The Office of Compliance sent a warning letter to the firm and made an overall recommendation of “Withhold” approval. The Sponsor’s proposed release specifications of oxidation products were not acceptable. The proposed shelf-life specifications for subunit content, oxidation products, and benzyl alcohol content were not acceptable.

Based upon the recommendation of the Clinical and CMC reviewers and the consult from CDRH, the application received a non-approvable letter on November 29, 2000. In the non-approvable letter, the Sponsor was advised to conduct clinical trials using Follistim®-AQ Cartridge in patients undergoing Assisted Reproductive Technology (ART) and Ovulation Induction (OI) protocols. The Sponsor was further advised that the studies must demonstrate the safety and effectiveness of the product for the proposed indications, including demonstration of patient comprehension of a proposed patient instruction manual, patient ability to correctly handle and assemble the pen injector device prior to dose administration, and patient ability to determine and administer the correct doses of Follistim®-AQ Cartridge as indicated by a health care provider.

Further, the information included in the patient instruction manual should also be included in the Physician Insert under INFORMATION FOR THE PATIENT. In addition, the Sponsor was advised that all CMC deficiencies were to be successfully addressed and the West Orange, N.J. manufacturing facility must have a satisfactory cGMP inspection. With respect to the BD Pen injector the following information was required:

- Additional information about the Pen Injector and its performance were to be submitted to the MAF to support the new intended use or the equivalent information to CDER to support the new intended use
- A description of the dose measure that the BD Pen is calibrated to deliver. The dose measure for the BD Pen injector should be directly related to the international unit. A description of the incrementing dose unit and the accuracy tolerance for the BD injector. A description of the difference in dose volume and quantity between adjacent clicks of the device
- Bench testing data to demonstrate the dosing accuracy of the BD Pen for both Follistim® formulations. A comparison to the dosing accuracy of the BD Pen and the dosing accuracy of conventional administration by syringe and needle for both such formulations.
- An evaluation and mitigation of the patient risks that may arise from two different concentrations being available in the same container type that fits into the same injector device.
- A description of operations performed by the secondary packaging facility for co-packaging the device and cartridges must be provided.
- The BIs used for validation of containers, closures and filling machine parts. The results of the BIs in the validation cycles must be provided. The organism, source, spore concentration and D-value must be included in this information.
- The sensitivity of the dye ingress test must be provided.

On March 30, 2001, Organon sent in a submission to respond to the non-approvable letter deficiencies. This submission was judged as an incomplete response. The incomplete letter noted that the following deficiencies from the action letter still needed to be addressed:

- Sufficient information to support the safe and effective use of Follistim®-AQ Cartridge
- Draft labeling
- Precision data, specifically, precision testing

On December 24, 2002, a class 2 resubmission was received. This resubmission was supported by information on the accuracy of the BD Pen injector, two Phase 3 clinical trials (one OI and one ART), and labeling. The NDA was filed on February 21, 2003.

Clinical Efficacy and Safety

In support of their NDA submission the Sponsor has submitted two comprehension studies (one each for the indication of Ovulation Induction and multiple follicular development in ART). Both of these studies utilize an observer questionnaire and patient reported "Ease of Use" questionnaire as primary efficacy outcome variables. Both studies had the same objective to demonstrate that the use of the Follistim®-AQ Cartridge is well understood by the patient. Both trials were conducted during the time period January 2002 to September 2002

Study 142-001: "An open-label, non-controlled multi-center study to evaluate subject comprehension, ease of use, safety and efficacy of the Follistim® Pen for the

self-administration of Follistim®-AQ Cartridge during Controlled Ovarian Hyperstimulation (COH) in subjects scheduled for IVF or ICSI.”

This non-randomized non-comparative study was conducted in 50 healthy female partners of infertile couples previously scheduled for in vitro fertilization (IVF), with or without intracytoplasmic sperm injection (ICSI) who satisfied all of the enrollment criteria. The enrollment criteria were consistent with the usual criteria for studies of subjects undergoing ART (see primary MO review). Prior to starting treatment each subject had a standardized instruction on how to use and store the Pen Injector. Each subject received a starting dose of 150 to 225 IU of Follistim®-AQ Cartridge depending on the demographics and history of the subject. The selected starting dose of follitropin beta was fixed for the first five days of treatment. After this, the dose was adjusted for the individual patient based on their ovarian response as assessed by ultrasound.

Human chorionic gonadotropin (hCG) was administered when adequate ovarian response was observed (at least 3 follicles \geq 17 mm). The maximum treatment period was 19 days. The maximum daily dose for Follistim®-AQ Cartridge is not mentioned in the protocol. Antagon™ was used in this protocol to prevent premature LH surges. Antagon™ was used in a daily dose (250 mcg subcutaneously) and initiated when one or more follicles \geq 14 mm were seen on ultrasound. Treatment with Antagon™ was continued up to and including the day of hCG. Ten thousand (1,000) IU hCG was administered when there were at least three follicles \geq 17mm.

Subject comprehension was assessed by collecting results from observing the subject when she prepared and practiced injections using placebo cartridges (mock run) and then with Follistim®-AQ Cartridge (comprehension questionnaire for efficacy), a “Ease of Use” questionnaire, a local tolerance questionnaire and serious adverse events. After the mock injection 100% of subjects inserted the cartridge correctly, 98% selected the correct dose, 87.5% were able to correct a dosing error and 33% required re-instruction to accomplish these goals. The results of the comprehension questionnaire taken during with Follistim®-AQ Cartridge run are depicted in Table 1.

Table 1: Frequency Distribution of Selected Observer Questionnaire Step Results for the Actual Follistim®-AQ Cartridge Injection on Treatment Day 2.

Step	Trial 142-001 “IVF/ICSI” N=60 total subjects
1. Inserting Cartridge correctly*	27/27 (100%)
2. Selecting the correct dose	60/60 (100%)
3. The Pen self-primed	34/60 (56.7%)
3a. Patient then properly primed the Pen	24/29 (82.8%)
4. Correcting a dosing error	6/6 (100%)
5. Pen seated at zero following injection	60/60 (100%)
6. Re-instruction rate	12/60 (20%)
*Subjects came to study with Follistim®-AQ Cartridge already loaded.	

* “IVF/ICSI – *in vitro* fertilization with or without intracytoplasmic sperm injection”

The results of the observer questionnaire demonstrated that when instructed (in this trial setting) subjects could load and administer the dose (successfully completing all steps). Twenty percent (20%) of subjects required re-instruction but this appeared to be related to actual self-injection of the drug product (wrong site, incorrect timing before needle withdrawn and swabbing of site when the needle was withdrawn) rather than the assembly and use of the pen.

The "Ease of Use" questionnaire was summarized as mean score per question, mean score for the entire questionnaire and overall rating of the device (a one question response at the end of the "Ease of Use" questionnaire). Mean overall scores for each individual question was 4.8 out of a maximum possible score of 5.0 on Day 2 of treatment in Study 142-001. The sponsor and the Division had previously agreed that that an average score per question should be ≥ 4.0 . (See the Division letter dated May 22, 2002 and the Sponsor's response letter dated June 28, 2002). The mean total score for the questionnaire was 96.9 on Day 2 of treatment in trial 142-001 (The sponsor indicated that an average score ≥ 60 was considered to indicate that the Follistim Pen™ is easy to use). On Day 2 of treatment 81.8% of patients rated the Follistim Pen™ as "very good" overall, and this improved on Day 6 of treatment to 90%.

Secondary efficacy outcomes for total dose (IU), number of days of treatment, number of oocytes retrieved and fertilization rates were collected. The results of these variables in this non-randomized, non-controlled open label study were summarized with descriptive statistics.

The most important non-pregnancy related adverse events to analyze in controlled ovarian stimulation are incidence of ovarian hyperstimulation syndrome (OHSS) and incidence of abdominal pain. The incidence of OHSS in Study 142-001 is 3.3%, while the incidence of abdominal pain was 25%. There was no comparator arm to assess the meaning of this rate in this small non-comparative trial. Cross-study comparisons to the rates seen in studies for Follistim® approval suggest that this is not an unusually high rate. But one must use caution in interpreting such cross-study comparisons, particularly in ART where the laboratory procedures and drug interventions have significantly evolved in the time period since the conduct of the original Follistim® trials.

Local tolerance appeared to be acceptable in this small study.

Study 142-002: "An open-label, non-controlled multi-center study to evaluate subject comprehension, ease of use, safety and efficacy of the Follistim® Pen for the self-administration of Follistim®-AQ Cartridge for induction of ovulation in clomiphene-resistant women with chronic anovulation (WHO group II)."

This non-randomized non-comparative study was conducted in a similar manner to Study 142-001 except the 50 healthy female partners of infertile couples were previously scheduled for ovulation induction and satisfied all of the enrollment criteria consistent for trials of subjects undergoing ovulation induction (see primary MO review). Each subject received a starting dose of 75 IU of Follistim®-AQ Cartridge that was fixed for the first seven days of treatment. After this, the dose was to be adjusted for the individual patient based on their ovarian response as assessed by ultrasound. If there was no ovarian response on Day 8 (upon ultrasound measurement) prior to Follistim®-AQ Cartridge injection, the dosage increase was decided by the investigator (but not to be greater than 25-50 IU). If ovarian response still did not occur, the dose of Follistim®-AQ Cartridge could be increased 25-50 IU again. If an

ovarian response (as measured by ultrasound) was observed, the Follistim®-AQ Cartridge dose was to remain the same and to be continued until a complete ovarian response was observed. This was defined as one follicle with a diameter ≥ 18 mm and/or 2-3 follicles with a diameter of ≥ 15 mm. Human chorionic gonadotropin (hCG) was administered within 36 hours of the last Follistim®-AQ Cartridge injection. Either intercourse or intrauterine insemination was to occur approximately 36 – 44 hours after hCG administration. The results of the comprehension questionnaire taken during with Follistim®-AQ Cartridge run are depicted in Table 2

Table 2: Frequency Distribution of Selected Observer Questionnaire Step Results for the Actual Follistim®-AQ Cartridge injection on Treatment Day 2.

Step	Trial 142-002 "OI"*** N=43 total subjects
1. Inserting Cartridge correctly*	27/27 (100%)
2. Selecting the correct dose	43/43 (100%)
3. The Pen self-primed	29/43 (67.4%)
3a. Patient then properly primed the Pen	12/14 (85.7%)
4. Correcting a dosing error	3/3 (100%)
5. Pen seated at zero following injection	43/43 (100%)
6. Re-instruction rate	10/43 (23.3%)
*Subjects came to study with Follistim®-AQ Cartridge already loaded.	

*** "OI – ovulation induction"

All of the subjects were able to follow the instruction, correctly inserted the cartridge and select the dose. Twenty-three percent required re-instruction. On the "Ease of Use" questionnaire, the mean overall scores for each individual question was 4.9 out of a maximum possible score of 5.0 on Day 2 of treatment in Study 142-002. (with an acceptable score determined as greater than 4.0 as previously mentioned in Study 142-001). The mean total score for the questionnaire was 97.9 on Day 2 of treatment in Study 142-002. (with an acceptable score being ≥ 60 as previously mentioned for trial 142-001. Approximate ninety – one percent (91%) of subjects rated the BD Pen 1 as "very good" for S142-002, and this improved on Day 8 of treatment to 95.2% respectively.

Secondary efficacy outcomes for mean total dose (IU), number of days of treatment, and ovulation rates were collected. The results of these variables in this non-randomized, non-controlled open label study were summarized with descriptive statistics.

The incidence of OHSS in Study 142-002 is 9.3%, while the incidence of abdominal pain was 25%. There was no comparator arm to assess the meaning of this rate in this small non-comparative trial. Cross study comparisons to the rates seen in studies for Follistim® approval suggest that this is a higher rate than that previously labeled for similar drug products for ovulation induction. Again caution must be used in interpreting such cross-study comparisons. Local tolerance appeared to be acceptable in this small study.

The Sponsor conducted these two phase 3 open-label, non-randomized clinical trials with the primary objective to provide evidence of subject comprehension and use of Follistim®-AQ Cartridge. There is sufficient evidence to conclude from these two comprehension trials that the Follistim Pen™ device was well understood by the subjects in both clinical trials.

In contrast, the two clinical trials do not provide adequate evidence to conclude that there is therapeutic equivalence between Follistim® and Follistim®-AQ Cartridge based on clinical outcomes. The major efficacy support for Follistim®-AQ Cartridge was to be based on bioequivalence to the approved Follistim® product. The higher bioavailability supports that Follistim®-AQ cartridge has effect but that it is not bioequivalent to Follistim®. The outstanding clinical question is whether the higher bioavailability of Follistim®-AQ as delivered by the BD results in significant clinical safety issues. The Sponsor needed to provide substantial evidence that the higher bioavailability of Follistim®-AQ cartridge does not result in higher rates of adverse events normally associated with this class of drug products. The information obtained from these two small non-comparative trials does not provide such evidence. In fact, comparison of results for incidence rates of OHSS in Study 142-002 with labeled incidence rates in others studies suggests a possible higher incidence rate.

Further, the safety information from Follistim® can not be reference to provide for recommendation for dosage and administration and the information obtained in these two small, non-randomized, non-comparator comprehension trials is insufficient for this purpose.

Biopharmaceutics

See discussion above and review and conclusion of Office of Clinical Pharmacology and Biopharmaceutics from the previous review.

Chemistry/Manufacturing

With the exception to the cGMP status of manufacturing sites for _____ and Organon in Oss Netherlands and Swords, Ireland all of the previous chemistry deficiencies have been satisfactorily addressed. The Chemistry recommendation is approvable pending satisfactory labeling and GMP status. A final recommendation for cGMP status is pending from the FDA Office of Compliance. Due to the Agency-wide restrictions on foreign travel, inspection of the above manufacturing sites were postponed.

Pen Injector Device

The Sponsor's responses to the deficiencies noted for the BD pen were reviewed by CDRH. CDRH found the Sponsor's response to be acceptable. With respect to dose accuracy validation, the CDRH review states "dose accuracy validation : _____ has been addressed by the pen injector meeting the dose accuracy requirements of ISO 11608, as determined by testing by _____. Although ISO 11608 has not been included in the FDA Consensus Standards Program, its testing requirements are appropriate and acceptable".

CDRH recommendations are: "CDRH has no objections to the use of the BD Pen injector with the Follistim®-AQ Cartridge, _____. The BD Pen injector has no differences in intended use or technological characteristics from legally marketed pen injector that would raise new questions of safety and effectiveness for the proposed use, and is substantially equivalent to predicate devices with classification 21CFR880.5860, procode 80FMF." The Sponsor did not provide data to support their statement that the pen injector offers "safer...injection" (2002: vol.1.2, page 0028, 0234). CDRH does not recommend approval of the "safer" claim, or any other superiority claim for the device.

Despite the CDRH recommendation, the clinical reviewers note several problems with the BD Pen₁ - injector.

1. Alignment of dose in dosage window appears to depend upon which angle the pen is held.
2. The BD Pen₁ - permits changes in dose as small as 8.3 IU, yet the Sponsor holds that this incremental adjustment will not be used. If these are not to be used in adjusting the dose, they should not be available in that this may cause confusion under situations of "real" use.
3. Step 4 of the instructions on assembly and use of the pen under INSERTING THE FOLLISTIM® AQ CARTRIDGE INTO THE CARTRIDGE HOLDER – SCREWING OF THE FOLLISTEM PEN™ BODY call for the patient to align the arrow on the Cartridge Holder to the middle of the yellow alignment mark on the blue Pen Body. There are actually two arrows, but only one yellow mark; this provides an additional step for possible confusion for the patient.

*Appears This Way
On Original*

Product Name

A previous consult from OPDRA (August 4, 2000) specified that from a safety perspective, there was no objection to the use of the name Follistim®-AQ Cartridge.

Pre-clinical Pharmacology and Toxicology

Please refer to Pharmacology and Toxicology comments from the original review cycle

Discussion and Conclusions

It was previously shown that Follistim®-AQ Cartridge with BD Pen – injector was not bioequivalent to Follistim® as delivered by conventional syringe and needle, with the former showing an approximately 20% higher bioavailability. The Sponsor now submits two open label non-comparator patient comprehension studies in support of approval of Follistim®-AQ-Cartridge for the indications of OI and multiple follicular development in ART. The findings of the Clinical Review are that while the comprehension studies support that after instruction, the patient is able to assemble the BD Pen – injector and administer the dose as instructed, the information provided is not sufficient alone to support safety and efficacy of the Follistim®-AQ Cartridge. The higher bioavailability supports that the drug product has efficacy, but the open label non-comparator trials do not provide sufficient information to safely and appropriately advise the physician and patient on dosage. Further, the labeling submitted by the Sponsor advises that Follistim® and Follistim®-AQ Cartridge should not be used interchangeably but provides no information to the patient or physician as to how to proceed if this is done. There was a higher rate (when making a cross study comparison) of OHSS in the comprehension study for ovulation induction, however, the significance of this can not be determined because there was no comparator trial. It is possible that the higher bioavailability of Follistim®-AQ Cartridge may lead to misjudgement on the part of the physician when assessing how much of a dose adjustment to make for the patient undergoing a OI cycle with Follistim®-AQ cartridge use when that judgement is based on prior experience with Follistim® delivered by the conventional syringe method.

I concur with the primary clinical review and recommend that Follistim®-AQ Cartridge not be approved.

In the absence of data establishing the bioequivalence of Follistim®-AQ Cartridge to Follistim®, therapeutic equivalence of Follistim®-AQ Cartridge to Follistim® to establish safety and efficacy for Follistim®-AQ Cartridge should be demonstrated in a randomized, blinded active-controlled clinical trial of Follistim®-AQ Cartridge with Follistim® as the comparator.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Shelley Slaughter
6/23/03 05:18:16 PM
MEDICAL OFFICER

Donna Griebel
6/23/03 06:06:28 PM
MEDICAL OFFICER

I concur that the applicant has provided insufficient evidence to support the safety of the product (given the higher incidence of ovarian hyperstimulation syndrome in one of the trials submitte) and its efficacy, in light of the lack of a comparator arm.

Follistim[®]-AQ Cartridge

NDA 21-211

CLINICAL REVIEW

Medical Officer's Review
NDA 21-211/N-000-BZ.

Date NDA Submitted: December 23, 2002
Date NDA Received: December 23, 2002
Review Completed: June 20, 2003

Medical Officer's Review (Original Review)

Sponsor: Organon, Inc.
375 Mount Pleasant Avenue
West Orange, NJ 07052

Drug name:
Generic: follitropin beta for injection
Trade: Follistim®-AQ Cartridge
Chemical: recombinant human follicle stimulating hormone (r-hFSH)

Pharmacologic category: Infertility

Dosage/Strength: Sterile aqueous solution for subcutaneous or intramuscular injection that is filled into ready-for use disposable Cartridges designed to fit Becton-Dickinson Follistim® Pens for adjustable administration. Each Cartridge contains 833 IU of follicle stimulating hormone (FSH) per milliliter. Glass multi-dose vials containing 300 or 600 IU of follitropin beta can be administered using the pen-injector device.

Administration: For ART patients: A starting dose of 150 to 225 IU of Follistim®-AQ Cartridge follitropin beta for injection is recommended for at least the first four days of treatment. After this, the dose may be adjusted for the individual patient base on their ovarian response. In previous clinical studies with patients who are responding to Follistim® (follitropin beta), daily maintenance dosages range from 75 to 300 IU for six to twelve days were sufficient, although longer treatment may be necessary. The maximum daily dose that Follistim® has been used is 600 IU.

For ovulation Induction: Treatment is usually started with a 75 IU daily dose of Follistim®, which is continued at least 14 days. The dose should be increased by 25 to 50 IU increments at weekly intervals until follicular growth and/or serum estradiol levels indicated an adequate response. The maximum, individualized, daily dose of Follistim® that has been used safely for ovulation induction in patients during clinical trials is 300 IU.

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Proposed indications: Women: Follistim®-AQ Cartridge is indicated for the induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure. Follistim®-AQ Cartridge is also indicated for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology program.

