

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-684

MEDICAL REVIEW(S)

Gonal-f® RFF Pen (follitropin alfa injection)
Team Leader Review – Cycle 2

NDA: 21-684

Drug: Gonal-f® RFF Pen (follitropin alfa injection)

Indication:

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

Dosage/Form/Strength:

- A. One Gonal-f® RFF Pen (a prefilled drug delivery system) with 0.5 mL to deliver a minimum of 300 IU (22µg) and 5 single-use disposable 29G x ½” needles
- B. One Gonal-f® RFF Pen (a prefilled drug delivery system) with 0.75 mL to deliver a minimum of 450 IU (22µg) and 7 single-use disposable 29G x ½” needles
- C. One Gonal-f® RFF Pen (a prefilled drug delivery system) with 1.5 mL to deliver a minimum of 900 IU (22µg) and 14 single-use disposable 29G x ½” needles

Applicant: Serono, Inc

Original Receipt Date: July 29, 2003

Primary Review Completed: November 25, 2003

Team Leader Memorandum: November 25, 2003

Decision Following First Cycle Review Complete Response: March 25, 2004

Cycle 2 Primary Review: March 26, 2004

Date of this Memorandum: May 24, 2004

May 25, 2004

Background

Gonal-f® 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. The original formulation for Gonal-f® is a lyophilized formulation (filled by IU) for reconstitution with water for injection. As part of a Phase 4 commitment to ensure stability of the product, the Sponsor modified the original formulation by adding methionine and polysorbate 20. This revised formulation was manufactured using fill-by-mass technology. To link the filled-by-mass revised

formulation to the original formulation filled-by-IU formulation, the Sponsor conducted two clinical pharmacology studies, IMP 218159 and 22596, to demonstrate bioequivalence. However upon review by the Office of Clinical Pharmacology and Biopharmaceutics, the two formulations were determined not to be bioequivalent.

At a May 5, 2003 meeting with the Division, the Sponsor proposed submission of two previously completed clinical studies in women to support approval for the filled-by-mass revised formulation. The sponsor also requested to concurrently submit an application for a liquid revised formulation of follitropin alfa (filled-by-mass) to be supported by bioequivalence to the lyophilized filled-by-mass revised formulation of follitropin alfa. The Sponsor was told that they could do so at their own risk in that the outcome of the application for the liquid formulation of follitropin alfa (filled-by-mass) would be dependent upon a successful outcome (approval) of the lyophilized filled-by-mass revised formulation of follitropin alfa.

The application for the liquid revised formulation (filled-by-mass) was submitted on July 29, 2003 supported by a single bioequivalence study, Study 23572 comparing the liquid filled by mass revised formulation of follitropin alfa with the lyophilized filled-by-mass revised formulation of follitropin alfa. The application received a Not Approvable decision on November 23, 2003. This decision was based on the findings that a non-approved drug product (the lyophilized filled-by-mass revised formulation) was used as the reference product in Study 23572, the supporting bioequivalence study.

NDA 21-765 for the lyophilized filled-by-mass revised formulation of follitropin alfa was submitted as NDA 20-378/S-32 on May 28, 2003. This NDA was under review during the original review cycle of NDA 21-684. NDA 21-765 received an Approval on March 25, 2004

Chemistry/Manufacturing

See CMC review # 1 and #2 in the original review cycle. See also CMC review # 3 for the second cycle.

Product Name

The Division of Medical Errors and Technical Support (DMETS) has recommended against the proprietary names for the liquid revised formulation (or the lyophilized formulation) of follitropin alfa that combine a modifier with the tradename Gonal-f®. See DMETS consults dated March 26, 2004 and May 14, 2004. Serono proposed Gonal-f® - or Gonal-f® - as the proprietary name for the lyophilized revised formulation. The company further proposed that the word Pen be added to the designated modifier as the proprietary name for the liquid formulation delivered by pen injector. DMETS rejected these proprietary names stating that the modifiers did not convey to the practitioner the differences between the revised formulation and the original formulation. Further that the modifiers inferred that a

The Sponsor subsequently submitted four proposed names: Gonal-f® - , Gonal-f® - Gonal-f® - , or Gonal-f® - . DMETS recommended against these, stating that all the modifiers describe characteristics of the new vial presentation and the benefits that this presentation will offer to patients and healthcare practitioners, but do not communicate that the revised formulation

(s) and the original formulation can not be interchanged, are not indicated for use in the same population or dosed the same for all of the indications of use.

Pre-clinical Pharmacology and Toxicology

See Pre-clinical Pharmacology and Toxicology review in the original review cycle

Division of Scientific Investigations (DSI)-Clinical Inspection Summary

DSI inspected

the laboratories that conducted the clinical and analytical portions of Study 23572 (bioequivalence trial). The following deficiencies were noted:

1. Failure to consistently follow the protocol down-regulation criterion.
2. Failure to retain reserve samples of the test drugs in unit dose packets.
3. Assay accuracy at the low range was not demonstrated.
4. Matrix interferences was not sufficiently demonstrated.

DSI recommended that the subject concentration data not be accepted for Agency review until the issues of assay accuracy delineated under items 3 and 4 are successfully addressed. They further recommended that data from two subjects, #1114 and # 1116, be excluded from the study to address item 1.

Additional data was provided by _____ to support assay performance. DSI concluded that the additional data did not resolve the issue of assay performance at the low range for this study and, therefore, upheld their earlier recommendation.

Biopharmaceutics

For the approval of this multidose liquid formulation intended to be delivered by pen-injector, the Sponsor conducted a bioequivalence study to establish equivalency between this test formulation and a reference formulation (lyophilized revised formulation filled-by-mass), which was approved under NDA 21-765 on March 24, 2004. See the Office of Clinical Pharmacology and Biopharmaceutics review in the original review cycle.

The Biopharmaceutic reviewers concluded that the liquid filled-by-mass revised formulation delivered by pen injector is bioequivalent to the lyophilized filled-by-mass revised formulation.

A DSI inspection of the bioequivalence study, Study 23572, was requested because this study formed the basis for request for approval of the liquid formulation. The DSI report, as presented above, noted several deficiencies. However, OCPB determined that the deficiencies did not compromise the findings or integrity of the study. The OCP reviewer determined:

- The Matrix effect on the samples that may have affected the analysis of the lower range of the samples (0.5 – 5 IU/L) was similar on both the treatment arms (test and reference), and hence, neutralized the error (if any)
- The two subjects who were violators of the inclusions criteria had C_{max} and AUC values well within the range of the observations from the other subjects, and may not affect the outcome of the BE Study.

Therefore, based on the above OCPB has elected not to follow the DSI recommendation and accepts the results of the Bioequivalence study and concludes that the two (reference and test) formulations are bioequivalent.

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 the follitropin alfa Pen was submitted in this NDA. The Sponsor based the application on a bioequivalence study that compared the liquid revised formulation of follitropin-alfa (filled-by-mass) to the lyophilized revised formulation of follitropin alfa (filled by mass). The two products were assessed to be bioequivalent. During the original review the reference drug product (lyophilized filled-by-mass revised formulation) was not an approved drug product. The referenced drug product, the lyophilized filled-by-mass revised formulation was approved under NDA 21-765 on March 25, 2004 thus clearing the way for a complete response resubmission of NDA 21-684. DSI noted some deficiencies on inspection of the laboratory site that conducted Study 23572, the bioequivalence study. However, OCPB has determined that these deficiencies do not compromise the findings of the study. Therefore, I recommend approval of the liquid revised filled-by-mass formulation of follitropin-alfa based on its bioequivalence to the lyophilized revised-filled-by-mass formulation of follitropin alfa.

The agreed upon label is appended to this review. DMETS for the reasons stated above had recommended that the proprietary name Gonalf® not be included with a modifier as the proprietary name and that a totally new name be selected. The clinical reviewing team determined that the modifier RFF (revised formulation for female) is a modifier that would catch the prescriber's or patient's attention and prompt them to read the label; thus facilitating recognition of the differences between the revised formulation of follitropin alfa and the original formulation. This modifier, along with the educational piece proposed by Serono to apprise practitioners of the difference between the two formulations, was agreeable to both FDA and the Sponsor.