Related Submissions: IND 54,981, NDA 20-582, NDA 21-273

Related documents: Original Follistim® freeze dried cake product (NDA 20-582) was approved on September 29, 1997, a pre-NDA meeting for Follistim AQ Cartridge March 18, 1999, Original submission for Follistim®-AQ Cartridge on January 28, 2000, Original Medical Officer's Review dated November 13, 2000, Biopharmacologist's Review (of bioequivalence study 37626) dated November 15, 2000, Team Leader Review dated November 15, 2000, Not Approvable Letter dated November 29, 2000, Memo to File (CDRH Review) dated February 7, 2001, Sponsor's response to the Not Approvable Action dated February 14, 2001, Incomplete Response Letter dated May 11, 2001, Response to Incomplete Response (NDA 21-211 N-000-BZ) dated December 23, 2002, , DDMAC consult dated March 20, 2003, Division of Drug Risk Review dated April 4, 2003, CDRH Consult #2 dated April 23, 2003, ODS/DSCRCS Review dated May 5, 2003, Post-marketing update for NDA 21-211 dated May 20, 2003.

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Clinical Review for NDA 21-211

Executive Summary

I. Recommendations

A. Recommendation on Approvability

In the opinion of this reviewer, a Not Approvable Action for the submission is recommended for Follistim®-AQ Cartridge from a clinical perspective. This decision was based on a bioequivalence study, an accuracy study on the injector pen and two supportive clinical trials. The clinical trials were reviewed, evaluated, and do not provide substantial evidence that Follistim®-AQ Cartridge was bioequivalent to the approved Follistim® formulation as delivered by conventional syringe and needle. The two supportive clinical comprehension trials provide limited information on the overall safety and efficacy of Follistim®-AQ Cartridge. Follistim®-AQ Cartridge is an injectable solution loaded into a cartridge that fits into a pen-injector device. The remaining unanswered question and issues are whether the increased dose of Follistim® delivered by the Follistim Pen™ device results in a clinically significant safety issues and how to advise on the appropriate and safe dose of Follistim-AQ to be delivered to the patient. These questions remain unanswered and should be addressed with additional studies.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Not applicable as the recommendation is non-approvable

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The original Follistim® freeze dried cake product (NDA 20-582) was approved by the Agency on September 29, 1997 for the indications of development of multiple follicles (controlled ovarian stimulation) 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.

On March 18, 1999, a pre-NDA meeting was held with the Division to discuss a bioequivalence study as the basis of a new NDA submission. The sponsor proposed a new presentation of the approved product Follistim®. Follistim® is formulated as a freeze-dried cake to be administered after reconstitution with water for each injection.

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The new product, Follistim®-AQ Cartridge is an aqueous solution of 300 IU or 600 IU of follitropin beta in a multi-dose cartridge, to be injected with a pen injector.

The sponsor presented a bioequivalence study (37626) that compared a single dose of 150 IU of the original formulation of Follistim® with a single dose of 150 IU using Follistim®-AQ Cartridge administered with the pen injector. The results were non-equivalent. The sponsor stated that the pen-injector accurately delivered the dose to which it was set, and handling of the Follistim® cake formulation (to prepare the syringe) actually cause decreased the amount of follitropin beta delivered _____). Inaccuracies of dead volume and removal of excess air in the syringe in preparing the approved Follistim® product resulted in approximately 18% higher dose with the cartridge than the conventional syringe. To address the non-equivalence of the dosage forms, the Sponsor was presented with the three approaches to resolve the bioequivalence issue:

- The sponsor could conduct another bioequivalence study by altering the dose delivered by the pen-injector to match the dose delivered by the cake formulation.
- As a significant risk could exist for patients who switch from cake to pen or vice versa, the issue should be addressed by providing a justification for the use either product and allowing the physician to decide the choice of product, dose and mode of administration.
- Since it would be difficult to change the label of the approved product, the delivery volume should be clearly addressed in the labeling for the new formulation administered by the pen-injector device.

The NDA for Follistim®-AQ Cartridge was submitted on January 28, 2000. The sponsor decided to approach the non-equivalence of the dosage formulation by addressing whether there was clinical relevance for the known difference between administering Follistim®-AQ Cartridge with a pen injector device and administering reconstituted Follistim® with a syringe. It was the sponsor's opinion that the difference of 18% was not expected to be clinically noticeable, particularly when the pen-injector device is used exclusively throughout a treatment cycle. The sponsor proposed handling the observed 18% higher dose with the pen-injector device by adding the following statement to the PRECAUTIONS section of the labeling:

“Changes in brand (manufacturer), type (recombinant, urinary, etc.) and /or method of administration (Pen-Injector device, syringe, etc.) may result in the need to adjust the dose. Therefore, it is recommended that Follistim®-AQ Cartridge and other FSH products not be used interchangeably during a given cycle.”

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A teleconference between the Agency and the Sponsor was held on March 22, 2000. In the teleconference, the Deputy Division Director reiterated to the sponsor the discussion points of the March 18, 1999 meeting. The Sponsor was told that the safety and efficacy of the Pen-Injector must be linked to Follistim® by establishing bio-equivalence. The sponsor was told that the Division did not accept the sponsor's position that the higher bioavailability of the dose delivered with the Pen-Injector was of no clinical concern. On March 29, 2000 the Sponsor submitted a proposal to the Agency for a conversion table to translate the dosing units of Follistim® (original cake formulation) to that of Follistim®-AQ (liquid formulation) that is to be used with the Pen-Injector. The sponsor also submitted an instruction manual for the Follistim® Pen-Injector (on September 28, 2000) and revised draft labeling (on October 30, 2000). No clinical trial data was included with the original NDA application. The Division concluded that the higher bioavailability of the dose delivered by the Pen-Injector would be a review issue rather than a filing issue and the NDA was filed on March 31, 2000.

The original medical officer's (Dr. Bennett) clinical review was completed November 13, 2000. He concluded that approval of NDA 21-211 was not recommended. The medical officer was concerned that safe and effective use of Follistim®-AQ Cartridge was not provided in the current NDA submission. The medical officer also observed that the proposed draft labeling for Follistim®-AQ Cartridge (including the incorporated conversion table) contains several inaccuracies and had confusing instructions. The sponsor also did not adequately address the higher bioavailability with the pen-injector, which is a significant safety issue. Furthermore, the Sponsor did not adequately justify to the Division a patient population that would benefit from use of the pen-injector. The Reproductive Team Leader and the Division Director concurred with the Not Approvable recommendation. Subsequently, a Not Approvable letter was sent November 29, 2000 to the Sponsor. The Division was subsequently requested to clarify the non-approvable issues, and the sponsor submitted a response on March 19, 2001. The FDA reviewed the sponsor's resubmission, and felt that the following issues remained:

- The proposed conversion table for the observed differences in dose administered by the Cartridge pen-injector system and the vial syringe was confusing, complex inaccurate and unacceptable.
- The pen injector device is also confusing with 21 pages of instruction and a dosing scale of numbers plus marks and audible clicks, and is a safety concern.

The Division sent an Incomplete Response letter on May 11, 2001 noting that unresolved issues remained. A teleconference between the FDA and the sponsor was held on November 1, 2001 and two decisions were reached:

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- Performance data are needed to verify the accuracy of each click of the pen injector; intermediate clicks are of concern; data to confirm that the clicks are statistically meaningful and there is no overlap of clicks is recommended.
- DRUDP will determine the margin of error for the pen injector; there is clinical concern about the precision of the pen with the drug product that remains a concern.

In addition, one action item was requested during the teleconference:

- The sponsor should submit any available data for clinical review and provide a clinical rationale/justification for the accuracy of the pen and clinical data to show that drug delivery is safe and efficacious for use.

The sponsor responded to the Incomplete Response Letter by submitting protocols for two phase 3 clinical trials using Follistim®-AQ Cartridge to IND 54,981 on July 31, 2001. The sponsor proposed two open-label, non-controlled, multi-center clinical trials that would be conducted entirely in the United States. The primary objective of the two trials was virtually identical: to demonstrate that use of Follistim Pen™ was well understood by the subjects. The sponsor stated that serious adverse events (OHSS) and a patient's questionnaire of handling of the Pen would document the safe and adequate use of the Follistim Pen™. To demonstrate the safe and adequate use of the Follistim Pen™, the sponsor proposed using different questionnaires (a patient questionnaire and an observer questionnaire) to test subject comprehension regarding use of the Follistim Pen™. In addition, information on clinical outcomes, a local tolerance questionnaire, and adverse events would also be monitored. The sponsor did not address the issue of higher bioavailability of the pen-injector in these two clinical trials.

The medical officer (Dr. Bennett) and a social science analyst (Dr. Lechter in the Office of Drug Safety reviewed the protocols for the two clinical trials).

The two reviewers voiced several concerns about the observer questionnaire, the main tool in assessing subject comprehension of the loading and administering of the Follistim Pen™. Two major concerns voiced in a letter to the sponsor dated May 22, 2002 included:

- 1) When should the observer questionnaire consider a patient as a comprehension failure?
- 2) What should be a "passing score" for the observer questionnaire?

The Division also requested clarification of the re-instruction process performed if errors occurred in loading or use of the device. The Division requested clarification on how this re-instruction process would be scored.

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The two phase 3 clinical trial results (labeled 142-001 and 142-002) were submitted December 23, 2002 as amendment N-000-BZ. The differences in the two clinical trials were in the diagnosis of infertility (ovulatory versus anovulatory) and type of infertility therapy [ovulation induction versus *in vitro* fertilization (IVF)/ intra-cytoplasmic sperm injection (ICSI)]. All trials consist of one cycle of gonadotropin treatment. In the two supportive studies, a total of 104 patients were treated for one cycle with 96 patients completing their treatment regimen.

Reviewer's comments: The two submitted clinical trials addressed the issue of patient comprehension of the pen-injector. The clinical trials did not address the safety issue of the higher bioavailability of the Follistim®-AQ cartridge delivery system.

B. Efficacy

The original Follistim®-AQ Cartridge application (NDA 21-211) was based on the assumption that Follistim®-AQ was clinically equivalent to the approved Follistim® cake formulation. The proposed indications are: 1) Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program. 2) Induction of ovulation and pregnancy in anovulatory, infertile patients in whom the cause of infertility is functional and is not due to primary ovarian failure. The indications claimed are the same indications for the approved drug product Follistim®.

The first concern of the Division was whether subjects could use the Follistim Pen™ in an effective manner during a treatment cycle. The sponsor chose to answer this efficacy question by using primary efficacy endpoints (for both clinical trials) that were questionnaires. The first questionnaire, an observer questionnaire, was summarized as the percentage of respondents who could load, select, and administer the correct dose of Follistim®-AQ Cartridge. This questionnaire was performed after instruction as monitored by a trained staff member. In addition, patients also received an instructional manual for the Follistim Pen™ and watched videotape of proper assembly and use. The sponsor collected results from observer questionnaires prior to the 1st day of treatment and repeated observer questionnaires on the second day of treatment to provide adequate assessment of subject comprehension.

The results of the observer questionnaire for trials 142-001 and 142-002 report that greater than 95% of patients in both trials could properly load, select and correct dosing errors using the Follistim Pen™ after instruction. (See Appendix 1 – Tables 1 and 2). Although approximately half (greater than 50% in both trials) of the pen-injector devices self primed, most patients (greater than 80%) could prime the pen properly by the second day of treatment during an actual Follistim®-AQ Cartridge injection. (Appendix 1 – Table 2)

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For all steps, the actual injection showed improved results of assembly and use of the Follistim Pen™ compared to mock injection (See Appendix 1 – Table 2).

However, re-instruction prior to the first dose was necessary in 33.3% of patients in trial 142-001 and 58.1% of patients in trial 142-002. (Appendix 1 – Tables 1 and 2) It is not clear from the study report what degree of repetition of instruction was required prior to correct use of the pen-injector system or whether certain steps were more difficult and required more re-instruction than others. Re-instruction concerns were addressed using several different methods. First, re-instruction dropped significantly by the second injection to 20% for trial 142-001 and 23.3% for trial 142-002. (Appendix 1 – Tables 1 and 2) Second, self-injection errors reported did not seem unique to the Follistim Pen™ usage, but more to the injection process itself. (See Appendix 1 - Table 3) The reasons for re-instruction also did not reveal problems unique to the Follistim Pen™. (See Appendix 1 – Table 4) The additional fact that 99 of 103 subjects who used the Follistim Pen™ then completed therapy (by receiving human chorionic gonadotropin at the end of the treatment cycle) also supports acceptable use of Follistim Pen™ in a clinical setting.

In conclusion, it appears that when subjects receive thorough instruction on assembly and use of the device there are no specific steps in assembly or use of the Follistim Pen™ that create unusual problems for patients compared to those problems normally encountered with syringe injection. Furthermore, the problems that are encountered with the Follistim Pen™ appear to be correctable with appropriate re-instruction.

The sponsor also submitted an “Ease of Use” questionnaire as an additional primary efficacy endpoint. The questionnaire rated the self-administration process of the Follistim Pen™ and additionally, the patient self-rated her overall experience with the pen-injector. The a summary of the results of the Ease of Use questionnaires do provide supporting data for the two clinical trials that subjects generally understood directions of the Follistim®-AQ Cartridge on Day 2 of treatment. (See Appendix 1 – Table 5 and 6) However, the team (Drs. Bennett and Lechter) that originally reviewed the protocol for the “Ease of Use questionnaire” commented that the ratings obtained from the questionnaire did not necessarily translate into ease of use. This reviewer concurs that the “Ease of Use questionnaire” provides a limited recall of patient opinion of Follistim Pen™ use, and does not prove concrete efficacy or use information.

Effective use of the Follistim Pen™ in these two non-comparative trials was addressed by simple descriptive statistics of the secondary endpoints of oocyte retrieval or percentage of patients who ovulated. Ninety-seven percent (97%) of patients in the ART study had oocyte retrieval and 95 % of patients in the ovulation induction study ovulated.

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An additional secondary endpoints in the two clinical trials, mean number of treatment days also supports the fact that patients completed treatment in a reasonable time frame (less than two weeks) (See Appendix 1 – Tables 7 and 8). Other key secondary endpoints including mean total number of oocytes retrieved (13.9 oocytes for trial 142-001) and ovulation rate (95.3% for trial 142-002) also provide additional support to correct use of the Follistim Pen™. (See Appendix 1 – Tables 7 and 8)

Reviewer's comment: In this reviewer's opinion, the key secondary parameters point to subject comprehension of correct use of Follistim®-AQ Cartridge resulting in cycle completion as demonstrated by both the primary and secondary efficacy parameters.

The question of increased dose delivery of Follistim® liquid by the BI— pen injector can be only indirectly answered by a comparison of the ovulation induction trial (142-002) to a small ovulation induction trial using Follistim® liquid (submitted to NDA 21-273 – Protocol 058004). The demographics and design of the two trials (142-002 and 058004) are similar. (See in Appendix 1 – Table 9). However, one must always use caution in making cross study comparisons

Reviewer's comment: From the limited data available, it is unknown whether the increased dose of Follistim® liquid delivered by the Follistim Pen™ significantly alters clinical pregnancy rates or the surrogate efficacy endpoints for clinical pregnancy. In fact, using these calculations, the Follistim Pen™ requires more total International Units to achieve ovulation, although mean days of treatment are almost identical. (See Appendix 1 – Table 10)

- 1. Larger comparative studies would be needed to demonstrate differences in efficacy between the approved Follistim® and Follistim®-AQ Cartridge to make a definitive conclusion on the actual efficacy of Follistim®-AQ Cartridge.**
- 2. The sponsor used a patient population in study 142-001 that included two separate types of insemination (in vitro fertilization and intra-cytoplasm injection). The Division's position is that these two types of inseminations produce different clinical outcomes (and pregnancy rates) and therefore the data should be stratified for type of insemination. Study 142-001 had a small number of patients, and the effects of the type of insemination on the efficacy endpoints cannot be determined.**
- 3. The Division continues to regard a serum progesterone level of ≥ 10 ng/mL as the accepted endpoint for ovulation induction studies for efficacy. Study 142-002 does not use this endpoint. Study 142-002 is acceptable for the purposes of determining safe use of the pen-injector device itself but not for the purpose of an efficacy claim for ovulation induction.**

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C. Safety

Follistim®-AQ Cartridge differs from the approved Follistim® in the pharmaceutical presentation and delivery system. Data on clinical safety contained in NDA 20-582 and two supportive clinical trials (142-001 and 142-002) for Follistim®-AQ Cartridge comprise the safety database for Follistim®-AQ Cartridge. The sponsor stated in the original protocol submitted to NDA 21-211 (for both clinical trials 142-001 and 142-002) that the safe and adequate use of the Follistim Pen™ for ovulation induction would be documented by collecting (serious) adverse events (e.g. injection site disorders, ovarian hyperstimulation syndrome). Two major issues were safety concerns of the Division: the safety of the Follistim Pen™ device itself, and the concerns surrounding increased daily dose delivery of Follistim® delivered by the Follistim Pen™ compared to the approved product Follistim®.

The safety of the Follistim Pen™ device is evaluated by combining both clinical trials and using two specific parameters related to injection issues, cellulitis and injection site reactions. The overall rate of cellulitis was less than 1% (one subject out of 103). Injection site reactions noted by patient report (e.g. itching, pain, bruising, swelling and redness) were reported as none or mild in most subjects. (See Appendix 2 – Table 1). [One patient reported moderate swelling noted 24 hours post injection in trial 142-001 and three patients had moderate bruising on the 7th day of injections] No severe local tolerance reactions were recorded 24 hours post first injection or on the 7th day of injections. No patient discontinued therapy with the Follistim Pen™ secondary to problems with assembly, loading or administration of the dose using the Follistim Pen™. (See Appendix 2 – Table 2) From this data, it is reasonable to conclude that no local tolerance issues with use of the Follistim Pen™ device were seen.

The issue of increased dose of Follistim® delivered by the Follistim Pen™ compared to the approved Follistim® product is not addressed in these clinical trials. The key adverse event rates for both clinical trials are presented in Appendix 2 – Tables 3 and 4. The adverse event rate of concern with all gonadotropin use is the risk and/or rate of ovarian hyperstimulation syndrome. The rate of ovarian hyperstimulation syndrome in the *in vitro* fertilization trial (142-001) is 3.3% - similar to previous clinical trials using the approved Follistim® product (5.2%) (See NDA 20-582) and also to recent clinical trials of *in vitro* fertilization (IVF)/ intra-cytoplasmic sperm injection (ICSI) (5% and 5.1%).^{1,2}

The rate of ovarian hyperstimulation syndrome in the ovulation induction trial was compared to a previous recent clinical trial using Follistim® liquid formulation (NDA 21-273 – Protocol 058004). The two clinical trials (142-002 and 058004) similar in both demographics and trial design. (See Appendix 1 – Table 9)

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The results showed a somewhat higher percentage of patients (9.3%) in trial 142-002 had ovarian hyperstimulation compared to Protocol 058004 (4.8%), although the actual number of total patients experiencing ovarian hyperstimulation syndrome in both trials were small (4 patients in trial 142-002 and 3 patients in trial 058004). A recently completed ovulation induction study, Protocol 058004 for Follistim®-AQ liquid, had a high patient discontinuation for the “risk of hyperstimulation” (9.7%) compared to trial 142-002 (2.3%).

In addition, a urinary derived follicle stimulating hormone (Repronex® used subcutaneously), had a rate of ovarian hyperstimulation (8.3%) in a similarly designed ovulation induction study.³ The numbers of patients with ovarian hyperstimulation in both the Repronex® and Follistim®-AQ study 142-002 appear to be somewhat comparable.

Reviewer’s comments:

- 1. The post hoc analysis of ovulation induction comparing Follistim® AQ Cartridge to previously performed studies are extremely limited. However, the increased rate of ovarian hyperstimulation syndrome in oligo-anovulatory patients that used Follistim® AQ Cartridge may be a safety signal an that there is increased bioavailability in this suceptible population.**
- 2. Additional information will be required with an appropriate approved Follistim® comparator arm to determine appropriate dosing and collect an larger and more adequate safety database.**

Additional safety information on ovarian hyperstimulation syndrome is also found in the patient discontinuation information from the two supportive clinical trials. (See Appendix 2 – Table 2). The risk or occurrence of ovarian hyperstimulation syndrome did not appear to significantly impact cycle cancellations in either trial (1.7% [1 in 60 patients treated] in trial 142-001 and 2.3% [1 patient in 43 treated] in trial 142-002. The risk and/or rates of ovarian hyperstimulation with Follistim®-AQ Cartridge can not be adequately determined with the limited information available from these two supportive clinical trials.