Shelley R. Slaughter, MD, Ph.D.
Reproductive Medical Team Leader

cc: Division File NDA 21-684
D. Shames, MD
A. Gassman, MD
S. Al-Habet, Ph.D.
D. Chatterjee
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/s/

Shelley Slaughter
5/25/04 04:47:26 PM
MEDICAL OFFICER

Daniel A. Shames
5/25/04 05:00:13 PM
MEDICAL OFFICER

Gonal-f® RFF Pen (liquid follitropin alfa formulation in a pen-injector device)

MEMORANDUM OF REVIEW

SUBMISSION DATE: March 26, 2004
FROM: Audrey Gassman, M.D. (HFD-580)
THROUGH: Shelley Slaughter, M.D., Ph.D. Team Leader (HFD-580)
RE: Review of Complete Response to Not Approvable Letter for NDA 21-684 (Gonal-f® RFF Pen)

NDA: 21-684 **Serial:** N-000
Sponsor: Serono, Inc.
Type of Submission: Commercial NDA
Trade/Established Names: Gonal-f® RFF Pen (follitropin alfa for injection)
Drug Dosage: A. One Gonal-f® RFF pen-injector (a prefilled drug delivery system) with 0.5 mL to deliver a minimum of 300 IU and 5 single-use disposable 29G x ½” needles
B. One Gonal-f® RFF pen-injector (a prefilled drug delivery system) with 0.75 mL to deliver a minimum of 450 IU and 7 single-use disposable 29G x ½” needles
C. One Gonal-f® RFF pen-injector (a prefilled drug delivery system) with 1.5 mL to deliver a minimum of 900 IU and 14 single-use disposable 29G x ½” needles
Route of Administration: Delivered by subcutaneous injection
Proposed Indications: Women: Gonal-f® RFF 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. Gonal-f® RFF is also indicated for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology program.

Original Submission

Received: March 26, 2004
Date Complete Response Received: March 26, 2004
Review Finalized On: May 25, 2004

Reviewer: Audrey Gassman, MD
Related NDAs: 20-378 Gonal-f® (follitropin alfa for injection)
21-756 Gonal-f® RFF (follitropin alfa for injection)
Related IND: 38,712

Background for NDA 21-684:

The Sponsor has developed a pen-injector device to be used with a new liquid formulation (Gonal-f® RFF) of recombinant human follicle stimulating hormone (r-hFSH) for the treatment of infertile women. The two proposed indications in women for the Gonal-f® RFF Pen (follitropin alfa injection) are identical to the indications for the approved Gonal-f® drug product. The application for the liquid r-hFSH (Gonal-f® RFF Pen) was submitted with a single clinical bioequivalence study (23572) comparing the liquid filled-by-mass formulation of Gonal-f® RFF with the lyophilized filled-by-mass Gonal-f® formulation in 44 total subjects.

The sponsor had planned to submit this application for a liquid formulation of Gonal-f® RFF (r-hFSH in a filled-by-mass formulation) in a pen-device using one clinical pharmacology study that demonstrated equivalence to a new lyophilized Gonal-f® RFF formulation (filled-by-mass). However, the application for the lyophilized formulation depended on two pharmacokinetic studies (IMP 218159 and 22596) designed to demonstrate bioequivalence of the new lyophilized filled-by-mass formulation of r-hFSH to the approved Gonal-f® product. The Biopharmaceutics Division reviewed studies IMP 21859 and 22596 and determined that the new lyophilized r-hFSH formulation was **not** bioequivalent to the approved Gonal-f® formulation (review date November 30, 2001). The sponsor was informed of this lack of bioequivalence at a December 2002 meeting. The sponsor requested an additional meeting with the Division to discuss the lack of bioequivalence between the new r-hFSH filled-by-mass formulation (Gonal-f® RFF) and the approved Gonal-f® formulation.

A meeting with the Division was held May 5, 2003. At the May meeting, the sponsor proposed submission of two completed clinical studies in women to evaluate therapeutic equivalence of the new r-hFSH formulation (filled by mass) to the currently approved formulation of Gonal-f®. The Division agreed to evaluate the two phase III clinical studies (Studies 21884 and 22240) and the clinical data from the studies was submitted electronically on May 28, 2003. The protocols for Studies 21884 and 22240 were originally submitted March 17, 2000 (IND 38,712 – serial number 083) and February 20, 2001 (IND 38,712 – serial number 094), respectively. The sponsor requested to submit the application for the liquid formulation of Gonal-f® RFF in a pen-device (NDA 21-684) concurrently with the application for the lyophilized r-hFSH filled-by-mass formulation (NDA 21-765). The Sponsor was told that they could do so at their own risk in that the outcome of the application for the Gonal-f® RFF liquid was dependent upon a successful outcome of the lyophilized filled-by-mass r-hFSH product (NDA 21-765).

Background for NDA 21-684 (continued):

A Not Approvable Letter was sent to the Sponsor on November 25, 2003 for liquid formulation of Gonal-f® RFF (r-hFSH in a filled-by-mass liquid formulation) with the following deficiencies noted:

1. A non-approved product (the fill-by-mass lyophilized product was used as the reference product in Study 23572, the bioequivalence trial submitted to support this NDA.
2. Inspection of the clinical trial site for Study 23572 was pending.

The application for NDA 21-765 (the reference product) was approved on March 25, 2004. The sponsor submitted a complete response with draft labeling that incorporated requested changes to NDA 21-765.

Reviewer's comment:

1. **The bioequivalence study (23572) to support the application for Gonal-f® RFF Pen was previously reviewed (See Review Memorandum for NDA 21-684 No. 000 dated November 25, 2003. No clinically significant adverse events or abnormal laboratories were noted in this bioequivalence study for this liquid r-hFSH formulation.**

Labeling:

- A revised label for the Gonal-f® RFF Pen (NDA 21-684) was submitted based on the labeling for NDA 21-765 (See Appendix 1). The label for Gonal-f® RFF in a pen-injector is identical to the current label for the fill-by-mass formulation (NDA 21-765) except for the directions to use the pen-injector device.
- The Patient Package Insert has been re-reviewed and comments have been sent to the sponsor (See Appendix 2).

Reviewer's comments:

1. **A copy of the proposed label is attached to this review and is acceptable. (See Appendix)**
2. **An ODS consult dated October 15, 2003 has made a number of proposed changes to patient package insert (PPI) labeling for the Gonal-f® RFF Pen.**

The Medical Officer concurs with the overall recommendations of ODS.

Overall recommendation:

- **The lyophilized filled-by-mass formulation of r-hFSH, the reference drug product for the bioequivalence study (23572), is now an approved drug product. Recommend that the liquid filled-by-mass drug product in a pen-injector be approved.**
- **The following changes are recommended for the proposed physician label (Appendix 1) and patient package insert (Appendix 2) for Gonal-f RFF in a pen-injector. These changes were sent to the sponsor in an information request letter for NDA 21-684 (dated May 10, 2004)**

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/s/

Audrey Gassman
5/25/04 01:40:42 PM
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Shelley Slaughter
5/25/04 02:00:13 PM
MEDICAL OFFICER
I concur.

Gonal-f Pen®
Team Leader Review

NDA: 21-684

Drug: Gonal-f® Pen(follitropin alfa for injection)

Indication:

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

Dosage/Form/Strength:

- A. One Gonal-f® Pen (a prefilled drug delivery system) with 0.5 mL to deliver a minimum of 300 IU (22µg) and 5 single-use disposable 29G x ½” needles
- B. One Gonal-f® Pen (a prefilled drug delivery system) with 0.75 mL to deliver a minimum of 450 IU (22µg) and 7 single-use disposable 29G x ½” needles
- C. One Gonal-f® Pen (a prefilled drug delivery system) with 1.5 mL to deliver a minimum of 900 IU (22µg) and 14 single-use disposable 29G x ½” needles

Applicant: Serono, Inc
Original Receipt Date: July 29, 2003
Review Completed: November 25, 2003
Date of Memorandum: November 25, 2003

Background

Gonal-f® 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. The original formulation for Gonal-f® is a lyophilized formulation (filled by IU) for reconstitution with water for injection. As part of a Phase 4 commitment to ensure stability of the product, the Sponsor modified the original formulation by adding methionine and polysorbate 20 as — This revised formulation was manufactured using fill-by-mass technology. To link the filled-by-mass revised formulation to the original formulation filled-by-IU formulation, the Sponsor conducted two clinical pharmacology studies, IMP 218159 and 22596, to demonstrate bioequivalence. However upon review by the Office of Clinical Pharmacology and Biopharmaceutics, the two formulations were determined not to be bioequivalent.

At a May 5, 2003 meeting with the Division, the Sponsor proposed submission of two previously completed clinical studies in women to support approval for the filled-by-mass revised formulation. The sponsor also requested to concurrently submit an application for a liquid formulation of Gonal-f® (filled-by-mass) to be supported by bioequivalence to the lyophilized filled-by-mass revised formulation of Gonal-f®. The Sponsor was told that they could do so at their own risk in that the outcome of the application for the Gonal-f® liquid formulation would be dependent upon a successful outcome (approval) of the lyophilized filled-by-mass Gonal-f® revised formulation.