Other key adverse events for both supportive clinical trials using Follistim®-AQ Cartridge were evaluated. [See Appendix 2 – Tables 3 and 4] The only two adverse events of concern in trial 142-001 were reports of abdominal pain (25%) and nausea (16.7%). These numbers appears to be high, however it is difficult to reach conclusions as there was no diagnosis attached to the complaint, and no grading of the complaint as experienced by the subject.

For abdominal pain, varying amounts of pain can occur during *in vitro* fertilization cycles during and after retrieval, depending on the individual patient and the type of anesthesia used.^{4,5} Furthermore, the small numbers of subjects in the clinical trials (without a comparison group) prevent definitive conclusions.

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Other small in vitro fertilization clinical trials have also shown abdominal pain/cramping rates of as high as 16%.⁶ The rate of abdominal pain is increased in trial 142-001, but without a comparator arm the information is incomplete, and no conclusions can be drawn. Additionally, in trial 142-002 the rate of abdominal pain did not appear to be increased compared to either trial 142-001 or protocol 058004 (See Appendix 2 – Tables 3 and 4). Similarly, the rate of nausea appears increased only in trial 142-001, and not in trial 142-002 (See Appendix 2 – Tables 3 and 4).

Reviewer's comment: Detecting trends in the rate of ovarian hyperstimulation syndrome with Follistim®-AQ Cartridge use would require a larger clinical database with a comparator arm for a final determination.

D. Dosing

Protocol 142-001 subjects received 150 to 225 IU of Follistim®-AQ Cartridge depending on the patient demographics and history. The selected starting dose was fixed during the first five days of treatment. After the initial treatment period, the dose of Follistim®-AQ Cartridge was then adjusted depending on the individual ovarian response as assessed by ultrasound. Human chorionic gonadotropin (hCG) was administered when adequate ovarian response was observed (at least 3 follicles \geq 17mm).

Protocol 142-002 subjects received a fixed dose of 75 IU for the first seven days of treatment. After the initial treatment period the dose of Follistim®-AQ Cartridge the increment in change of dose was decided by the investigator, based on subject characteristics, but not greater than 25-50 IU. If no ovarian response was determined (one or more follicles greater than 12 mm at Day 8 or 15) the dose was to be increased to a maximum of 175 IU. When a satisfactory ovarian response (one follicle with \geq 18 mm diameter and/or two to three follicles with a diameter \geq 15mm) was determined, human chorionic gonadotropin (hCG) was administered.

Reviewer's comment: Neither protocol specifically addressed the issue of the higher availability of Follistim®-AQ liquid when delivered by the pen-injector device. There was no Follistim® comparator arm in either study

E. Special Populations

This drug is being approved for conditions that occur only in women. The studied indications for gonadotropin treatment for Follistim®-AQ Cartridge of controlled ovarian hyperstimulation and ovulation induction do not apply to pediatric or geriatric populations. This drug is contraindicated in pregnancy.

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I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Name: Follitropin beta for injection

Proposed Trade Name: Follistim® -AQ Cartridge

Drug Class: Infertility

Sponsor's Proposed

Indications:

1. Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program.
2. Induction of ovulation and pregnancy in anovulatory, infertile patients in whom the cause of infertility is functional and is not due to primary ovarian failure.

Dosage/Form/Strength:

Sterile aqueous solution for subcutaneous or intramuscular injection that is filled into ready-for use disposable Cartridges designed to fit Becton-Dickinson Follistim® Pens for adjustable administration. Each Cartridge contains 833 IU of follicle stimulating hormone (FSH) per milliliter. Glass multi-dose vials containing 300 or 600 IU of follitropin beta can be administered using the pen-injector device.

Dosage Regime:

1. Assisted Reproductive Technologies:

A starting dose of 150 to 225 IU of Follistim®-AQ Cartridge follitropin beta for injection is recommended for at least the first four days of treatment. After this, the dose may be adjusted for the individual patient base on their ovarian response. In previous clinical studies with patients who are responding to Follistim® (follitropin beta) daily maintenance dosages range from 75 to 300 IU for six to twelve days were sufficient, although longer treatment may be necessary. The maximum daily dose that Follistim® has been used is 600 IU.

When a sufficient number of follicles of adequate size are present, the final maturation of follicles is induced by administered human chorionic gonadotropin (hCG). Oocyte retrieval is performed 34 to 36 hours later. The administration of hCG can be withheld in cases where the ovaries are abnormally enlarged on the last day of Follistim® therapy; this will reduce the change of developing ovarian hyperstimulation syndrome.

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2. Ovulation Induction:

Treatment is usually started with a 75 IU daily dose of Follistim®, which is continued at least 14 days. The dose should be increased by 25 to 50 IU increments at weekly intervals until follicular growth and/or serum estradiol levels indicated an adequate response. The maximum, individualized, daily dose of Follistim® that has been used safely for ovulation induction in patients during clinical trials is 300 IU. The patient should be treated until ultrasound visualizations and/or serum estradiol levels indicate pre-ovulatory conditions equivalent to or greater than those of the normal individual followed by injection of human chorionic gonadotropin (hCG) do. If the ovaries are abnormally enlarged on the last day of Follistim® therapy; hCG may be withheld during this course of treatment; this will reduce the chance of developing ovarian hyperstimulation syndrome.

Reviewer's comment: The sponsor is proposing a dose administration schedule for Follistim®-AQ Cartridge based on the dose administration schedule for the approved Follistim® product. The clinical impact of the higher delivered dose of Follistim®-AQ Cartridge compared to the approved Follistim® product is not adequately addressed by the two supportive clinical trials (142-001 and 142-002) since there is no comparator arm. Therefore, the two supportive clinical trials are insufficient evidence to conclude that is no clinical impact of the higher bioavailability delivered by Follistim®-AQ Cartridge on patients. Therefore, the two submitted clinical trials are unable to support a dose and administration labeling section to date.

B. State of Armamentarium for Indication(s)

There are six gonadotropin products in the United States that are used for controlled ovarian hyperstimulation and ovulation induction. Follistim®-AQ Cartridge is a new pharmacologic presentation of the approved product Follistim®, administered with a pen-injector device. The currently approved product formulation is a freeze-dried cake formulation, that is administered after reconstitution with WFI, whereas Follistim®-AQ Cartridge is an injectable aqueous solution filled into ready-for use disposable Cartridges designed to fit a Becton-Dickinson Follistim Pen™ for adjustable administration. Each Cartridge contains 833 IU of follicle stimulating hormone (FSH) per milliliter. Glass multi-dose vials containing 300 or 600 IU of follitropin beta are administered using the pen-injector device.

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Follistim®-AQ Cartridge is one of many recombinant FSH products available in the United States marketplace. It is the second gonadotropin formulation that will use a pen-injector as a delivery system rather than a syringe. The sponsor states that the ready-to-use Follistim®-AQ formulation will be more convenient than previous cake formulations since the Follistim®-AQ Cartridge requires less handling.

C. Important Milestones in Product Development

Recognition of the therapeutic potential of gonadotropins began in the 1950's with the extraction and purification of human menopausal gonadotropins (both follicle stimulating hormone and luteinizing hormone) from both human pituitaries and urine sources. Successful clinical pregnancies resulting from the use of these human derived gonadotropins were first reported in the 1960's. Further improvement in purification resulted in separating follicle stimulating hormone (FSH) from other proteins in human menopausal urine. Purified FSH was first introduced in 1982 and continued to improve pregnancy rates after gonadotropin treatment. In the 1990's cells that are capable of producing biologically active FSH in culture produced follicle stimulating hormone (FSH). This recombinant derived FSH from *in vitro* cultured cells does not appear to be different from native human FSH clinically.

D. Other Relevant Information

Consultations for the original NDA were obtained from the Office of Post-Marketing Drug Risk Assessment and the Center for Devices and Radiological Health and are numbered 00-0134 and 00-0263. Both consultations had safety concerns regarding the proposed packaging configuration and the pen-injector delivery system.

CDRH has reviewed additional information concerning the Follistim Pen™ (Becton Dickinson Pen) the sponsor provided on April 11, 2003. CDRH concluded that use of the Follistim Pen™ had no differences in intended use of technological characteristics from legally marketed pen injector that would raise new questions of safety and effectiveness for the proposed use. CDRH has no objections to the Follistim Pen™,

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E. Important Issues with Pharmacologically Related Agents

All adverse events associated with gonadotropin therapy result from ovarian stimulation, follicular development and ovulation. The most concerning serious adverse events are ovarian hyperstimulation syndrome and thromboembolism.

Ovarian hyperstimulation syndrome is the least common complication of gonadotropin therapy, but the most serious one. The underlying pathology is unknown, but results in increased vascular permeability.

Treatment for this ovarian hyperstimulation syndrome is usually conservative, with management of the complications from increased vascular permeability. Several deaths have been reported from severe ovarian hyperstimulation in the literature.

Thromboembolism is usually seen in less than 1% of patients with moderate and severe ovarian hyperstimulation. The mechanism for development of thromboembolism may occur in the presence of high serum estradiol levels during gonadotropin treatment.

Since the development of Follistim®-AQ Cartridge formulation, no new concerns regarding adverse event profiles have been identified in the worldwide safety data for the approved product Follistim® (NDA 20-582) or Follistim®-AQ liquid (NDA 21-273).

F. Foreign Approvals of Follistim®-AQ Cartridge:

A worldwide safety update was provided for NDA 21-273 that contained additional information on Follistim®-AQ Cartridge formulation overseas. Follistim®-AQ Cartridge was approved in the United Kingdom and Ireland in 2000. Subsequently, Australia, Denmark, Iceland, France, Finland, Germany, Greece, Norway, Spain, Sweden, and Switzerland have given approval for the Follistim®-AQ liquid in Cartridge formulation.

G. Other Pharmacologically Related Agents Under Study:

Follistim®-AQ liquid is a solution for injection to be administered with a syringe. It is approved in Europe. Follistim®-AQ liquid has a pending application in the United States (NDA 21-273).

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II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

The sponsor originally requested a biowaiver for Follistim®-AQ Cartridge based on a bioequivalence (BE) study following subcutaneous administration (submitted in NDA 21-211). The Clinical Pharmacology and Biopharmaceutics section reviewed the study, and felt that Follistim®-AQ Cartridge was not bioequivalent to the approved Follistim® cake formulation.

Chemistry review of NDA 21-211 reported stability and manufacturing concerns. Certificates of analysis for the samples and reference standards, and material safety and data sheets (MSDS) of the drug substance and drug product components were requested. The chemistry review also noted that the site of stability testing and the site for manufacturing facilities needed clarification.

The sponsor responded to these deficiencies with method validation testing and confirmation of the sites where stability testing and manufacturing would occur.

Eight observations were recorded during the inspection of the West Orange New Jersey plant site after inspection of the West Orange, NJ manufacturing plant between July 17 and August 23, 2000. The inspection resulted in a Compliance recommendation of "Withhold". The Office of Compliance issued this "withhold" recommendation on October 30, 2002. The seriousness of the violations ultimately contributed to the submission (NDA 21-211) receiving a Not Approvable action.

An additional accuracy study performed on the pen by the manufacturer of the pen (Becton Dickinson) was submitted with the amendment to NDA 21-211 on December 23, 2002. The dosing range tested was from 50-450 IU in minimum increments of 25 IU. There are two intermediate positions (clicks) between each marked 25 IU increment for the Follistim Pen™. The pen manufacturer states that these clicks are not intended to be ultra-fine adjustments of the dose of medication. The relative error in dosing with the pen-injector ranged from 0.9 to 1.7% for all doses above 50 IU.

Reviewer's comment: The sponsor has stated the intermediate clicks are not for ultra-fine adjustment, however patients may find these clicks confusing. The potential exists that patients without sufficient instructions may confuse individual clicks with adjustments and this could potentially have serious consequences.

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III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The sponsor initially submitted a biowaiver request based on an existing bioequivalence study (37626). The pharmacokinetic study was to determine whether FSH pharmacokinetics after subcutaneous administration of follitropin beta by a pen injector device containing the liquid formulation of Follistim® in a Cartridge was bioequivalent to those after subcutaneous injection by conventional syringe containing a dissolved cake. Clinical Pharmacology and Biopharmaceutics section reviewed the bioequivalence study and concluded that there were significant differences between the approved formulation and the current proposed formulation; thus resulting in a failure to demonstrate bioequivalence between Follistim®-AQ Cartridge and Follistim®. Since the dosing differences in the proposed formulation could potentially affect the bioavailability, a conversion table was submitted proposing a correction factor to adjust the dose (submitted in NDA 21-211) without additional clinical trial data. The Clinical and Biopharmaceutics review felt that the conversion table was not practical for clinical practice, inaccurate, and incomplete.

B. Pharmacodynamics

Please refer to the pharmacologist's review of NDA 21-211 on November 15, 2000 for further information.

IV. Description of Clinical Data and Sources

A. Overall Data

Clinical trials (37603, 37604, 37608, 37609, 37611, 37613, and 37617) were submitted in NDA 20-582 for the original product Follistim® to demonstrate efficacy and safety. Follistim® was demonstrated to be non-inferior in efficacy compared to Metrodin® (Protocols 37608, 37609). Data in these clinical trials demonstrated clinically relevant safety parameters for both IM and SC administration of Follistim® treatment (please see the original medical officer's review dated December 13, 1996).

The following materials were reviewed:

- 1) Trial 142-001 - "An open-label, non-controlled multi-center study to evaluate subject comprehension, ease of use, safety and efficacy of the Follistim Pen™ for the self-administration of Follistim®-AQ Cartridge during Controlled Ovarian Hyperstimulation (COH) in subjects scheduled for *in vitro* fertilization (IVF) or intra-cytoplasmic injection (ICSI).

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- 2) Trial 142-002 – “An open-label, non-controlled multi-center study to evaluate subject comprehension, ease of use, safety and efficacy of the Follistim Pen™ for the self-administration of Follistim®-AQ Cartridge for induction of ovulation in clomiphene-resistant women with chronic anovulation (WHO group II).

B. Tables Listing the Clinical Trials

The tables listing the original clinical trials are contained in NDA 20-582 and 21-273 are incorporated into this review by cross-reference. Clinical data tables of the two submitted clinical trials (142-001 and 142-002) are included as Appendix 1 and 2).

C. Post-marketing Experience

The original Follistim® product was approved in 1997 in the United States. No unusual long-term adverse events or significant trends have been reported in this time frame. Additional information on Follistim®-AQ Cartridge was submitted in an update to NDA 21-211 on May 21, 2003. In this update, the sponsor stated that on February 10, 2000, a multi-dose presentation of Puregon (tradename Follistim® in the United States) using a liquid solution in Cartridges with a pen-injector device, a presentation similar to that of Follistim®-AQ Cartridge, was reported to have been launched in Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, India, Iran, Korea, Luxembourg, Malaysia, the Netherlands, New Zealand, Norway, Spain, Sweden, Switzerland, Taiwan, Thailand and the United Kingdom.

No post-marketing experience or additional data was reported in the original submission or amendments to the NDA. The sponsor should supply a safety update for this NDA (21-211) with the European adverse event data in the near future.

One death was reported in the safety data from worldwide experience submitted to NDA 21-211. A 26 year old female patient (case report 199800041) was reported in Australia. The death occurred 9 days after Puregon use, and an autopsy is now conclusive for an overdose of tricyclic antidepressants.

A second death with use of Puregon/Follistim® was reported to NDA 21-273. The death occurred 14 days after receiving the last dose of Puregon and both the cause of death and results of the autopsy are unknown. The directorate of the hospital and the doctors who treated the patient were contacted, but were not willing to discuss this case. The Ministry of Health for Vietnam and the physicians involved has closed this case. From the limited descriptions of the cases, the deaths do not appear to be directly related to the drug product.

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No additional post-marketing experience specifically related to Follistim®-AQ Cartridge was reported in the original or the amendments to the NDA. The sponsor should supply this information in a Safety Update when it is obtained.

D. Literature Review

See the NDA 20-582 and 21-273 for the original medical officer reviews. References for this review is listed as Appendix 3 – Reference List.

V. Clinical Review Methods

A. How the Review was Conducted

The two supportive clinical trials were reviewed in detail and these reviews are attached as Appendices 1, 2 and 3. Both clinical trials 142-001 and 142-002 were submitted in entirety. One patient death that occurred overseas after use of Follistim® (Puregon is the trade name overseas) was submitted to NDA 21-211 is attached as Appendix 3 (see section IV. C above)

B. Overview of Materials Consulted in Review

This application was submitted in paper only. The review also refers to the original medical officer's review of Follistim®-AQ Cartridge dated November 13, 2000. Additional volumes reviewed included protocols 142-001 and 142-002 were submitted with NDA 21-211 submitted December 23, 2002. An additional safety data submission (NDA 21-211, N-000-BM) dated March 14, 2003 was also included in this review.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No DSI inspections were conducted for this re-review. The sponsor reported that a Clinical Quality Assurance (CQA) department, independent of the department that performs clinical development, audited selected sites. The audit ensures that clinical trials are performed and data generated, documented, and reported in compliance with Good Clinical Practice. For trial 142-001, a protocol audit was carried out at trial sites 03 and 07. For trial 142-002, a protocol audit was carried out at trial site 01.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

All seven principal investigators for both protocols submitted FDA Form 1572. The informed consent document was implemented according to the current revision of the Declaration of Helsinki, the ICH Guideline for Good Clinical Practice and applicable regulatory requirements.

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A sample informed consent was submitted for both clinical trials 142-001 and 142-002. In the opinion of this reviewer, the sample informed consents were acceptable.

E. Evaluation of Financial Disclosure

The Curriculum Vitae (CV) for each principal investigator was provided for the two clinical trials, and from these CVs limited financial disclosure information was obtained. The disclosure of financial interests for each individual investigator was not present in the NDA submission for the two supportive clinical trials.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The sponsor has presented two supportive clinical trials that Follistim®-AQ Cartridge measured subject comprehension and “ease of use” of the device by using observer and patient questionnaires. The observer questionnaire demonstrates that greater than 85% of patients can correctly perform all steps in assembly and use of the Follistim Pen™ after instruction. The “Ease of Use questionnaire which asked the patient’s opinion on the individual steps of assembly and use of the Follistim Pen™ had mean overall scores for individual questions on the “Ease of Use questionnaire” that were greater than 4 (out of a maximum of 5) for both trials 142-001 and 142-002. (See Appendix 1 – Tables 5 and 6) The mean scores of the “Ease of Use questionnaire” also support the sponsor’s claim that the opinion of most subjects is that they comprehend Follistim Pen™ use.

Three secondary endpoints also support subject comprehension and correct use of Follistim®-AQ Cartridge. These secondary efficacy endpoints include: 1) Ninety-five percent of patients successfully completed treatment by receiving human chorionic gonadotropin 2) Mean number of oocytes retrieved (13.9 ± 10.3 for trial 142-001) and 3) Ovulation rate (95.3% by luteal phase serum progesterone levels of greater than > 5 ng/mL for trial 142-002). These endpoints are supportive that users of the Follistim Pen™ are able to successfully complete treatment when given complete and detailed instruction as in the conduct of these two trials.

Reviewer’s comments:

- 1. The Division continues to recommend that clinical pregnancy should be the preferred endpoint for all clinical trials using gonadotropins.**
- 2. The Division’s position is that a serum progesterone level of 10 ng/mL is the recommended endpoint to demonstrate ovulation.**

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3. Finally, the additional clinical question of whether the increased dose delivered by Follistim®-AQ Cartridge (compared to the original Follistim® formulation) has clinical impact is not addressed by the two clinical trials. Secondary efficacy endpoints were assessed in both supportive studies. These secondary endpoint parameters include: total mean days of treatment using Follistim®-AQ Cartridge and total mean Follistim® exposure (as measured by total mean international units per patient in a treatment cycle) measure dose delivery for each type of treatment (ovulation induction or *in vitro* fertilization) per cycle. (See Appendix 1 - Tables 7 and 8). However, without sufficient information from a comparator arm to determine the correct dose of Follistim®-Q Cartridge, a significant safety issue remains unanswered.

Secondary efficacy parameters can be compared to those in a previous trial performed with Follistim® liquid formulation. Trials 142-002 and previous trial 058004 (submitted to NDA 21-273) are not significantly different in demographics or trial design (See Appendix 1 – Table 9) Secondary endpoint parameters for trial 142-002 are not significantly different from the previous trial (058004) with Follistim® liquid formulation. (See Appendix 1 – Table 10) Lack of a comparison group, non-randomization and small numbers of patients in the trial limited the ovulation induction trial 142-002. However, contrast to a comparative clinical trial (058004) does demonstrate that induction of ovulation is results in similar secondary outcomes when endpoints are compared.

Reviewer's comment: One must always use caution when interpreting the significance of cross study comparisons. The significant amount of time that has lapsed between the previous trials used in this review make any direct comparison between clinical trials in the past very limited. IVF pregnancy rates have significantly improved over the past 5 years, especially in regard to oocyte/embryo culture techniques. This improvement in culture techniques in turn improves primary and secondary endpoints such as fertilization rate and pregnancy. In reviewer's opinion, it is still unknown whether Follistim®-AQ Cartridge alters the clinical outcomes with use of the pen-injector compared to the approved Follistim® as measured by surrogate IVF clinical endpoints or pregnancy outcome.

The proposed indications are:

1. Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program.
2. Induction of ovulation and pregnancy in anovulatory, infertile patients in whom the cause of infertility is functional and is not due to primary ovarian failure.

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B. General Approach to Review of the Efficacy of the Drug

The efficacy database consists of two supportive clinical trials. The protocol was originally submitted to IND 54,981. These two clinical trials (142-001 and 142-002) were submitted in paper and reviewed in detail (see Appendices 1).

C. Detailed Review of Trials by Indication

1. Title of the First Study (142-001):

“An open-label, non-controlled multi-center study to evaluate subject comprehension, ease of use, safety and efficacy of the Follistim® Pen for the self-administration of Follistim®-AQ Cartridge during Controlled Ovarian Hyperstimulation (COH) in subjects scheduled for IVF or ICS”

2. Investigators and Study Sites:

<u>Site</u>	<u>Principal Investigators</u>
01	Kaplan, B, Highland Park IVF Center, Highland Park, IL
02	Karande V, Center for Human Reproduction, Hoffman Estates, IL
03	Pang, S, Reproductive Science Center of Boston, Waltham, MA
04	Westphal, L, Stanford University Medical Center, Stanford, CA
05	Scott, R, Reproductive Medicine Associates of New Jersey, Morristown, NJ
06	Sacks, P, Columbia Fertility Associates, Washington, DC
06	Givens, C, Pacific Fertility Center, San Francisco, CA

All sites participated in the study and enrolled subjects

3. Objectives of the First Study:

The primary objective of the study was to demonstrate that the use of the Follistim Pen™ was well understood by the subjects. Further objectives were to demonstrate that the subcutaneous self-administration of Follistim®-AQ Cartridge with the pen is safe, effective and easy to use for patients undergoing controlled ovarian hyperstimulation.

4. Rationale for the First Study:

This study was conducted to demonstrate effective use for the first indication; in patients previously scheduled for *in vitro* fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI).

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Reviewer's comment: The Division concludes that there is a significant difference in the surrogate endpoints and pregnancy rates between *in vitro* fertilization (IVF) and intra-cytoplasmic injection (ICSI). Therefore, for the purposes of an efficacy and safety study to determine a clinical equivalence issue, clinical endpoints would need to be analyzed separately.

5. Method of Assignment to Treatment:

The investigator or sub-investigator approached women who were scheduled to undergo an Assisted Reproductive Technology (ART) procedure [*in vitro* fertilization (IVF) with or without intra-cytoplasmic sperm injection (ICSI)]. These women were then asked if they would participate in the clinical trial. The subjects were fully informed of the nature of the trial and the risks of the trial. When the subject had given written consent, screening assessments were performed. If all inclusion criteria were met, and none of the exclusion criteria were present, the subject was entered into the study.

6. Number of Subjects:

60 subjects were enrolled in the study, which were 10 more than the original protocol required.

7. Duration of Treatment:

One cycle, a maximum treatment of 19 days.

8. Inclusion Criteria:

Subjects were eligible for enrollment in the study if they had the following criteria:

- a. Subjects to be infertile women with an indication for controlled ovarian hyperstimulation and IVF/ICSI, between the ages of 18 and 39, and normal menstrual cycling (Between 24-35 days)
- b. Subjects were to have a BMI of between ≥ 18 and ≤ 32 kg/m²
- c. Willing to give written informed consent

9. Exclusion Criteria:

Subjects were excluded from the study if they had the any of the following conditions:

- a. History of/or current endocrine abnormalities such as PCOS with abnormal hormone values (subjects with only PCOS-like ovaries on ultrasound may be included), (treated) hyperprolactinemia or evidence of ovarian dysfunction
- b. Three unsuccessful COH cycles for assisted reproduction since last established ongoing pregnancy (if applicable)

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9. Exclusion Criteria (continued):

- c. History of non- or low ovarian response to FSH/hMG treatment
- d. Any clinically relevant hormone value outside the reference range during the early follicular phase (menstrual cycle day 2-7) as measured by the local laboratory (FSH \geq 10 IU/L or LH \geq 10 IU/L estradiol, progesterone, total testosterone and prolactin)
- e. Any clinically relevant abnormal laboratory value
- f. Any ovarian and/or abdominal abnormality interfering with ultrasound examination.
- g. Hydrosalpinx (visible on ultrasound; uni- or bilateral)
- h. Abnormal cervical smear according to the Papanicolaou scale (\geq class III) or Bethesda (\geq CIN 1) scale
- i. Contraindications for the use of gonadotropins (e.g. tumors, pregnancy/lactation, undiagnosed vaginal bleeding, hypersensitivity, ovarian cysts)
- j. Epilepsy, cardiovascular gastrointestinal, hepatic, renal, pulmonary or abdominal disease
- k. History or presence of alcohol or drug abuse within 12 months prior to signing the informed consent
- l. Hypersensitivity to AntagonTM or any of its components or to gonadotropin releasing hormone (GnRH) or its analogs
- m. Administration of investigational drugs within three months prior to screening

10. Trial Period:

January 2002 to September 2002.

11. Dosage and Mode of Administration:

Each subject received a starting dose of 150 to 225 IU of Follistim®-AQ Cartridge depending on the demographics and history of the subject. The selected starting dose of follitropin beta was fixed for the first five days of treatment. After this, the dose was be adjusted for the individual patient based on their ovarian response as assessed by ultrasound.

Human chorionic gonadotropin (hCG) was administered when adequate ovarian response was observed (at least 3 follicles \geq 17 mm). The maximum treatment period was 19 days. The maximum daily dose for Follistim®-AQ Cartridge is not mentioned in the protocol. It should be noted that AntagonTM (an approved gonadotropin releasing hormone antagonist) was used in this protocol to prevent premature LH surges. AntagonTM was used in a daily dose (250 mcg subcutaneously) and initiated when one or more follicles \geq 14 mm were seen on ultrasound.

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Treatment with Antagon™ was continued up to and including the day of hCG. The Follistim®-AQ Cartridge and Antagon™ were to be given around the same time during the day. Antagon™ was also given on the day of hCG whereas the Follistim®-AQ Cartridge did not need to be administered on the day of hCG.

12. Primary Efficacy Assessment:

An observer questionnaire and an “Ease of Use “ questionnaire were both submitted as outcome measures for study 142-001. The observer questionnaire was summarized in a by the sponsor as a frequency distribution for the ITT group (the percentage of respondents who could load, select, and administer the correct dose of Follistim®-AQ Cartridge after instruction as monitored by a trained staff member).

For trial 142-001, the observer questionnaire demonstrated that when instructed most subjects (greater than 95%) could load and administer the correct dose (successfully completed all steps) using the Follistim®-AQ Cartridge with improvement on the Day 2 of treatment. (See Appendix 1 – Tables 1 and 2). The exception to this was that the Follistim Pen™ only self-primed in approximately 50% of patients. However, by Day 2 of treatment, over 80% of patients could properly prime the device, even if it did not self-prime.

Re-instruction by the investigator was required in 33% prior to the first injection, dropping to 20% of subjects during the second injection. This number appears high. However, the problems the problems (identified by the observer questionnaire) resulting in the need for re-instruction were related to overall injection issues rather than issues with the assembly of use of the injector device itself. (See Appendix – Table 3)

The reasons for re-instruction can be combined for both trials (See Appendix – Table 4) These reasons did not appear to be the same for both trials, and was not the same in the mock injection when compared to the actual injection. The only exception to this was priming the needle, which occurred in 5 subjects in each of the trials. However, even problems with priming the Follistim Pen™ did not recur after re-instruction

An additional primary efficacy endpoint for trial 142-001 was summarized for the “Ease of Use Questionnaire”. (See Appendix 1 – Table 5) Summaries of the questionnaire results were reported as: mean score per question, mean score for the entire questionnaire, and an overall rating of the device (a one question response at the end of the “Ease of Use questionnaire”).

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- Mean overall scores for each individual question was 4.8 out of a maximum possible score of 5.0 on Day 2 of treatment in trial 142-001. The sponsor and the Division had previously agreed that that an average score per question should be ≥ 4.0 . (See the Division letter dated May 22, 2002 and the sponsor's response letter dated June 28, 2002)
- Mean total scores (Questions #1-19) for the entire questionnaire was also calculated with a range from 20 to 100. The mean total score for the questionnaire was 96.9 on Day 2 of treatment in trial 142-001 (The sponsor indicated that an average score ≥ 60 was considered to indicate that the Follistim Pen™ is easy to use).
- One question from the "Ease of Use questionnaire" (Labeled Part II) was separated by the sponsor to rate the overall experience with the Follistim Pen™ (with 1 being the worst overall experience and 5 being the best). The overall rating score for each rating from one to five was then calculated as a percentage of the total subjects who responded to the questionnaire. On Day 2 of treatment 81.8% of patients rated the Follistim Pen™ as "very good" overall, and this improved on Day 6 of treatment to 90%.

Reviewer's comment: The results of the two questionnaires do provide supporting data that patients in the study correctly understood directions for assembly and use of the Follistim®-AQ Cartridge. However, "Ease of Use" may not be the appropriate conclusion to draw from the results of the "Ease of Use questionnaire". The rating system for the "Ease of Use questionnaire" does not directly translate into "easy use" by an individual patient in the setting of usual use. Therefore, the results of the combined questionnaire do support the sponsor's claim that the Follistim Pen™ device may be used correctly if patients are given appropriate instruction and instructional materials. However, the conclusion cannot be made that the Follistim Pen™ is necessarily easy to use. To address a true "easy to use" claim, the sponsor would have needed to compare the device to a conventional syringe or other pen-injector device. This reviewer would recommend against any claims of "ease of use" being included in potential labeling for this product

Subject comprehension of the Follistim Pen™ device can also be indirectly assessed by multiple secondary efficacy parameters. The key secondary efficacy parameters include: Cycle Cancellation rate, Fertilization Rate, Mean Dose (IU) of Follistim®-AQ Cartridge, Mean Number of Treatment Days, Serum Estradiol (E2) level and Total Oocytes Retrieved. These secondary efficacy parameters were summarized by using: n, mean, standard deviation, minimum, median and maximum. Since this was not a comparative trial, no statistical tests were performed on these secondary efficacy parameters. (For a table of the key secondary efficacy parameters for trial 142-001 please see Appendix 1 – Tables 7 and 8)

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The sponsor also included the “biochemical” pregnancy rate for Follistim®-AQ Cartridge as a secondary efficacy parameter for trial 142-001:

- The biochemical pregnancy rate was 56.7% (34/60 subjects) per attempt
- The biochemical pregnancy rate was 61.8% (34/55 subjects) per embryo transfer.

Reviewer’s comments:

1. **It is important to note that ongoing pregnancy rates were not submitted or tabulated. The literature has stated that “a slight un-sustained rise in the hCG level is properly termed a “chemical” pregnancy, and should not be counted as a success.”⁴ The author further concludes, “The most important indicators of success are the delivery rate per retrieval and delivery rate per cycle initiated.⁴ Biochemical pregnancy data would not be relied upon to provide any efficacy evidence on pregnancy.**
2. **The sponsor did not address the issue of the differing pregnancy rates between intra-cytoplasmic injection and *in vitro* fertilization. This clinical study was too small to derive adequate stratification of patients by type of insemination. Since *in vitro* fertilization and intra-cytoplasmic injection represent two different patient populations, comparison of efficacy with respect to other previous clinical trials is not feasible.**

Subject comprehension was also indirectly reported by using the number of total patients who completed treatment (58 out of 60 subjects in trial 142-001 and 41 of 43 subjects in trial 142-002) received human chorionic gonadotropin. Since there is no comparison group in either trial 142-001 or trial 142-002 using the original approved Follistim® product, the secondary efficacy parameters give only indirect information on Follistim®-AQ Cartridge use. (See Appendix 1 – Tables 9 and 10)

Reviewer’s comment:

The two submitted clinical studies are open-label, non-comparative studies. No efficacy conclusions can be reached regarding the higher bioavailability of the delivery system for Follistim®-AQ compared to Follistim® using the results from the two submitted studies.

Comparison of the data from trial 142-001 using Follistim®-AQ Cartridge to the original Follistim® product is limited by significant improvements in assisted reproductive technology (ART) that have occurred (e.g. increased pregnancy rate with IVF, use of ICSI, different media, etc.) since the original clinical trials for Follistim® were initiated in the 1990s. Furthermore, changes in the methods of determining serum hormone levels also limit comparison of the two clinical trials.

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Reviewer's comments: These developments in assisted reproductive technology (ART) limit post-hoc analysis from comparing data derived from Follistim®-AQ Cartridge to the original Follistim® product.

A limited cross trial comparison of trial 142-001 to one of the trials performed using the approved Follistim® product is shown in Appendix 1. The demographics and trial designs are comparable, although study 37611 was completed in 1994 (See Appendix 1 – Table 11). Conclusions from comparison of the *in vitro* fertilization trials is limited by the improvements in assisted technology that have occurred (e.g. improvements treating male infertility, measurement of serum hormone levels, etc.) since the original clinical trials were initiated (1994). Although these developments that have occurred in ART prohibit post-hoc analysis of the two sets of data derived from Follistim® and Follistim®-AQ Cartridge. The cross study comparison would seem to suggest that no major changes in efficacy from the approved Follistim® product are seen (See Appendix 1 – Table 12). However, cross study comparisons should be interpreted with caution.

Reviewer's comments: The efficacy database from the two clinical trials (142-001 and 142-002) demonstrates that patients can successfully use the Follistim Pen™ after instruction. However, the second concern of whether the increased dose delivered by the Follistim Pen™ has significant clinical impact has not been addressed with this database. The efficacy database:

1. Does not answer the question of whether the increased dose effects the key efficacy endpoints of clinical pregnancy or a surrogate endpoint.
2. Does not address the issue of having a mixed patient population with regard to type of insemination in trial 142-001.
3. Does not address how the dose of Follistim®-AQ Cartridge would need to be adjusted when switching to the approved Follistim® product.

1. Title of the Study (142-002):

“An open-label, non-controlled multi-center study to evaluate subject comprehension, ease of use, safety and efficacy of the Follistim® Pen for the self-administration of Follistim®-AQ Cartridge for induction of ovulation in clomiphene-resistant women with chronic anovulation (WHO group II).”

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2. Investigators and Study Sites:

Site Principal Investigators

- 01 Kettel, L, San Diego Fertility Center, San Diego, CA
- 02 Scholl , G, North Shore University Hospital, Manhasset, NY
- 03 Bonaventura, L, Midwest Reproductive Medicine, Indianapolis, IN
- 04 Pang, S, Reproductive Science Center of Boston, Waltham, MA
- 05 Grunert, G, Obstetrical and Gynecologic Associates, P.A., Houston, TX*
- 06 Sacks, P, Columbia Fertility Associates, Washington, DC
- 07 Chantilis, S, Presbyterian Hospital, Dallas, TX

Six of the seven sites participated in the study and enrolled subjects.

* Indicates this site did not enroll any subjects in this study

3. Objectives of the Study:

The primary objective of the study was to demonstrate that the use of the Follistim Pen™ was well understood by the subjects. Further objectives were to demonstrate that the pen is a safe, effective and easy to use device for subcutaneous self-administration of Follistim®-AQ Cartridge to induce ovulation in clomiphene-resistant anovulatory women.

4. Rationale for the Study:

The rationale for this study is identical to study 142-001. This study (142-002) was to demonstrate effective use for the second indication; clomiphene-resistant patients (WHO group II) scheduled for ovulation induction.

5. Method of Assignment to Treatment:

The investigator or sub-investigator approached subjects for participation in the trial. The subjects were fully informed of the nature and risks of the trial, and given written and oral information. When the subject had given written consent, screening assessments were performed. If all inclusion criteria were met, and none of the exclusion criteria were present, the subject was entered into the study.

6. Number of Subjects:

44 subjects were enrolled in the study; this was 6 less than the original protocol required.

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7. Duration of Treatment:

One cycle, a maximum treatment of 19 days

8. Inclusion Criteria:

Subjects were eligible for enrollment in the study if they had the following criteria:

- a. Oligoamenorrhea (cycle length ≥ 41 days) or amenorrhea (cycle length ≥ 6 months) and/or chronic anovulatory women
- b. No conception despite apparent ovulation induced by clomiphene citrate (CC) for a period of time equal to or greater than 3 treatment cycles or failure to ovulate at a maximum dose of 150 mg of CC per day for 5 days in one treatment cycle
- c. At least age 18 and at most 39 years of age at the time of screening
- d. A BMI of between ≥ 18 and ≤ 32 kg/m² (deleted May 2002)
- e. Serum FSH levels within normal limits (1-10 IU/L)
- f. Normal serum prolactin and TSH levels
- g. Progesterone induced withdrawal bleeding or spontaneous menstrual bleeding
- h. Patency and apparent normalcy of both fallopian tubes (modified to at least one fallopian tube May 2002) and uterine cavity as documented by hysterosalpingography or laparoscopy within three years
- i. Normal semen analysis for the male partner
- j. Willing to give informed consent

8. Exclusion Criteria:

Subjects were excluded from the study if they had the any of the following conditions:

- a. Ovarian cysts or enlarged ovaries not related to polycystic ovarian disease (PCOS)
- b. Malformations of the sexual organs incompatible with pregnancy
- c. Any clinically relevant abnormal laboratory value
- d. Any ovarian and/or abdominal abnormality interfering with ultrasound examination.
- e. Hydrosalpinx (visible on ultrasound; uni- or bilateral)
- f. Abnormal cervical smear according to the Papanicolaou (\geq class III) or Bethesda (\geq CIN 1) scale
- g. Contraindications for the use of gonadotropins (e.g. tumors, pregnancy /lactation, undiagnosed vaginal bleeding, hypersensitivity, ovarian cysts)
- h. Epilepsy, cardiovascular gastrointestinal, hepatic, renal, pulmonary or abdominal disease

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8. Exclusion Criteria (continued):

- i. History or presence of alcohol or drug abuse within 12 months prior to signing the informed consent
- j. Administration of investigational drugs within three months prior to screening

9. Trial Period:

January 2002 to September 2002.

10. Dosage and Mode of Administration:

Each subject received a starting dose of 75 IU of Follistim®-AQ Cartridge that was fixed for the first seven days of treatment. After this, the dose was be adjusted for the individual patient based on their ovarian response as assessed by ultrasound. If there was no ovarian response on day 8 (upon ultrasound measurement) prior to Follistim®-AQ Cartridge injection, the dosage increase was decided by the investigator (but not to be greater than 25-50 IU). If ovarian response still did not occur, the dose of Follistim®-AQ Cartridge could be increased 25-50 IU again. If an ovarian response (as measured by ultrasound) was observed, the Follistim®-AQ Cartridge dose was to remain the same and to be continued until a complete ovarian response was observed. This was defined as one follicle with a diameter ≥ 18 mm and/or 2-3 follicles with a diameter of ≥ 15 mm. Human chorionic gonadotropin (hCG) was administered within 36 hours of the last Follistim®-AQ Cartridge injection. The maximum treatment period was 21 days. The maximum daily dose administered was 175 IU. It should be noted that conception could be attempted via sexual intercourse or intrauterine insemination (IUI) approximately 36-44 hours after hCG administration. More than one IUI was permitted, but one must have occurred during the time interval.