The clinical data from Studies 21884 and 22240, two phase 3 non-inferiority studies to support the indications of multiple follicular development for IVF and ovulation induction, respectively were submitted electronically as NDA 20-378/S-32 on May 28, 2003. This NDA is currently under review.

This application for the Gonal-f® liquid formulation (filled-by-mass) was submitted on July 29, 2003 supported by a single bioequivalence study, Study 23572 comparing the liquid filled by mass formulation of Gonal-f® with the lyophilized filled-by-mass Gonal-f® revised formulation.

Chemistry/Manufacturing

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

The drug substance, follitropin alfa, 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 20-378. Since the approval of the NDA, there have been no significant manufacturing changes in the currently approved drug substance manufacturing process.

The drug product is a new sterile aqueous solution formulation. The solution dosage form is packaged in sterile pre-filled cartridges which are assembled into disposable, multi-dose, pen injectors at the manufacturing site. The solution drug product contains Poloxamer 188 USP, sucrose NF, methionine USP, m-cresol USP, 0-phosphoric acid USP, sodium hydroxide USP and

The drug product is packaged in a pre-filled multi-dose disposable pen-injector, which is enclosed in a carton with 29 G x 0.5 in. needles. The pen injector features an adjustable dosing system for administering the drug [see Center for Devices and Radiological Health review (CDRH)]. Each pen injector delivers at minimum the labeled dosage strength of 300 IU, 450 IU or 900 IU. Inside each pen-injector is a glass cartridge pre-filled with the solution product. At one end, the cartridge barrel is closed with a plunger stopper. At the other end, the cartridge barrel is closed by a crimp-cap. The assembly of the pre-filled cartridge and pen-injector is completed at the manufacturing site.

Expiry

12 months at 2-8 °C (includes the option of storing at 20-25 °C for up to one month or until expiry, whichever occurs first). This expiry is based on satisfactory data at 5 °C and data at 25 °C for 6 batches (2 batches for each dosage strength), and

1 month at room temperature during use and with the 12-month expiry. This in-use storage is based on satisfactory — data at 25 °C with used pen injectors (puncture) closures from 4 batches (2 batches of 300 IU and 2 batches of 900 IU) and satisfactory — data at 25 °C for 1 developmental batch (closed pen injectors with and without the outside carton).

A recommendation for approval was made by CDRH on the pen-injector of September 16, 2003. The Microbiology reviewers made a recommendation for approval. The three manufacturing sites subject to inspection were all recommended for acceptance

From the Chemistry, Manufacturing and Controls perspective, the NDA is approvable.

Product Name

The Division of Medical Errors and Technical Support specified (see consult November 7, 2003) that from a safety perspective, there was no objection to the use of the name Gonal-f® Pen.

Pre-clinical Pharmacology and Toxicology

The introduction of methionine —, the replacement of polysorbate 20 by Poloxamer 188 —, and the replacement of the — benzyl alcohol, by m-cresol did not affect the local tolerance profile of the drug product in a local tolerance study done in rabbits. Since the liquid formulation contains r-hFSH similar to that used in the approved lyophilized powder formulation (NDA20-378), and as the dosage and dosing regimens are identical to that of the approved Gonal-f® formulation, Pharmacology recommends approval of the formulation of Gonal-f®.

Biopharmaceutics

For the approval of this multidose liquid formulation intended to be delivered by pen-injector, the Sponsor conducted a bioequivalence study to establish equivalency between the reference formulation (lyophilized revised formulation filled-by-mass), which is currently under review (NDA 20-378, S-032) and the new multidose liquid formulation (test). The reference formulation B (lyophilized powder filled-by-mass) is not bioequivalent to the approved formulation (lyophilized powder filled-by-IU).

The bioequivalence study was conducted by administering with syringe and needle, a single dose of 300 IU (20 µg) of r-hFSH for the reference and the test formulation. The study was conducted in 44 subjects comprised of 22 males and 22 females. Prior to receiving r-hFSH, both female and male subjects received down-regulation of the pituitary with Zoladex® (3.6 mg sc). Down-regulation was confirmed by serum FSH. AUC, C_{max}, and t_{max}, were measured. Adverse events, vital signs and clinical laboratory analysis were documented. The total number of subjects completing the study was 39.