11. Primary Efficacy Assessment:

The observer questionnaire was the primary efficacy parameter for study 142-002; identical in administration and content to the one used in trial 142-001. The observer questionnaire was summarized as a frequency distribution for the ITT group (the percentage of respondents who could load, select and administer the correct dose of Follistim®-AQ Cartridge after instruction as monitored by a trained staff member) in the same method as for trial 142-001.

For trial 142-002, the observer questionnaire showed 100% of the subjects (prior to the first injection and during the second injection) could properly load the Follistim®-AQ Cartridge (see Appendix 1 – Table 1 and 2). The correct dose was selected by 95.3% (prior to the first injection) and 100% (during the second injection) respectively (See Appendix 1 - Tables 1 and 2). Similar to trial 142-001, patients when the Follistim Pen™ did not self-prime, 85% of patients properly primed the device.

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Re-instruction was required for 58.1% of subjects prior to the first injection, and 23.3% of subjects during the second injection. These numbers also appear high, however again, the problems encountered appeared to be related to the injection process and not the Follistim Pen™. (See Appendix 1 – Table 3). The reasons for re-instruction for trial 142-002 are almost identical to that of trial 142-001. (See Appendix – Table 4) Again, issues of concern to subjects at the mock injection were different from the issues that were encountered during Day 2 of treatment.

Trial 142-002 used the same Ease of Use questionnaire as in trial 142-001. The only difference in the Ease of Use questionnaires between the trial 142-002 and 142-001 was that the second Ease of Use questionnaire was repeated on treatment Day 8 instead of Day 6 in trial 142-001. The difference in treatment days is not significant in the context of comparison of the two trials. The questionnaire was identical to the one administered in trial 142-001 in rating both the steps and the overall experience in using the Follistim Pen™. The questions were scored in the same method as trial 142-001, and presented in frequency tables in an identical fashion. (See Appendix 1 – Table 6)

- Mean overall scores for each individual question was 4.9 out of a maximum possible score of 5.0 on Day 2 of treatment in trial 142-002. (With an acceptable score determined as greater than 4.0 as previously mentioned in trial 142-001)
- Mean total scores (Questions #1-19) for the entire questionnaire was also calculated with a range from 20 to 100. The mean total score for the questionnaire was 97.9 on Day 2 of treatment in trial 142-002. (with an acceptable score being ≥ 60 as previously mentioned for trial 142-001)
- One question from the “Ease of Use questionnaire” (Labeled Part II) was separated by the sponsor to rate the overall experience with the Follistim Pen™ (with 1 being the worst overall experience and 5 being the best). The overall rating score for each rating from one to five was then calculated as a percentage of the total subjects who responded to the questionnaire. For this question, on Day 2 of treatment, 90.7% of subjects rated the Pen as “very good” for trial 142-002, and this improved on Day 8 of treatment to 95.2% respectively.

To address the clinical impact Follistim®-AQ Cartridge had on treatment, multiple secondary efficacy parameters were reported in a similar manner to trial 142-001. The key secondary efficacy parameters include: Cycle Cancellation rate, Mean Dose (IU) of Follistim®-AQ Cartridge, Mean Number of Treatment Days, Ovulation Rate, and Serum Estradiol (E2) level. The sponsor reported all secondary efficacy parameters using summary statistics identical to those for trial 142-001: n, mean, standard deviation, minimum, median and maximum.

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Statistical tests were not performed on the secondary efficacy parameters (as there was no second treatment arm for comparison). [For a table of the key secondary efficacy parameters for trial 142-002 please see Appendix 1 – Tables 6 and 7]

The sponsor also included the “biochemical” pregnancy rate for Follistim®-AQ Cartridge as a secondary efficacy parameter for trial 142-002:

- The biochemical pregnancy rate was 34.9% (15/43 subjects) per attempt (e.g. per completed treatment cycle)

Reviewer’s comments:

1. **Ongoing pregnancy rates were not tabulated. The Division’s position is that biochemical pregnancy rate are not adequate evidence of efficacy for Follistim®-AQ Cartridge.**
2. **The secondary efficacy parameters also conclude that most subjects (41 out of 43) used Follistim®-AQ Cartridge and successfully completed treatment (receiving human chorionic gonadotropin). This is useful information, however, without a comparator arm, the information is limited at best.**

A cross study comparison of the secondary efficacy parameters in trial 142-002 using Follistim®-AQ Cartridge was made to trial 058004 that used the liquid Follistim® formulation. (See Appendix 1 – Table 9).

This comparison of the ovulation induction studies 142-002 (for Follistim®-AQ Cartridge) and trial 058004 (for Follistim®-AQ liquid solution) were comparable in trial design and characteristics. (see Appendix 1 – Table 9).

Reviewer’s comments:

1. **The comparison between the results of the two trials for Follistim® liquid (058004) and Follistim®-AQ Cartridge (142-002) reveals the efficacy parameters are relatively similar in their results. (See Appendix – Table 10). However, the comparisons are limited given that the post-hoc analysis of data was derived from two separate clinical trials; one for Follistim®-AQ liquid and one for Follistim®-AQ Cartridge. It appears in accuracy and precision of delivery of Follistim® may not drastically alter clinical outcomes as measured by a limited comparison of secondary endpoints to previous trials for the approved Follistim® product. In this reviewer’ opinion, post hoc analysis will not answer the questions raised by the lack of bioequivalence of Follistim®-AQ Cartridge, a randomized, controlled ovulation induction trial with a comparator arm would be required.**
2. **The Division continues to recommend that the surrogate endpoint for ovulation induction trials be a serum progesterone level of ≥ 10 ng/mL.**

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D. Efficacy Conclusions

The sponsor conducted these two phase 3 open-label, non-randomized clinical trials with the primary objective to provide evidence of subject comprehension and use of Follistim®-AQ Cartridge. A direct comparison between the two clinical trials (142-001 and 142-002) did not reveal significant issues with instruction or re-instruction that were directly related to the Follistim Pen™ (as most issues were related to the injection process in general). Also of note is that ninety-six percent of patients (99 patients out of 103) in the two supportive clinical trials successfully completed treatment (i.e. received human chorionic gonadotropin). The limited secondary efficacy data for the two clinical trials for Follistim®-AQ Cartridge (142-001 and 142-002) did not demonstrate drastically difference clinical outcomes from selected trials conducted for Follistim®. This is sufficient evidence to conclude that the Follistim Pen™ device was well understood by the subjects in both clinical trials.

In contrast, the two clinical trials do not provide adequate evidence to conclude that there is therapeutic equivalence between Follistim® and Follistim®-AQ Cartridge based solely on clinical outcomes. The major efficacy support for Follistim®-AQ Cartridge was to be based on bioequivalence to the approved Follistim® product. The higher bioavailability supports that Follistim®-AQ cartridge is efficacious but not bioequivalent to Follistim®. The outstanding clinical question is whether the higher bioavailability of Follistim-AQ as delivered by the BD— results in significant clinical safety issues (see below).

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The two major safety concerns for Follistim®-AQ Cartridge are: 1) Whether the pen-injector device be safely used by an individual patient and 2) Whether the safety information from Follistim®-AQ Cartridge can be referenced from Follistim®. The two formulations were bio-inequivalent; therefore, the sponsor needed to provide evidence that the higher bioavailability of Follistim®-AQ cartridge does not result in higher rates of adverse events normally associated with this class of drug products.

Reviewer's Comments: The sponsor has resolved the first safety concern in a satisfactory manner. Appropriate numbers of patients were exposed to Follistim®-AQ Cartridge to answer questions about the safety of the injection procedures with the BD – pen. The safety profile (local tolerance and discontinuation rates) for the injection procedure appears to be within acceptable limits.

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The second safety concern, whether the increased dose of Follistim®-AQ Cartridge delivered by the pen-injector device has an adverse effect on the clinical outcome was not answered by the two supportive clinical studies with the adverse event database.

The incidence of three key adverse events: ovarian hyperstimulation syndrome (OHSS), abdominal pain and nausea should be evaluated. In making cross trial comparison to one of the trial used to support approval of Follistim® (NDAs 20-582, Study 37608), Trial 142-001(IVF) appears to have a higher rate of overall abdominal pain but similar incidence of OHSS. Nausea was not assessed in the previous trial of Follistim®: Protocol 058004 –In making a similar cross trial comparison for the ovulation induction indication, the overall incidence of ovarian pain and OHSS were higher in Trial 142-002 as compared to Trial 058004 (NDA 20-582). The significance of this seemingly higher rate of OHSS in Trials 142-002 can not be assessed, as there was no comparator arm in that study. Answering the question of the significance of this apparent higher rate of OHSS and abdominal pain would require a comparative, blinded, clinical trial with a significantly larger number of patients.

In conclusion, safety of Follistim®-AQ Cartridge cannot be based on these two supportive clinical trials. These two clinical trials do not contain adequate evidence support a conclusion that the increased dose delivered by the Follistim Pen™ is not of clinical concern. The safety database provided by these two clinical trials is would require a comparator arm to detect whether the increased dose delivered by the pen-injector device presents a significant safety issue.

B. Description of Patient Exposure

Patient exposure for the approved product Follistim® is adequate and the safety profile for the approved product Follistim® has been well defined. For Follistim®-AQ Cartridge, the data is drawn from the 104 patients that were enrolled in the two supportive clinical trials (142-001 and 142-002) that were conducted in the United States. (See Appendix 2 – Table 4) The two trials showed sixty patients enrolled in trial 142-001 and forty-four in trial 142-002. In both supportive studies, patients received Follistim®-AQ Cartridge for a total of one treatment cycle, with a maximum treatment time of twenty-one days.

C. Methods and Specific Findings of Safety Review

Integrated summaries of safety for the supportive trials (142-001 and 142-002) were reviewed for safety in detail.

The first major safety concern was safe use of the Follistim Pen™. For this concern, the two supportive trials can be combined, as the injection process was identical for both patient groups.

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Demographic characteristics of the patients enrolled in the two supportive studies are shown in Appendix 2 - Table 4. Two methods of evaluating whether the Follistim Pen™ could be safely used was evaluating the adverse injection site reactions when using the device was used. The first method was examining the local tolerance data for both trials that used Follistim®-AQ Cartridge. The local tolerance data is summarized in Appendix 2 – Table 1. Patients experienced skin reactions such as itching and bruising, but only one patient in 103 treated (for both trials) developed cellulitis (less than 1%). [See Appendix 2 – Table 1]

Overall local tolerance (patients with symptoms) can be totaled for all complaints in all categories (using the percentage of subjects with moderate or severe symptoms). (See Appendix 2 – Table 1) The overall rate of significant problems with local tolerance is 2.3% in trial 142-001 and 6.7% [including the one patient that had cellulitis] in trial 142-002. These problems with local tolerance are similar to the overall moderate and severe local tolerance problems are much lower than that seen with the approved Follistim® product when administered in a similar route (subcutaneously - 18.6% in protocol 37613 for NDA 20-582). The incidence of bruising on the 7th day of treatment in trial 142-002 is high (41% of patients had moderate or mild bruising). However, these types of local tolerance issues were also seen in the local tolerance data for the approved Follistim® product (study 37613 in NDA 20-582 demonstrated approximately 50% of patients had mild to moderate bruising using a subcutaneous injection route).

Reviewer's comment: The local tolerance results do support the sponsor's claim that the Follistim Pen™ was used safely without significant local tolerance problems. However, in order to make a separate safety claim for improved local tolerance, a separate clinical trial with a randomized control looking specifically at injection site application would need to be submitted.

The reasons for treatment discontinuation also give indirect information on whether there was safe use of the Follistim Pen™. This information is summarized in Appendix 2 - Table 2. Patients discontinued for several reasons, including withdrawal of consent and ovarian hyperstimulation. No patient discontinued because of issues with device assembly or injection problems. Finally, 99 out of 103 total subjects (96%) successfully completed treatment with human chorionic gonadotropin in both trials. (See Appendix 2 – Table 5)

Reviewer's comment: This safety database provides significant indirect evidence that subjects could appropriately use of the Follistim Pen™ to complete a treatment cycle without significant local adverse events related to the device. It appears that the Follistim Pen™ can be safely by patients after adequate instruction. One remaining issue (as mentioned in the efficacy section) is how much instruction (and re-instruction), in terms of time and teaching, will be required for safe use of the Follistim Pen™.

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The second safety concern deals with the increased dose delivery of Follistim® by the Follistim Pen™. This increased dose delivery of Follistim® was evaluated indirectly using several key secondary endpoints: serious adverse events rate, rate of ovarian hyperstimulation events, and abnormal laboratory parameters (including white blood cell count and liver function tests). The adverse events are separated for the two clinical trials (See Appendix 1 – Tables 3 and 4)

Reviewer's comment: It is not possible to combine the adverse event data (other than the local tolerance data) for the two supportive clinical trials for four general reasons:

- 1. Treatment regimes for ovulation induction starts at much lower doses of Follistim® compared to *in vitro* fertilization trials.**
- 2. Treatment goals for ovulation induction are geared to produce one or two dominant follicles. *In vitro* fertilization treatment regimes attempt to produce at least one dominant follicle and three or four other mature follicles, more follicles than desired for ovulation induction.**
- 3. In most *in vitro* fertilization treatment cycles, Gonadotropin-Releasing Hormone (GnRH) agonists or antagonists [to prevent premature luteinization] are added, sometimes altering the course of treatment.**
- 4. Finally, key secondary endpoints are somewhat different (mean oocyte numbers for *in vitro* trials compared to serum progesterone levels) in ovulation induction trials.**

The adverse event of greatest concern with gonadotropins, especially when a potential of increased dose delivery exists is the rate of ovarian hyperstimulation (as defined using WHO criteria 1973).

Reviewer's comments: The rate of ovarian hyperstimulation syndrome seen in trial 142-001 after *in vitro* fertilization (3.3%) is lower than the ovarian hyperstimulation rate during an *in vitro* fertilization trial (37608) with the approved product Follistim® (5.2%). [See Appendix 2 – Table 3] However, there have been many changes in the stimulation protocols since the original Follistim® trial 37608 was performed in the 1990s, so a more recent comparison of ovarian hyperstimulation rates is more appropriate. Comparison of the rate of adverse events occurring with Follistim®-AQ Cartridge to previous clinical trials with Follistim® is limited because of the improvements in technology and stimulation protocols that have occurred since the original Follistim® trials were performed in the 1990s.

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Recent clinical trials of recombinant FSH in an *in vitro* fertilization (IVF)/intra-cytoplasmic sperm injection (ICSI) trial revealed ovarian hyperstimulation rates of 5 and 5.1%^{1,2} again similar to the rate of ovarian hyperstimulation syndrome resulting from trial 142-001.

The rate of ovarian hyperstimulation for trial 142-002 after ovulation induction (9.3%) was significantly higher than a recent ovulation induction trial (058004) for a liquid formulation of Follistim® (Follistim -AQ®) that demonstrated an overall rate for ovarian hyperstimulation syndrome of 4.8%)

Reviewer's comments:

- 1. Of note, the rates of ovarian hyperstimulation syndrome in the supportive clinical trial for ovulation induction (142-002) is similar to other published clinical trials using recombinant FSH used in an ovulation induction trial (8.3%).³**
- 2. However, although the rates of ovarian hyperstimulation for ovulation induction in trial 142-002 do not appear to be excessive, there appears to be an increased risk in use of Follistim®-AQ cartridge in for clomiphene-resistant patients. To answer this safety concern requires an additional appropriate blinded, randomized clinical trial with a comparator arm.**

Key adverse events were chosen based on the previous safety profile information obtained from previous clinical trials for the approved product Follistim®. The key adverse events for trials 142-001 and trial 142-002 are presented in Appendix 2 – Tables 3 and 4. The overall adverse event rate for trial 142-001 is compared to a previous clinical trial using the approved Follistim® product [NDA 20-582 – trial 37608]. (See Appendix 2 – Table 3) The overall adverse event rate for trial 142-002 can be compared to a previous clinical trial using Follistim® liquid [NDA 21-273 – Protocol 058004]. (See Appendix 2 – Table 4)

Other than the incidence of ovarian hyperstimulation, the a second adverse event that appeared to be increased was the occurrence of abdominal pain in trial 142-001 (25%). [See Appendix 2 – Table 3].

Reviewer's comments:

- 1. The reason for the increased occurrence of abdominal pain is unclear. Abdominal pain is one of the symptoms of ovarian hyperstimulation and diagnosis of pain often overlaps with the diagnosis of ovarian hyperstimulation syndrome. Thus, the increased abdominal and/or ovarian pain events may represent under-reported cases of ovarian hyperstimulation. However, the overall diagnosis of ovarian hyperstimulation syndrome (with or without abdominal pain) and grading of the ovarian hyperstimulation is made by the individual investigator at the time the patient presents to the clinic.**

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2. Secondly, it is difficult to reach conclusions from this high rate of abdominal pain, as there was no diagnosis attached to the abdominal pain, and no grading of the amount of pain experienced by the subject. Varying amounts of pain can occur during *in vitro* fertilization cycles during and after retrieval, depending on the individual patient and the type of anesthesia used.^{4,5}
3. Furthermore, the small numbers of subjects in the clinical trials (without a comparison group) prevent more definitive conclusions. Other small *in vitro* clinical trials have also shown abdominal pain/cramping rates of as high as 16%.⁶ In conclusion, although the rate of abdominal pain is increased in trial 142-001, the rate may have resulted from other etiologies (anesthesia type, post-retrieval pain). The limitations of the two clinical trials in terms of establishing adverse event rates and the ovarian hyperstimulation syndrome rates requires additional clinical studies using Follistim®-AQ Cartridge to provide an appropriate safety profile.

Another key adverse event, nausea, appeared to be increased in trial 142-001 (16.7%). Again, the etiology of this adverse event rate is even unclear than abdominal pain. The rates of nausea vary between *in vitro* fertilization trials from less than 1% to 10.3%.^{1,2} Nausea can be dependent on the patient population and on the type of anesthesia chosen. The rate of nausea is also less concerning as the rate in trial 142-002 was much lower (less than 1%) also supports the theory that the rate of nausea in trial 142-001 was related to the patient population or the *in vitro* treatment rather than the study drug. The sponsor reported that some of the nausea was related to gastrointestinal etiologies, which would bring the rate of nausea related to the study drug to an acceptable 6.7%. A fourth key adverse event, thromboembolism, was not seen in this study (probably secondary to the small number of patients in the clinical trials).

Reviewer's comment: In addition, the multiple birth rate could not be evaluated without ongoing pregnancy data. The impact Follistim®-AQ Cartridge will have on the multiple birth rate, nausea and other key adverse events will require a much larger safety database and additional clinical trials.

Abnormal laboratory results of interest include:

- Hematology parameters - revealed ten subjects (16.7%) in trial 142-001 and three subjects (7.0%) in trial 142-002 had a clinically significant high neutrophil level at baseline. These numbers are consistent with the original safety database for the approved Follistim® product, which showed that more than 10% of patients treated subcutaneously had notable upward shifts in neutrophils. (See NDA 20-582 and the medical officer's review dated December 13, 1996) and may be caused by subcutaneous injection of the gonadotropin.

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- Biochemistry parameters - revealed that no subjects in trial 142-001 and one subject (2.3%) in trial 142-002 had a high SGOT and SGPT post-treatment. This small number of patients with elevated liver function testing post-treatment is consistent with a previous clinical trial using Follistim® liquid (Protocol 058004 in NDA 21-273). (See Appendix 2 - Table 4)

Reviewer's comments:

1. **No other abnormal laboratory parameters for the two clinical trials (142-001 and 142-002) appeared to be concerning (greater than 5% occurrence in both trials).**
2. **The answer to whether the increased dose delivery system of the Follistim Pen™ will alter the ovarian hyperstimulation rate or adverse event rate upward will require separate clinical studies using a comparator group. In this reviewer's opinion, it is not possible to conclude whether delivery of Follistim® alters the clinical outcomes of using Follistim®-AQ Cartridge as measured by the adverse event safety profile.**

D. Adequacy of Safety Testing

Monitoring of the safety for the original formulation of Follistim® has been ongoing since 1997 in the United States and Europe and in Europe since 1999 for the liquid formulation (the liquid formulation is not approved to date in the United States). The approved product Follistim® has an adequate patient exposure and a well defined safety profile. It is unknown whether the new Follistim Pen™ device will change safety profile from the approved Follistim® product, given that the increased delivery by the pen-injector device.

E. Summary of Critical Safety Findings and Limitations of Data

The adverse event database from the sponsor is included two clinical trials (142-001 and 142-002) and reports no deaths. The adverse event data do not demonstrate significantly different adverse events from the original formulation of Follistim®, and do not appear to produce new safety concerns with use.

Reviewer's comments:

1. **The two supportive trials were not powered to answer whether the increased dose delivery system with use of the Follistim Pen™ will generate increased numbers (or more severe cases) of ovarian hyperstimulation syndrome compared to the original formulation of Follistim®.**
2. **It is possible that use of the pen-injector device, could decrease cases of ovarian hyperstimulation syndrome by preventing mixing errors occurring with the previously approved Follistim® product.**

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3. **Questions about the increased dose delivered by the Follistim Pen™ remain. This increase may or may not be statistically significant given the limitations of the clinical trial.**
4. **The rate of significant ovarian hyperstimulation syndrome could be secondary to patient selection issues, the size of the trial, or directly related to the formulation.**

In conclusion, the unresolved question is the issue of an increased dose delivery of Follistim®-AQ dose by the Follistim Pen™. It is unknown whether this increase dose delivery of Follistim® will be directly related to an increase in adverse outcomes (in terms of increased significant ovarian hyperstimulation or other adverse events).

Additional clinical trials to compare the safety Follistim®-AQ Cartridge will be required to determine the safety profile. In conclusion, the safety database from the two clinical trials does support approval of Follistim®-AQ Cartridge.

VIII. Dosing, Regimen, and Administration Issues

The dosing and regimen will be identical to that for the original Follistim® product. This is unacceptable based on the lack of bioequivalence to the approved Follistim® product. The dosing regime derived from the two supportive clinical trials (142-001 and 142-002) does not provide sufficient information to determine the correct dosage and administration schedule required. In addition, the two supportive clinical studies do not address how patients would alter their dosing schedule should they require switching to another gonadotropin product.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Approval is sought for Follistim®-AQ Cartridge for conditions that occur only in women.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Clinical studies of Follistim® did not include patients aged 65 and over. Follistim® and Follistim®-AQ Cartridge are contraindicated in pregnancy.

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C. Evaluation of Pediatric Program

Follistim®-AQ Cartridge is not indicated for use in pediatric populations and safety and efficacy in such patients have not been established.

X. Conclusions and Recommendations

A. Conclusions

The sponsor has adequately addressed the issue of the safe and effective use of the Follistim Pen™. The second issue whether the Follistim®-AQ Cartridge is clinically equivalent to the original Follistim® formulation was not adequately addressed in the two supportive clinical trials. This reviewer recommends that the risks of the increased dose delivery system need to be adequately addressed by the sponsor to allow proper safe and effective labeling of the Follistim®-AQ Cartridge. The lack of bioequivalency of Follistim® AQ Cartridge to the approved Follistim® product requires additional well-controlled, randomized clinical trials with an appropriate comparator arm so that a safety and efficacy profile for Follistim®-AQ Cartridge can be obtained as well as dose and administration information for labeling.

B. Recommendations

Not Approval of this application is recommended.

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Appendix 1

Table 1: Frequency distribution of selected observer questionnaire step results for the mock injection prior to actual Follistim®-AQ Cartridge treatment.

Selected Step Results	Trial 142-001 “IVF/ICSI*” n/(n%)	Trial 142-002 “OI” n/(n%)
1. Inserting Cartridge correctly	60/60 (100%)	43/43 (100%)
2. Selecting the correct dose	59/60 (98.3%)	41/43 (95.3%)
3. The Pen self-primed	34/60 (56.7%)	23/43 (53.5%)
3a. Patient then properly primed Pen†	29/33 (87.5%)	11/21 (52.4%)
4. Correcting a dosing error	7/8 (87.5%)	15/15 (100%)
5. Re-instruction rate	20/60 (33.3%)	25/43 (58.1%)
† Some patients primed the Pen even though the Pen was already self-primed.		

* “IVF/ICSI – *in vitro* fertilization with or without intracytoplasmic sperm injection”

** “OI – ovulation induction”

Table 2: Frequency distribution of selected observer questionnaire step results for the actual Follistim®-AQ Cartridge injection on Treatment Day 2.

Step	Trial 142-001 “IVF/ICSI*” n/(n%)	Trial 142-002 “OI**” n/(n%)
1. Inserting Cartridge correctly†	27/27 (100%)	27/27 (100%)
2. Selecting the correct dose	60/60 (100%)	43/43 (100%)
3. The Pen self-primed	34/60 (56.7%)	29/43 (67.4%)
3a. Patient then properly Primed the Pen	24/29 (82.8%)	12/14 (85.7%)
4. Correcting a dosing error	6/6 (100%)	3/3 (100%)
5. Pen seated at zero following injection	60/60 (100%)	43/43 (100%)
6. Re-instruction rate	12/60 (20%)	10/43 (23.3%)
†Subjects came to study with Follistim®-AQ Cartridge already loaded.		

* “IVF/ICSI – *in vitro* fertilization with or without intracytoplasmic sperm injection”

** “OI – ovulation induction”

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Table 3: Problems encountered during the observer questionnaire steps during the actual Follistim®-AQ Cartridge injection on Treatment Day 2 (Number of subjects).

Step	Trial 142-001 “IVF/ICSI*” (n)	Trial 142-002 “OI**” (n)
5A. Self-injection	Did not choose correct self-injection site (1) Did not wait five seconds prior to removing needle from skin (1) Did not cover injection site with a disinfectant swab (2)	Did not insert needle at 90 degree angle (1) Did not wait five seconds prior to removing needle from skin (1) Did not cover injection site with a disinfectant swab (3)

* “IVF/ICSI – *in vitro* fertilization with or without intracytoplasmic sperm injection”

** “OI – ovulation induction”

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Table 4: Reasons for re-instruction during the actual Follistim®-AQ Cartridge injection on Treatment Day 2 (Number of subjects)*.

Step	Trial 142-001 “IVF/ICSI**” (n)	Trial 142-002 “OI***” (n)
1. Priming the needle before each use	5 subjects	5 subjects
2. Covering injection site with a disinfectant	3 subjects	0 subjects
3. Cleaning Cartridge top after each use	2 subjects	0 subjects
4. Technique of removing or replacing needle cap	0 subjects	3 subjects
5. Not waiting 5 seconds prior to removing needle from skin	0 subjects	1 subject
6. Aseptic technique	0 subjects	1 subject
7. Alternating injection site	0 subjects	1 subject
8. Selection of the in-treatment dose instead of the dose used for mock injection in training	0 subjects	1 subject
Previously required re-instruction at mock injection*	9 of 10 subjects	8 of 12 subjects

*The issues that were of concern to these 9 subjects in trial 142-001, and to the subjects in trial 142-002 were not the same as in the first injection.

** “IVF/ICSI – *in vitro* fertilization with or without intracytoplasmic sperm injection”

*** “OI – ovulation induction”

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Table 5: Trial 142-001 Ease of Use Questionnaire (Sponsor submitted Table 16)

Table 16 Summary statistics on the ease of use of Follistim Pen™ questionnaire results on Day 2 Intent-to-Treat Group

Question ^a	n	Mean	SD	Min	Median	Max
Part I						
1. Did the Follistim Pen™ instruction manual prepare you enough to comfortably use the Follistim®AQ Cartridge and Follistim Pen™?	54	4.7	0.48	4	5.0	5
2. Did the patient leaflet prepare you enough to comfortably use the Follistim®AQ Cartridge and Follistim Pen™?	51	4.5	0.67	2	5.0	5
3. Did the Follistim Pen™ videotape prepare you enough to comfortably use the Follistim®AQ Cartridge and Follistim Pen™?	60	4.9	0.25	4	5.0	5
4. Did you feel comfortable putting the materials together for self-injection?	60	4.8	0.39	4	5.0	5
5. Were you comfortable putting together the pen injector?	60	4.9	0.34	4	5.0	5
6. Were you comfortable inserting the Follistim®AQ Cartridge?	60	4.9	0.32	4	5.0	5
7. Did you have any problems attaching the needle to the pen injector?	60	4.9	0.56	1	5.0	5
8. Did you have any problems priming the needle to get a drop to come out?	60	4.8	0.51	2	5.0	5
9. Did you feel comfortable in selecting and dialing up the dose for self-injection?	60	4.9	0.25	4	5.0	5
10. Did you have any problems when you dialed too high a dose?	24	4.8	0.68	2	5.0	5
11. Did you have any problems selecting an injection site?	60	5.0	0.22	4	5.0	5
12. Did you have any problems preparing the skin with an alcohol swab?	60	5.0	0.00	5	5.0	5
13. Did you have any problems injecting the Follistim®AQ Cartridge?	60	4.9	0.34	4	5.0	5
14. Were you comfortable giving partial doses from the old cartridge and completing the dose from the new cartridge?	22	4.0	1.29	1	4.5	5
15. Did you have any problems changing cartridge?	22	5.0	0.21	4	5.0	5
16. Were you satisfied with the self-administration process?	60	4.9	0.30	4	5.0	5
17. Did you have any problems taking apart the pen?	58	5.0	0.18	4	5.0	5
18. Did you have any problems removing and throwing away the needle?	60	4.7	0.66	2	5.0	5
19. Did you have any problems putting away the pen for future injection use?	60	5.0	0.18	4	5.0	5
Total score (Q1 – Q19)^b	59	96.9	3.67	82	97.5	100
Part II						
Overall experience: how would you rate the overall experience of self-injecting Follistim®AQ Cartridge using the Follistim®AQ Cartridge and Follistim Pen™ device?	60	4.8	0.39	4	5.0	5

^a Part I (questions 1-6, 9, 14, 16) and Part II question were scored based on the answer number (ranged 1-5). Part I, questions 7, 8, 10-13, 15, 17-19 were scored as 6 minus answer number (ranged 1-5).

^b The total score (ranged from 20-100) was derived by averaging all individual scores from all questions 1-19 then multiplied by 20 for subjects with at least 15 completed responses.

Data were taken from Tables 6.1.2.A and 6.1.2.B in Appendix F and Listings 15.A and 15.B in Appendix G

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Table 6: Trial 142-001 - Ease of Use Questionnaire (Sponsor submitted Table 17)

Table 17 Summary statistics on the ease of use of Follistim Pen[®] questionnaire results on Day 2 Intent-to-Treat group

Question ^a	n	Mean	SD	Min	Median	Max
Part I						
1. Did the Follistim Pen [™] instruction manual prepare you enough to comfortably use the Follistim [®] AQ Cartridge and Pen?	36	4.8	0.50	3	5.0	5
2. Did the patient leaflet prepare you enough to comfortably use the Follistim [®] AQ Cartridge and Pen?	35	4.7	0.53	3	5.0	5
3. Did the Follistim Pen [™] videotape prepare you enough to comfortably use the Follistim [®] AQ Cartridge and Pen?	39	4.8	0.37	4	5.0	5
4. Did you feel comfortable putting the materials together for self-injection?	43	5.0	0.15	4	5.0	5
5. Were you comfortable putting together the pen injector?	43	5.0	0.15	4	5.0	5
6. Were you comfortable inserting the Follistim [®] -AQ Cartridge?	43	5.0	0.00	5	5.0	5
7. Did you have any problems attaching the needle to the pen injector?	43	4.9	0.46	2	5.0	5
8. Did you have any problems priming the needle to get a drop to come out?	43	4.8	0.59	2	5.0	5
9. Did you feel comfortable in selecting and dialing up the dose for self-injection?	43	5.0	0.21	4	5.0	5
10. Did you have any problems when you dialed too high a dose?	23	4.9	0.29	4	5.0	5
11. Did you have any problems selecting an injection site?	43	5.0	0.00	5	5.0	5
12. Did you have any problems preparing the skin with an alcohol swab?	43	5.0	0.00	5	5.0	5
13. Did you have any problems injecting the Follistim [®] AQ Cartridge?	43	4.8	0.70	2	5.0	5
14. Were you comfortable giving partial doses from the old cartridge and completing the dose from the new cartridge?	10	3.8	1.75	1	5.0	5
15. Did you have any problems changing cartridge?	17	5.0	0.00	5	5.0	5
16. Were you satisfied with the self-administration process?	43	5.0	0.15	4	5.0	5
17. Did you have any problems taking apart the pen?	42	5.0	0.15	4	5.0	5

Table 17 Summary statistics on the ease of use of Follistim Pen[®] questionnaire results on Day 2 Intent-to-Treat Group (continued)

Question ^a	n	Mean	SD	Min	Median	Max
18. Did you have any problems removing and throwing away the needle?	43	4.9	0.50	2	5.0	5
19. Did you have any problems putting away the pen for future injection use?	43	5.0	0.00	5	5.0	5
Total score (Q1 – Q19)^b	36	97.9	2.63	89	98.8	100
Part II						
Overall experience: how would you rate the overall experience of self-injecting Follistim [®] using the Follistim [®] AQ Cartridge and Pen device?	43	4.9	0.29	4	5.0	5

^a Part I (questions 1-6, 9, 14,16) and Part II question were scored based on the answer number (ranged 1-5). Part I, questions 7,8,10-13,15,17-19 were scored as 6 minus answer number (ranged 1-5).

^b The total score (ranged from 20-100) was derived by averaging all individual scores from all questions 1-19 then multiplied by 20 for subjects with at least 15 completed responses.

Data were taken from Table 6.1.2A in Appendix F and Listing 17.B in Appendix G.

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Table 7: Secondary Efficacy Parameters – Trial 142-001

Parameter (Mean)	Trial 142-001 “In vitro fertilization/ intracytoplasmic injection” Mean(± Standard Deviation)
Total Dose (IU)	2188.3 (±709.8)
Number of Treatment Days	9.0 (±1.6)
# of follicles ≥ 17 mm	5.8 (±3.13)
# of oocytes retrieved	13.9 (±10.32)
Fertilization rate	64%*
Serum estradiol prior to hCG*	1617.6 (±1033.9)

* Median

Table 8: Secondary Efficacy Parameters – Trial 142-002

Parameter	Trial 142-002 “Ovulation Induction” Mean (±Standard Deviation)
Mean total dose (IU)	1070.3 (±580.31)
Mean # of Treatment Days	11.4(±4.17)
Ovulation achieved (%) by serum progesterone levels)	95.3%

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Table 9: Baseline and demographic characteristics for all-subjects-treated group

Characteristic – Mean (± Standard Deviation)	Trial 142-002 “Ovulation Induction” Mean (± Standard Deviation)	Trial 058004* “Ovulation Induction” Mean (± Standard Deviation)
Mean age (years)	31.0 (± 3.8)	31.09 (± 3.7)
Mean wt (kg)	70.3 (± 13.7)	66.73 (±12.6)
Mean Body Mass Index (kg/m ²)	26.1 (± 4.9)	24.63 (±4.6)
Mean duration of infertility (years)	3.1 (± 2.4)	2.59 (± 1.8)
Used Weekly “Step Up” Protocol base on ovarian response	Yes	Yes
Used Clomiphene Resistant (WHO Group II) Subjects	Yes	Yes

*submitted in the pending NDA for Follistim® AQ liquid (21-273)

Table 10: Secondary Efficacy Parameters – A comparison to the Follistim® liquid Protocol 058004 for the all-subjects-treated group

Parameter	Trial 142-002 “OI”*	Protocol 058004** “OI”*
Mean total dose (IU)	1070.3	821.3
Mean # of Treatment Days	11.4	9.0
Overall ovulation achieved (% ITT group)	95.3%	90.3%

*OI – ovulation induction

** submitted in the pending NDA for Follistim® AQ Liquid (21-273)

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Table 11: Baseline and demographic characteristics for all-subjects-treated group

Characteristic – Mean	Trial 141-001 “IVF/ICSI**”	Trial 37611* “IVF***”
Mean age (years)	32.5	32.2
Mean wt (kg)	66.2	59.3
Mean Body Mass Index (kg/m ²)	25.1	22.5
Mean duration of infertility (years)	4.2	5.4
Treatment type	IVF or IVF/ICSI	IVF only
Used subjects with normal cycling (24-35 days)	Yes	Yes
Used “Down-regulation of pituitary	Yes (Antagon®)	Yes (Decapeptyl®)
Cause of infertility (%):		
Tubal	35	66.7
Endometriosis	6.7	6.1
Tubal/Endometriosis	3.3	6.1
Male Factor	21.7	N/A
Other Factors/Combinations	33.3	21.2

*submitted in the original NDA for the approved product Follistim® (20-582)

** “IVF/ICSI – *in vitro* fertilization with or without intracytoplasmic sperm injection”

** “IVF – *in vitro* fertilization”

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Table 12: Secondary Efficacy Parameters – A comparison of trial 142-001 to trial 37611 of the approved Follistim® treated group.

Parameter (Mean)	Trial 142-001 “IVF/ICSI**” (n=60)	Protocol 37611* “IVF***” (n=57)
Total Dose [IU]	2188.3	2265
Number of Treatment Days	9.0	10.2
# of follicles \geq 17 mm	5.8	5.4
# of oocytes retrieved	13.9	9.7

*submitted in the original NDA for the approved Follistim® product (20-582)

** “IVF/ICSI – *in vitro* fertilization with or without intracytoplasmic sperm injection”

*** “IVF – *in vitro* fertilization”

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Appendix 2

Table 1: Local tolerance at the site of injection as recorded in number of subjects with symptoms 24 hours post injection and (/) and number of subjects with symptoms at the 7th injection.

Complaint	Trial 142-001 “IVF/ICSI*” (# patients complaining after first injection/# patients complaining after seventh injection)	Trial 142-002 “OI**” (# patients complaining after first injection/patients complaining after seventh injection)
Itching	2/0	0/1
Pain	4/6	10/11
Bruising	1/9	12/24*
Swelling	1/1	1/3
Redness	3/3	6/7
Cellulitis	1 patient	0 patients

* “IVF/ICSI” – *in vitro* fertilization with or without intracytoplasmic sperm injection”

** “OI” – Ovulation Induction

Table 2: The reasons for discontinuation by number of subjects as recorded on the End-of Trial form for all-subjects-treated.

Reason	Trial 142-001 “IVF/ICSI*” (n=subjects)	Trial 142-002 “OI**” (n=subjects)
Ovarian Hyperstimulation Syndrome (adverse event)	1	0
Insufficient Ovarian Response	2	0
Risk for Hyperstimulation	0	1
No/too few/bad quality Oocytes	1	N/A
Lost to follow-up	1	0
Consent withdrawn	0	1

* “IVF/ICSI” – *in vitro* fertilization with or without intracytoplasmic sperm injection”

** “OI” – Ovulation Induction

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Table 3: Incidence of adverse clinical events by WHO Dictionary Included Term for trial 142-001 and trial 37608 in all-subjects-treated group recorded as a percentage (%).

WHO dictionary included term	Trial 142-001 [<i>In vitro</i> Fertilization (n=60)]	Trial 37608** [<i>In vitro</i> Fertilization (n=591)]
Abdominal Pain (Gyn)	25%	5.2%
Ovarian Hyperstimulation Syndrome	3.3%	2.5%
Nausea	16.7%	N/A*
Ectopic Pregnancy	1.7%	3%

*N/A – The exact number and percentage of patients with nausea is not available, however, from the data presented in the medical officer’s review dated December 13, 1996, it is an adverse event of less than 5%.

** submitted in the original NDA for the approved Follistim® product 20-582

Table 4: Incidence of adverse clinical events by WHO Dictionary Included Term for trials 142-002 and 058004 in all-subjects-treated group reported as a percentage.