Specific injection volumes were used in the syringes for dosing – 1 mL of the reconstituted lyophilized revised formulation (containing 21.93 µg of r-FSH) vs. 0.480 mL of the liquid formulation (containing 20.08 µg of r-FSH) – both equivalent to 300 IU of r-FSH. The data show that the two formulations are bioequivalent (when both are administered with syringe and needle). The 90% CI was 0.8855, 0.9505 for C_{max} and 0.9222, 0.9810 for AUC_{last}. Based on an additional *in vitro* determination from the bioequivalence study, the expelled dose as measured by

r-hFSH protein content in the reference formulation was 8% higher than the test formulation (as per sponsor's correction provided on 11/4/03).

The intended commercial mode of administration is via a pen-injector, a device that was not used in the bioequivalence study as noted above. Hence, an essential component of the equivalence is to establish that similar volumes used for the liquid formulation in the bioequivalence study could be reproduced by the 'to-be-marketed' pen-injector (all other components of the formulations remain same). To establish this, the Sponsor conducted an *in vitro* study in which they measured expelled volumes from the injector pen at different temperatures. They used 37.5, 225 and 450 IU dose settings for determining the performance of the expelled volumes. The injector pens were weighed before and after each injection, and density of an expelled placebo solution (all components other than the drug) was used to convert the weight to the volume. All volumes were within the specification range (ranging $\pm 17\%$ for the 37.5 IU dose and $\pm 5\%$ for the higher doses). The volume expelled by the injector when set to 300 IU was calculated to be 0.483 mL [similar to the target volume of 0.48 mL (most of the values injected were between 0.481 – 0.495 mL) injected in the bioequivalence study with syringes. Similar results were also obtained when the study was repeated at other temperature conditions. The results show that the pen-injector is consistent in its ability to expel the intended volume.

The Biopharmaceutic reviewers have determined that the Sponsor has provided adequate evidence to prove that the pen-injector can predictably, accurately and reproducibly inject target volumes of the drug solution from different device settings and different temperatures. The volume injected from the 300 IU setting is the same as that injected as the liquid formulation from the syringe in the bioequivalence study. Because the bioequivalence study is key to the approval of the liquid formulation (there is no clinical information on the liquid formulation other than limited safety information from this bioequivalence study), an inspection has been requested for this Study 23572 with DSI. The above conclusion of bioequivalence is, contingent upon a satisfactory finding at inspection. The inspection is pending at the time of this review.

The overall adverse event incidences for both the lyophilized filled-by-mass revised formulation and liquid formulations of r-hFSH are similar to previous clinical studies for the approved Gonal-f® product. All subjects received EKG evaluation. No patients had widening of the PR, QRS or QT intervals with treatment. Eight of forty-four patients (18%) had QTc changes of greater than 30 msec after either treatment. The QTc changes will need further evaluation to determine the significance. The Biopharmaceutics and Clinical reviewers will request details on the conduct of the study and a re-submission of the data with Fridericia corrected values.

The Biopharmaceutic reviewers have concluded that the liquid formulation (solution of r-FSH – subject of the current submission) delivered by pen injector is deemed bioequivalent to the filled-by-mass revised lyophilized formulation from an Office of Clinical Pharmacology and Biopharmaceutics perspective. However, as mentioned above, marketability of the liquid formulation may not be granted until review of NDA 20-378/S-032 is completed and the lyophilized filled-by-mass revised formulation is found to be an acceptable reference.

Division of Scientific Investigations (DSI)-Clinical Inspection Summary

DSI inspection of Study 23572 (bioequivalence trial) is pending.

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 Gonal-f® Pen was submitted in this NDA. The Sponsor supports the application with a bioequivalence study comparing liquid revised formulation of Gonal-f® (filled-by-mass) to the lyophilized filled by mass revised formulation of Gonal-f®. The two products delivered by conventional syringe and needle are deemed bioequivalent. Further an *in-vitro* bridging study has shown that the pen-injector delivers the same volume of the liquid formulation as that delivered by conventional syringe in the bioequivalence trial. However, the reference drug product (lyophilized filled-by-mass revised formulation) is not an approved drug product. The lyophilized filled-by-mass revised formulation is the subject of an ongoing review under NDA 20-378/S-032 and the outcome has not been determined. Therefore, Gonal-f® Pen can not be approved until the lyophilized filled by mass revised formulation has successfully gained approval. The latter can not be accepted as a foregone conclusion. It is my recommendation that the Gonal-f® Pen be given a non-approval because the referenced drug is not approved

Shelley R. Slaughter, MD, Ph.D.
Reproductive Medical Team Leader

cc: Division File NDA 21-684
D. Shames, MD
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Shelley Slaughter
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