WHO dictionary included term	Trial 142-002 [Ovulation Induction (n=43)]	Trial 058004* [Follistim® liquid formulation n=62]
Ovarian Pain*	2.3%	0%
Abdominal Pain (Gyn)	2.3%	17.7%
Cramp Abdominal (Gyn)	0%	8.1%
Ectopic Pregnancy	0%	3.2%
Headache	2.3%	11.3%
Nausea	0%	14.5%
Ovarian Cyst*	2.3%	3.2%
Ovarian Hyperstimulation	9.3%	4.8%
Phlebitis	0%	1.6%
SGOT/SGPT increase	2.3%	1.6%
*recorded as ruptured ovarian cyst/pain in trial 142-002		

* an ovulation induction trial submitted in a pending NDA for Follistim®-AQ liquid (21-273)

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Table 5: Disposition of Subjects for the two sponsor submitted studies 142-001 and 142-002.

Number of Subjects:	Trial 142-001 "IVF/ICSI*"	Trial 142-002 "OI**"
Enrolled (n)	60	44
Treated [with Follistim®-AQ Cartridge and hCG†] (n)	58	43
Completing the Study (n)	55	41

† hCG (human chorionic gonadotropin)

* "IVF/ICSI" – *in vitro* fertilization with or without intracytoplasmic sperm injection"

** "OI" – Ovulation Induction

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Appendix 3

Reference List:

1. Efficacy and safety of highly purified menotropin versus recombinant follicle-stimulating hormone in in vitro fertilization/intracytoplasmic sperm injection cycles: a randomized, comparative trial. The European and Israeli Study Group on Highly Purified Menotropin versus Recombinant Follicle-Stimulating. *Fertil Steril* 2002; 78(3): 520-8.
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Audrey Gassman
6/23/03 05:05:14 PM
MEDICAL OFFICER

Shelley Slaughter
6/23/03 05:11:24 PM
MEDICAL OFFICER
I concur.

Donna Griebel
6/23/03 06:10:27 PM
MEDICAL OFFICER

Division Director Memorandum

NDA#: 21-211

Sponsor: Organon, Inc.

Drug: Follistim®-AQ Cartridge (Follitropin beta for injection)

Generic name: Recombinant follicle stimulating hormone (FSH)

Indications: Development of multiple follicles in ovulatory patients
Participating in an Assisted Reproductive Technology (ART) program

Induction of ovulation (OI) in the anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure

Dosage form and strength: Sterile, clear, aqueous solution prefilled into ready-for-use disposable cartridges intended for use with Becton-Dickinson Follistim® Pens for adjustable administration

833 IU FSH per ml in 300 IU and 600 IU cartridges

Date of submission: January 31, 2000

Date of memorandum: November 29, 2000

Background

Follistim®-AQ is a new formulation of a previously approved product, Follistim® (follitropin beta for injection, NDA 20-582). This new formulation is an injectable aqueous solution containing 833 IU of FSH per ml. Unlike the previously approved product (a freeze-dried cake in a glass vial requiring reconstitution with water prior to injection), Follistim®-AQ is a clear, colorless, sterile solution prefilled into 1.5 ml glass multidose cartridges containing either 300 IU or 600 IU FSH to be administered via a pen-injector device. The device itself is a modified BD Microfine insulin pen injector redesigned for use with Follistim®. Per the sponsor, this new formulation was developed as a more convenient, accurate and precise dosing form for patient and physician use.

In support of approval of this new formulation, the sponsor conducted an open-label, single-dose, crossover study in 22 women comparing the bioavailability of a 150 IU dose of Follistim®-AQ administered via the pen-injector and a 150 IU dose of reconstituted Follistim® from the vial administered via syringe. The two formulations were not found to be bioequivalent in this study, with Follistim®-AQ noted to have a 20% higher AUC and a 19% higher C_{max} than the comparator Follistim® formulation. The sponsor was given several options to address the lack of

bioequivalence of the two formulations, including (1) conducting another bioequivalence study following dose adjustment of Follistim®-AQ, (2) adjustment of the dose delivered by the pen-injector to match that delivered via syringe; this dosage adjustment had to be accompanied by appropriate labeling to convey bioequivalence of the new to the approved formulation (In this instance, the additional bioequivalence study would be waived); (3) altering the concentration of drug while maintaining the same administration volume for the new formulation and providing appropriate stability data; (4) conducting a clinical trial using the new formulation and demonstrating that this formulation is safe and effective for the proposed indications.

The sponsor proposed yet another option to address the bio-inequivalence of the two formulations, namely modifications in the proposed product label to reflect the difference in bioavailability between the two formulations. This option included a conversion table describing the numerical relationship between a dose delivered via the pen-injector and one delivered by the vial/syringe. Thus, this NDA contained the results of the single bioequivalence study, draft labeling incorporating the conversion table noted above, and a — instruction manual for patients. No clinical trial data demonstrating the safe and effective use of Follistim®-AQ delivered via the pen-injector device was presented in the NDA.

Biopharmaceutics:

In the bioequivalence study performed, it was noted that the conventional syringe (used to administer reconstituted Follistim® from a freeze-dried cake) delivered a — lower amount of Follistim® than the nominal dose. The sponsor analyzed the pharmacokinetic data from this study by dose correction per individual patient to account for losses due to removal of excess air and due to dead volume of the syringe. The mean correction factor for all patients in the study was 18%. Following application of this dose correction factor to the AUC and Cmax values for Follistim®-AQ, bioequivalence of the two formulations was demonstrated per the Biopharmaceutics review team.

Pharmacology/Toxicology:

The application was acceptable from this review discipline's perspective.

Other Review Disciplines:

Several other review disciplines (e.g., Chemistry, Microbiology, CDRH and Clinical) noted deficiencies in the application that prevent approval of Follistim®-AQ Cartridge at this time. These deficiencies include the following by discipline:

Chemistry:

From a chemistry perspective, the proposed release specifications for oxidation products (calculated by oxidized subunits) and the proposed shelf-life specifications for subunit content, oxidation products (calculated by oxidized subunits) and benzyl alcohol content were not acceptable. Data on the actual content of polysorbate 20 during stability testing were not provided. In addition, Organon, Inc.'s testing facility in West Orange, New Jersey was not in

compliance with cGMP and received a "withhold approval" recommendation on November 17, 2000. The application was not approvable per the chemistry review team.

Microbiology:

The biological indicators used for validation (

Per the Microbiology review team, these deficiencies require resolution prior to approval of this application.

A Discipline Review letter was sent to the sponsor on November 14, 2000 asking for information to address each of the chemistry and microbiology deficiencies noted above. A response to this correspondence was received from the sponsor on November 21, 2000, and review of this response was deferred during the current review cycle.

The Pen-Injector Device:

Per a consult obtained from CDRH, the safety and effectiveness of the BD Pen injector device could not be determined from information provided in the application. Several not-approvable deficiencies were identified by this center including: (1) failure to identify the dose measure and incrementing unit of the BD Pen — (2) lack of a description of the dose scale and dose display of the device; (3) failure to provide an evaluation of the comparative dosing accuracy of the BD Pen — injector to the syringe and needle for both formulations of Follistim®; (4) an unacceptable risk of dosing error due to the ability to fit either the 300 IU FSH-containing cartridge or the 600 IU FSH-containing cartridge into the same injector device; (5) failure to submit a 510(k) application to CDRH as required for an approved device that has been modified with a new indication for use.

Clinical:

As described in the primary and secondary clinical reviews, the proposed draft labeling and incorporated conversion table contain several inaccuracies and omissions that present an unacceptable risk of dosing error to the patient. The patient instruction manual is cumbersome and not thought to be easily interpretable. Per the clinical review team, Follistim®-AQ Cartridge offers no advantage to health care providers or patients as compared to the approved Follistim® formulation. In addition, the deficiencies in the proposed product label, patient instruction manual and design of the pen injector device pose risks for prescribing and dosing errors.

DDMAC and OPDRA:

DDMAC recommended that a patient package insert (PPI) be developed for this product prior to approval, noting that the PPI should contain a general description of Follistim®-AQ Cartridge, instructions for correct use of the product, and a description of benefit and risk information for the product. An appropriate version of the patient instruction manual can be included in the Physician Insert under INFORMATION FOR THE PATIENT to address this recommendation when this application is approvable.

Although OPDRA had no objections to the proposed product name, safety concerns similar to those noted by the clinical review team related to possible medication errors were also noted by OPDRA.

Conclusions and recommendations:

I agree with the conclusions of all review disciplines and recommend that this application not be approved. The specific deficiencies by discipline noted above will be communicated to the sponsor in a not-approvable letter.

Susan S. Allen, MD, MPH
Director, DRUDP

Cc: Division file for NDA 21-211
AllenSu

/s/

Susan Allen
11/29/00 12:46:53 PM
MEDICAL OFFICER

**Follistim-AQ Cartridge™
Team Leader Review**

NDA: 21-211

Drug: Follistim®-AQ Cartridge (Follitropin beta for injection)

Indication:

1. Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program.
2. Induction of ovulation in the anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure.

Dosage/Form/Strength: Sterile, clear, colorless aqueous solution filled into ready-for-use disposable cartridges intended to fit Becton-Dickinson Follistim Pens for adjustable administration. 833 IU FSH per ml in either 300 IU or 600 IU cartridges.

Applicant: Organon, Inc

Original Receipt Date: January 31, 2000

Review Completed: November 10, 2000

Date of Memorandum: November 15, 2000

Background

Follistim® was approved by the Agency on September 29, 1997 for the indications of development of multiple follicles (controlled ovarian stimulation) 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. Follistim® is a freeze-dried cake formulation for reconstitution with water for injection. On March 18, 1999, the Sponsor, Organon, met with the Agency in a pre-NDA guidance meeting to discuss a completed bioequivalence study of Follistim® vs. a new pharmaceutical presentation, Follistim®-AQ Cartridge. The bioequivalence study was proposed to support the NDA submission for the new formulation. No clinical trials were proposed or conducted. The completed bioequivalence study compared a single dose of 150 IU of Follistim® (2-vials of 75 IU dissolved in 1 ml of diluent) administered subcutaneously with a syringe to a single dose of 150 IU of Follistim®-AQ Cartridge administered subcutaneously with a pen-injector. The results were non-equivalent; the pen injector dose had a higher bioavailability. To address the non-equivalence of the dosage forms, the Sponsor was presented with the option of conducting another bioequivalence study after adjusting the dose of the Pen-Injector to match the dose delivered with the reconstituted freeze-dried cake formulation. It was also discussed that the labeling for Follistim®-AQ Cartridge with the Pen Injector should clearly address the delivery volume. Finally, because a significant safety risk could exist for patients switching from the cake formulation to Follistim®-AQ delivered via the Pen-Injector, the Sponsor was asked to address

this with a justification for the use of either product. Following acceptable justifications for the use of either product, the proposed labeling would then allow the physician to decide the choice of product, dose and mode of administration. It was decided at the pre-NDA meeting that the bioequivalence issues should be resolved before the NDA application was submitted.

The NDA for Follistim-AQ Cartridge was submitted on January 28, 2000. A teleconference between the Agency and the Sponsor was held on March 22, 2000. In this teleconference, the Deputy Division Director reiterated to the Sponsor the discussion points of the March 18, 1999 meeting (as presented in the previous paragraph). The Sponsor was told that the safety and efficacy of the Pen-Injector must be linked to Follistim® by establishing bioequivalence. The Sponsor was presented with alternatives to conducting another pharmacokinetics trial to establish bioequivalence and these are as follows:

1. Adjust the dose of the Pen-Injector to match the dose delivered by the syringe and label the product in a way to convey bioequivalence to the more familiar dose. This scenario would require that the Becton Dickinson Pen-Injector device be recalibrated to facilitate the ease and use by patients and physicians. Under this scenario, the bioequivalence study requirement would be waived.
2. Generate clinical trial data with the new formulation and the Pen-Injector to show that the higher bioavailability of the dose delivered with the Pen-Injector was both safe and effective.
3. Change the concentration of drug while maintaining the same administration volume. Stability data would be required with this new formulation.

The Sponsor was clearly told that the Division did not accept the Sponsor's position that the higher bioavailability of the dose delivered with the Pen-Injector is of no clinical concern. Subsequent to this meeting it was determined that the higher bioavailability of the dose delivered by the Pen-Injector would be a review issue rather than a filing issue and the NDA was filed on March 31, 2000.

In the NDA, the Sponsor represents that the multidose ready-to-use presentation of Follistim®-AQ Cartridge is more convenient and requires less handling than the approved product (Follistim®) and that the Pen-Injector device provides a more accurate and precise method of dosing as compared to the conventional syringe. In support of this NDA application for Follistim®-AQ Cartridge, Organon has submitted only the bioequivalence study comparing it to Follistim®. No clinical trial data is submitted. On March 29, 2000, the Sponsor submitted a proposal to the Agency for a conversion table to translate the dosing units of Follistim® to that for Follistim-AQ that is to be given with the pen-injector.

Chemistry/Manufacturing

The following summary addresses the major issues identified in the chemistry review.

The drug substance, follitropin beta, is a recombinant version of the human follicle stimulating hormone (FSH) genetically engineered from Chinese Hamster Ovary Cells and it was previously approved in NDA 20-582. Since the approval of the NDA, there have been no significant manufacturing changes of the drug substance. The drug substance is manufactured, packaged and tested by _____ The facility is in compliance with cGMP. A letter of authorizations was provided to allow for the cross-referencing of DMF _____ The DMF was reviewed and determined to be adequate to support NDA 20-582 for Follistim® (lyophilized powder for injection). The updated DMF was reviewed and determined to be adequate to support

this NDA. The Sponsor has also cross-referenced the drug substance information provided in NDA 20-582. The quality of follitropin beta is adequately controlled.

The drug product is a new presentation of the previously approved Follistim®. Follistim® is a sterile lyophilized drug product to be reconstituted with water for injection. The new presentation is a ready-for-use formulation of a solution filled into disposable cartridges designed for use with an injector pen. The solution drug product contains benzyl alcohol as a preservative and L-methionine as an anti-oxidant to stabilize the protein in solution.

The pre-filled cartridge is manufactured by Vetter Pharma-Fertigung GrmGH & Co. KG; packaged and tested by Organon Ltd. (Ireland) and Organon, Inc (West Orange, NJ); and secondary packaging is to be done by Organon Inc (Allentown, PA). Organon Inc is not in compliance with cGMP. The Office of Compliance sent a warning letter to the firm and made an overall recommendation of "Withhold" approval. The Sponsor's proposed release specifications of oxidation products are not acceptable. The proposed shelf-life specifications for subunit content, oxidation products, and benzyl alcohol content are not acceptable.

Based on the available real time data, up to 24 months from three full-scale production batches, an expiry date of 24-months is granted.

Becton Dickinson manufactures the injector pen (BD Follistim Pen). The injector pen was reviewed by CDRH which recommended that the device not be approved (see discussion below).

From the Chemistry, Manufacturing and Controls perspective, the NDA is not approvable.

Microbiology

Two deficiencies were noted in the Microbiology review (see review). From the Microbiology perspective, the NDA is approvable pending satisfactory resolution of the deficiencies.

Pen Injector Device

The following issues were identified in the review of the Pen-Injector by the Center for Devices and Radiological Health. The device is a BD Pen| - pen injector described in the device master file as a slightly modified BD Microfine| - insulin pen injector redesigned for use with Follistim®-AQ. The information contained in the device master file, MAF ~~---~~, and in the NDA did not describe the operating features of the device and its performance characteristics in a sufficient manner to demonstrate that the BD Pen| - is safe and effective for its intended use. Because the BD Pen| - is a Microfine| - pen injector that has been modified for a new indication-administration of Follistim instead of insulin, the BD Pen| - can not rely on the marketing status of the Microfine| - device. Additional information regarding the construction of the device, its performance, safety and effectiveness profiles, and labeling should be submitted to the master file for review. It was recommended that the Sponsor provide the following:

1. A description of the dose measure that the BD Pen| - is calibrated to deliver. The dose measure for the BD Pen| - should be directly related to the international unit that Follistim® is prescribed in.
2. A description of the incrementing dose unit and the accuracy tolerance for the BD| - . The BD pen uses clicks to change a dose. What is the difference in dose volume/quantity between adjacent clicks?
3. Bench testing data to demonstrate the dosing accuracy of the BD Pen| - for both Follistim presentations and a comparison to the dosing accuracy of conventional

administration by syringe and needle. Clinical data should include an evaluation and comparison of both devices, each delivering both Follistim presentations.

4. An evaluation and mitigation of the patient risks that may arise from two different concentrations being available in the same container type that fits into the same injector device.

The recommendation of the Center for Devices and Radiological Health was that the Pen-Injector device not be approved for the proposed use.

Product Name

The August 4, 2000 consult from OPDRA specified that from a safety perspective, there was no objection to the use of the name Follistim®-AQ.

Pre-clinical Pharmacology and Toxicology

Based on the structural and functional similarities of Follistim®-AQ with natural and approved urinary FSH and recombinant FSH, as well as extensive clinical experience with these products, the pharmacology reviewer recommended that from a pre-Clinical and Pharmacology view point the NDA should be approved.

Biopharmaceutics

One comparative bioavailability study with Follistim®-AQ Cartridge vs. Follistim® was conducted. 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 Follistim® (reconstituted-150 IU). Follistim®-AQ resulted in 20% higher AUC and 19% higher C_{max} than Follistim® delivered by the conventional syringe and the two formulations were found not to be bioequivalent. In this same study, the Sponsor weighed the syringes for Follistim® before and after the injection to each patient to determine the actual dose delivered. It was found that the conventional syringe delivered a lower amount than the nominal dose. The Sponsor calculated a correction factor for the dose administered to each patient by dividing the maximum (theoretical) weight of the syringe content by the actual weight administered. The mean correction factor was 18%. The Sponsor applied this 18% correction factor to the AUC and C_{max} values for Follistim® delivered with the conventional syringe and with this correction factor, the Pen-Injector was bioequivalent to Follistim®. The Sponsor proposed to reduce the dose of the Pen-Injector by 18% to match the actual dose delivered by the syringe and to include this in the labeling. Subsequently, the conversion table indicating the equivalent Pen-Injector dose and syringe dose was proposed for inclusion in the labeling. The Office of Clinical Pharmacology and Biopharmaceutics accepted this approach.

Division of Scientific Investigations (DSI)-Clinical Inspection Summary

No DSI inspections were conducted.

Clinical Efficacy and Safety

No clinical trials were submitted to the NDA.

Discussion and Conclusions

No clinical trial data supporting the safe and efficacious use of Follistim®-AQ was submitted in this NDA. The Sponsor supports this application with a bioequivalence study comparing Follistim®-AQ Cartridge with Follistim®. Bioequivalence of the two formulations was not demonstrated. The Sponsor was informed in the pre-NDA process that bioequivalence of the new formulation, Follistim®-AQ Cartridge to the approved formulation, Follistim® would need to be demonstrated. The Sponsor maintains that both preparations (Follistim® and Follistim®-AQ Cartridge) are bioequivalent when the administered doses are the same. According to the Sponsor, failure to demonstrate bioequivalence results from the comparison of the highly accurate Pen-Injector (assumed 100% in the bioavailability study) to the less than accurate conventional syringe mode of delivery. The Sponsor demonstrated that the syringe method of delivery of the reconstituted cake formulation of Follistim® results in as much as → lower delivery than the nominal dose. The Sponsor then calculated a mean dose correction factor based on the weight of the syringe before and after delivery and applied this correction factor to both the AUC and C_{max} values of the Pen-Injector to establish bioequivalence.

The Sponsor further suggests that the dosing differences (resulting from the higher dosing availability with the Pen Injector delivery of Follistim®-AQ) are clinically insignificant and can be effectively communicated to the physician with language in the labeling that provides a conversion from the usual dose of Follistim® to Follistim®-AQ Cartridge. This proposed conversion table utilizes the 18% correction factor derived in the bioavailability study (and used to establish bioequivalence). The Sponsor further represents that this conversion table will be important only in the instance where one is switching within a cycle from one formulation to the other. The consideration of the starting dose is overlooked with this argument. In the United States, the clinician's experience for dosing and administration of FSH products is based on the use of the conventional syringe delivery system. Despite the fact that dosing in a controlled ovarian stimulation cycle is adjusted in the course of the cycle according to the individual's serum estradiol levels and follicular development (demonstrated with ultrasound), the starting dose in any given cycle is determined by the physician based on the patient's history and the physician's experience. No clinical trial exists for physicians to guide the starting dose of Follistim®-AQ Cartridge. The Sponsor acknowledges that if a patient is switched from the Pen-Injector to a formulation requiring a conventional syringe, a correction should be made to account for the fact that a lower dose will be administered than the dose set with the pen. However, the Sponsor argues that this is of little relevance since the more advanced follicles are more susceptible to FSH and have a lesser requirement for FSH. The Sponsor presented no literature or clinical data to support this contention. Also not addressed by the Sponsor is the issue of the approximate dose (instead of actual conversion equivalent dose) being delivered to "hyper-responders", who according to the Sponsor is the class of individuals who would benefit most from this type of delivery system (ability to deliver smaller dosing increments).

The conversion table submitted by the Sponsor provides for a calculated correction based on data from the bioavailability study. Not every subject in the bioavailability study demonstrated a 20% higher bioavailability of the Pen-Injector delivered dose than the syringe-delivered dose. Universal application of this 18% correction factor would result in some subjects being given a lower dose than necessary. No clinical trial data exist to determine the significance of these possible dosing differences. The actual conversion table submitted by the Sponsor presents a column with 5 doses of Follistim®. The adjacent column has the "Cartridge/Pen-Injector Equivalent". A third column gives the "Dose-setting of the Pen" that if followed only approximates the dose equivalent for the Pen-injector. For example the 75 IU dose for the vial/

syringe would have a dose equivalent for the Cartridge/Pen-Injector of 62 IU, the dose setting of the Pen would be 50 + 2 marks which is actually 66.3 IU. The table has inaccuracies and is incomplete. The Pen-injector dose equivalent and pen setting that would approximate the 375 IU of Follistim® was omitted. The Pen-Injector equivalent and the Pen-Injector Setting for the Follistim® dose of 37.5 IU is not included. The footnote to the table indicates that each dose increment of 25 IU is divided into 2 smaller increments of 8.3 IU when it is actually divided into 3 smaller increments of 8.3 IU, each indicated by a mark on the dosage scale. The concept of having the patient make a dose setting correction on a pen, in order to administer the appropriate dose of medication prescribed by her physician, places an inappropriate burden on that patient. The proposed dosage and administration section of the labeling has the potential for confusion for both the physician and the patient and could lead to dosing errors. The physician would also need to have ready access to the conversion table any time that a call is received from or placed to a patient. This is not practical for clinical practice.

The revised draft labeling for Follistim®-AQ Cartridge and Pen-Injector (submitted 10/30/2000) is basically that of Follistim® which the company has adapted for use with the new formulation (including the conversion table). The labeling has numerous inaccuracies. For instance, the starting dose for the indication of ART for Follistim®-AQ Cartridge is given as 150 to 225 IU for at least the first 4 days. This is actually the starting dose for Follistim®. The correct dose for Follistim®-AQ would be 125 to 175 + 1 mark IU. Under ovulation induction, the starting dose listed is also that for Follistim® and not Follistim®-AQ Cartridge. The dose of Follistim® for ovulation induction can be adjusted by 37.5 IU increments. The conversion table does not provide for the appropriate pen injector units to achieve these adjustments.

The instruction manual for the patient, which was submitted to the Agency on September 28, 2000, consists of 23 pages with 7 steps of instructions for use (11 pages) and 5 pages devoted to how to address problems with administration ("If There Is Not Enough Drug" and "How to Eliminate Difficulties"). This manual is unduly cumbersome and no doubt would be a difficult and potentially unsafe (because of its complexity) for patients to follow.

The Follistim®-AQ Cartridges and Pen-Injector device consists of 15 parts and requires the patient handling and assembly before a dose can be administered. The device requires that the patient be able to set the pen to a numerical indicator as well as discern audible clicks in order to deliver the correct dose. The device allows for the selection of up to 54 different dosages. The conversion table submitted by the sponsor lists the approximate equivalent for the cake formulation delivered via conventional syringe for only 5 of these possible doses. The review of the Pen-Injector device by the Center for Devices and Radiological Health-Division of Dental, Infection Control and General Hospital Devices did not support the high accuracy of the Pen-Injector as represented by the Sponsor. This review concluded that a determination of the safety and efficacy of the device could not be made from the information provided in the NDA.

The Follistim®-AQ Cartridge and Pen-Injector offers no advantage to physician or patient. The conversion table is inaccurate and incomplete and is not applicable to all patients. It is felt that the use of this conversion table would lead to prescribing errors. The instruction manual is burdensome and not simple and easy to follow, as a patient instruction manual should be. The device itself is cumbersome to assemble and insufficient information was included in the NDA and the device master file to determine if it is safe and effective.

I concur with the recommendations of the clinical and chemistry reviewers that this NDA should not be approved.

 , MD, MPH 11/27/00
Shelley R. Slaughter, MD, Ph.D.
Reproductive Medical Team Leader

cc: Division File NDA 21-149

S. Allen, MD, MPH

D. Shames, MD

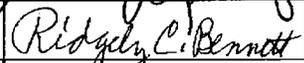
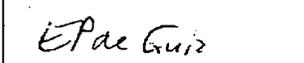
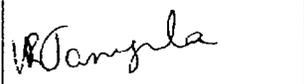
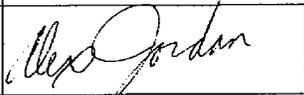
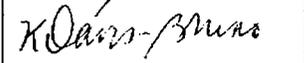
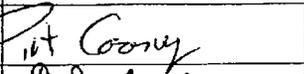
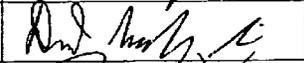
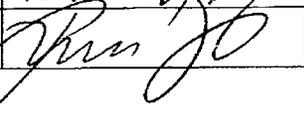
R. Bennett, MD, MPH

V. Jurugula, Ph.D.

E. Deguia

S. Slaughter, M.D., Ph.D.

NDA 21-211
Follistim - AQ (follitropin beta for injection) Cartridge
Organon, Inc.

Name	Title	Signature	Date
Susan Allen, M.D., M.P.H.	Senior Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)		11/29/00
Daniel Shames, M.D.	Senior Deputy Director, DRUDP (HFD-580)		11/23/00
Shelley Slaughter, M.D. Ph.D.	Medical Team Leader, DRUDP (HFD-580)		11/23/00
Ridgely Bennett, M.D.	Medical Officer, DRUDP (HFD-580)		11/21/00
Terri Rumble	Chief, Regulatory Project Management Staff, DRUDP (HFD-580)		11/24/00
Eufrecina DeGuia	Regulatory Project Manager, DRUDP (HFD- 580)		11/29/00
Ameeta Parekh, Ph.D.	Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)		11/21/00
Venkat Jarugula, Ph.D.	Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)		11/21/00
Alex Jordan, Ph.D.	Pharmacology Team Leader, DRUDP (HFD-580)		11/22/00
Karen Davis-Bruno, Ph.D.	Pharmacologist, DRUDP (HFD-580)		11/21/00
Moo-Jhong Rhee, Ph.D.	Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP; (HFD-580)		11/27/00
Peter Cooney, Ph.D.	Associate Director, ONDC (HFD-805)		11/21/00
David Lin, Ph.D.	Chemistry Reviewer, DRUDP(HFD-580)		11/27/00
Bryan Riley, Ph.D.	Microbiology Reviewer, ONDC (HFD-805)		11-21-00

/s/

Shelley Slaughter
11/27/00 05:03:58 PM
MEDICAL OFFICER

NOV 14 2000

1

Medical Officer's Original NDA Review

NDA Number: 21,211

Applicant: Organon, Inc.
375 Mount Pleasant Avenue
West Orange, New Jersey 07052
(973) 325-4833

Date of Submission: January 28, 2000

Date of Receipt: January 31, 2000

Date Review Completed: November 13, 2000

I. General Information:

A. Name of Drug:

1. Established Name: Follitropin beta for injection
2. Trade Name: Follistim® - AQ Cartridge
3. Laboratory Code Name: Org 32489

B. Pharmacologic Category:

Follicle stimulating hormone prepared by recombinant DNA technology

C. Proposed Indications:

1. Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program.
2. Induction of ovulation in the anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure.

D. Dosage Form:

Sterile, clear, colorless aqueous solution filled into ready-for-use disposable cartridges intended to fit Becton-Dickinson Follistim® Pens for adjustable administration.

E. Strength: 833 IU FSH per mL.

- F. Active Ingredient: Follicle stimulating hormone (recombinant)
- G. Prescription or OTC: Prescription
- H. Related Drug:

Follistim® is currently formulated and marketed as a freeze-dried product, to be administered after reconstitution with water for injection.

I. Dosages Recommended:

1. Assisted Reproductive Technologies:

A starting dose of 150 to 225 IU of follitropin beta for injection is recommended for at least the first four days of treatment. After this, the dose may be adjusted for the individual patient based upon their ovarian response. In clinical studies it was shown that maintenance dosages ranging from 75 to 375 IU for six to twelve days are sufficient, although longer treatment may be necessary. The maximum, individualized, daily dose of Follistim® that has been used in clinical studies is 600 IU. When a sufficient number of follicles of adequate size are present, the final maturation of the follicles is induced by administering hCG at a dose of 5,000 IU to 10,000 IU. Oocyte retrieval is performed 34 to 36 hours later. The administration of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of Follistim® therapy; this will reduce the chance of developing OHSS.

2. Ovulation Induction:

Treatment usually starts with a 75 IU daily dose of Follistim® which is continued for at least 14 days. If there is no ovarian response, the daily dose will then be increased by 37.5 IU of Follistim® at weekly intervals until follicular growth and/or serum estradiol levels indicate an adequate response. The maximum individualized, daily dose of Follistim® that has been safely used for ovulation induction in patients during clinical trials is 300 IU. The patient should be treated until ultrasonic visualizations and/or serum estradiol determinations indicate pre-ovulatory conditions equivalent to or greater than those of the normal individual followed by hCG, 5,000 IU to 10,000 IU. If the ovaries are abnormally enlarged on the last day of Follistim® therapy, hCG must be withheld during this course of treatment; this will reduce the chances of developing OHSS.

During treatment with Follistim® and during a two week post-

treatment period, patients should be examined at least every other day for signs of excessive ovarian stimulation. It is recommended that Follistim® administration be stopped if the ovaries become abnormally enlarged or abdominal pain occurs. Most OHSS occurs after treatment has been discontinued and reaches its maximum at about seven to ten days post-ovulation.

J. Therapeutic Class: Infertility

II. Manufacturing Controls: Please refer to chemist's review for details.

III. Pharmacology: Please refer to pharmacologist's review for details.

IV. Clinical Background:

Follistim® was approved in the United States September 29, 1997. Outside of the United States follitropin beta injection is known as Puregon and is marketed widely throughout most of the world.

V. Regulatory Background:

A. Organon came to the FDA March 18, 1999 for a pre-NDA guidance meeting to discuss the specific concerns regarding a completed bioequivalence study to support the approval of a new pharmaceutical presentation of Follistim®. The currently approved Follistim® is formulated as a freeze-dried cake to be administered after reconstitution with water for each injection. The new formulation, called Follistim® - AQ Cartridge, is formulated as an injectable aqueous solution of 300 IU and 600 IU of follitropin beta in a multidose cartridge, to be administered with a pen-injector device. The completed bioequivalence study compared a single dose of 150 IU of Follistim® administered subcutaneously with a syringe with a single dose of 150 IU of Follistim®-AQ Cartridge administered subcutaneously with a pen-injector device. The results were non-equivalent.

Organon stated that the pen-injector accurately delivered the dose to which it was set whereas the conventional syringe, due to filling, removing of excess air and the dead volume of the syringe, actually delivered an amount of follitropin beta that on average was lower than the nominal dose of 150 IU and that due to the high accuracy and precision of the device, pen-injector dosing resulted in an approximately 18% higher dose than the conventional syringe.

Organon used a "dose correction factor" which resulted in the two formulations being declared equivalent by them after normalization of the pharmacokinetic data for the dose of reconstituted Follistim® actually administered.

Several approaches to resolve the bioequivalence issues were identified:

- the sponsor could address the differences in the dose delivered by the two formulations by conducting another bioequivalence study after altering the dose delivered by the Pen-Injector to match the dose delivered by the cake formulation
- a significant risk could exist for patients who switch from cake to pen or vice versa; this issue should be addressed by providing a justification for the use of either product and allowing the physician to decide the choice of the product, dose and mode of administration
- since it would be difficult to change the label of the approved product, the delivery volume should be clearly addressed in the labeling for the new formulation administered by the pen-injector device

B. An NDA for Follistim®-AQ Cartridge was submitted January 28, 2000.

Organon stated that performing another bioequivalence study in which the dose delivered by the pen is reduced to match the dose delivered by the syringe (prospective correction) would confirm that the Pen-Injector has a higher level of accuracy of administration. They had already demonstrated this fact once, they said.

Modifying the Pen-Injector dial scale to decrease the actual delivered dose to the low accuracy level of the conventional syringe (keeping the nominal dose, however, identical) would lead to extremely confusing situations, but Organon did not enumerate any confusing situations.

Therefore, Organon chose to pursue the approach to address the clinical relevance of the difference between administering Follistim® - AQ (follitropin beta for injection) Cartridge with a Pen-Injector and administering reconstituted Follistim® (follitropin beta

for injection) with a syringe. It was their opinion that the observed difference of 18% is not expected to be clinically noticeable, particularly when the pen-injector device is used exclusively throughout a treatment cycle.

If the treatment cycle is started with the pen-injector device and a switch is made at the end of the cycle to the conventional syringe to give the final injections (e.g., in cases where it is not economical to continue with a new cartridge), a correction should be made because actually a somewhat lower dose would be administered with the syringe than the dose set with the pen-injector device. Organon states that this is of little relevance because at the end of the cycle when the follicles are more advanced in development, they are more susceptible to FSH and so their requirement for FSH becomes less.

Organon does agree that if a physician first determined the appropriate dose using the conventional syringe and then switched to the pen-injector device during the cycle, it would be appropriate to correct the dose in order to prevent administration of too high a dose.

Organon proposed handling the observed 18% higher dose with the pen-injector device by adding the following statement to the PRECAUTIONS section of the labeling:

"Changes in brand (manufacturer), type (recombinant, urinary, etc.), and/or method of administration (Pen-Injector device, syringe, etc.) may result in the need to adjust the dose. Therefore, it is recommended that Follistim® - AQ Cartridge and other FSH products not be used interchangeably during a given cycle."

- C. During a teleconference with Organon March 22, 2000, one option discussed was to modify the pen-injector device in such a way that it would equal the dose administered by a conventional syringe. This approach, leading to a discrepancy between nominal and actual dose, was not viable because it conflicts with pertinent International System of Operations guidances.

Organon's argument that the 18% higher dose with the cartridge was not relevant was not acceptable.

Organon proposed a more prominent inclusion in the labeling of the difference in bioavailability between the cartridge/pen-injector device system and the approved vial/conventional syringe product

including a conversion table indicating the numerical relationship between the vial/syringe dose and the dose delivered by the cartridge/pen-injector device system. The table, they said, would allow physicians to make proper adjustment of the dose to correct for the higher bioavailability of the cartridge/pen-injector system. Inclusion of the changes, including the table, they said, should eliminate any confusion that might arise from the difference in bioavailability.

- D. On March 29, 2000 Organon proposed adding the following text and table to the labeling:

- E. On September 28, 2000 Organon submitted an instruction manual for the Follistim® pen-injector.
- F. On October 30, 2000 Organon submitted revised draft labeling.

VI. Consultations:

Please refer to Office of Post-Marketing Drug Risk Assessment Consultation Responses 00-0134 and 00-0263 and Center for Devices and Radiological Health Consultation Response. They have safety concerns regarding the proposed packaging configuration and pen-injector delivery system.

VII. Foreign Registration:

An application was submitted to the 15 European Union member states via the centralized procedure November 25, 1998. The CPMP gave scientific approval September 23, 1999. Formal marketing authorization was expected in January 2000. An application has also been submitted to Canada, Ireland, New Zealand, Norway, and Switzerland.

VIII. Clinical Studies:

None. The only study performed is study 37626, a pharmacokinetic study to determine whether FSH pharmacokinetics after subcutaneous administration of follitropin beta by a pen-injector device containing a ready-for-use solution in a cartridge were bioequivalent to those after subcutaneous injection by conventional syringe containing a dissolved cake. Please refer to our pharmacokineticist's review of this study for details.

IX. Reviewer's Overall Evaluation and Conclusions:

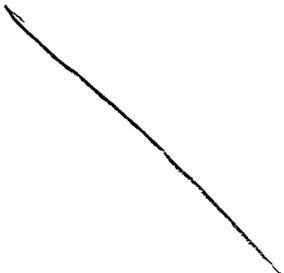
Organon submitted this NDA for what it calls a new pharmaceutical presentation of the approved Follistim®. The currently approved product is formulated as a freeze-dried cake, to be administered as a single dose after reconstitution with water for injection. The subject of this NDA is an injectable aqueous solution of 300 IU and 600 IU follitropin beta in a multidose cartridge, to be administered with a pen-injector device. Organon considers a multidose ready-to-use presentation to be more convenient and to require less handling than the approved product. The use of the pen-injector device provides a more accurate and precise method of dosing as compared to the conventional syringe according to Organon. This allows greater dosing flexibility and a more subtle treatment of hyper responders.

Organon seeks approval of Follistim® - AQ Cartridge based on a bioequivalence study with Follistim®, the approved product. In this study, the pharmacokinetics of Org 32489 after subcutaneous administration of two different formulations were compared for bioequivalence. A single

dose of Org 32489 was either injected by syringe (two vials of 75 IU of Org 32489 reconstituted in one mL solvent) or by Pen-Injector (ready -for-use solution containing 150 IU of Org 32489). Because of the mode of administration, it was assumed that exactly 150 IU was injected by Pen-injector. For injection by syringe, measurements of the weights of the syringe just before and after Org 32489 injection showed that the actually injected amount of Org 32489 was lower than the anticipated amount. Loss of Org 32489 solution can be attributed to the void volume of the syringe, and losses while filling the syringe or removing excess air. In this study, Follistim® - AQ resulted in 20% higher AUC than the approved Follistim® and the two formulations were found to be not bioequivalent. The higher bioavailability with the pen-injector device is a safety issue. The two formulations were declared bioequivalent after dose correction following normalization of the pharmacokinetic data for the dose of reconstituted Follistim® actually administered. The assumed accuracy and precision of the pen-injector device should be evaluated by our Center for Devices and Radiological Health. Accepting for the moment that the accuracy and precision of the pen-injector device as presented is true, the conversion table to be used in adapting the dose from the vial/syringe presentation to the cartridge/pen-injection device system was evaluated and assessed.

The conversion table proposed by Organon March 29 may be alright to include in the clinical pharmacology section of the labeling but I don't think it is appropriate for the dosage and administration section. It relates only calculated dosages based on data from one bioequivalence study which is not applicable to all patients and is unsupported by clinical trial data. It does not state a recommended dosage regimen which is the usual kind of information found in dosage and administration sections of labeling.

The multidose pen-injector is considered by Organon to be more convenient than the approved product "since its use requires less handling". This has not been documented by a head to head comparison of the two methods of administration. Such an assessment is desirable.



Even then, the dose is not accurate. A patient who wished to take 75 IU

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

0 § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

XI. Conclusions:

The proposed conversion table for the observed difference in dose administered by the cartridge pen-injector device and the vial syringe is confusing, complex, inaccurate, and unacceptable. The pen-injector device is also confusing with its _____ of instructions and a dosing scale of numbers plus marks and audible clicks and is a safety concern.

XII. Recommendations:

Approval of this application is not recommended.

It is recommended that the applicant conduct actual clinical studies utilizing the cartridge pen-injector device to determine the correct dosages and the safety and efficacy of the product to be marketed and to determine patient comprehension of the directions to follow in the administration of the drug dosages.

Ridgely C. Bennett
Ridgely C. Bennett, M.D., M.P.H.

I concur

Stacy R. [Signature]

11/14/02

NDA 21-211
Follistim® - AQ (follitropin beta injection)
Organon, Inc.

Safety Update Review

No Safety Update was submitted to this NDA. See sponsor's correspondence dated November 16, 2000.

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_____ § 552(b)(4) Trade Secret / Confidential

2 § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process