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APPLICATION NUMBER:

21-273

MEDICAL REVIEW

Follistim® AQ Liquid

Response to Third Approvable Letter NDA 21-273

Submission Number/Code:	N-000/AZ
FROM:	Audrey Gassman, M.D. (HFD-580)
THROUGH:	Shelley R. Slaughter, M.D., Ph.D. (HFD-580)
RE:	Review of Clinical Safety Update
TYPE OF SUBMISSION:	Commercial-Sponsor
SPONSOR:	Organon Inc. 56 Livingston Avenue Roseland, NJ 07068
Drug Name:	Follistim® AQ liquid/follitropin beta (recombinant follicle stimulating hormone [r-hFSH])
Formulation:	Sterile aqueous solution
Dosing Regimen:	150 to 225 IU of follitropin beta for the first four days of treatment. After this, the dose is adjusted for the individual patient response.
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
Therapeutic Class:	Infertility
Intended Population	Infertility patients
Date of Letter:	June 24, 2005
Date of Submission:	June 27, 2005
Goal Date:	August 26, 2005
Date Review Completed:	August 24, 2005

EXECUTIVE SUMMARY:

From a clinical perspective approval of this application is recommended based on: 1) An acceptable complete response with respect to clinical issues to the most recent Approvable Action letter dated 17-May-05 and 2) the acceptable demonstration of bioequivalence of this drug to that of the previously approved follitropin beta drug product, Follistim® reviewed by the Clinical Team in 2001 (see the Summary of this decision in the Medical Team Leader's Memorandum dated 24-May-01). This recommendation from a clinical perspective is in concurrence with the previous Medical Officer reviews which found the supportive clinical efficacy, safety and post-marketing data acceptable in terms of risk/benefit ratio (See NDA 21-273 Medical Officer clinical reviews dated 16-May-01, 16-Jul-03 and 13-May-05).

No Phase 4 studies are recommended, although the Applicant should continue to submit individual adverse event reports of post-marketing experience obtained where the drug is currently marketed, and monitor these reports for new safety trends.

Summary of Clinical Findings:

The latest clinical safety update submitted by the Applicant (CDER stamp date 27-Jun-05) does not reveal any new efficacy or safety concerns with Follistim® AQ liquid since the original Medical Officer's review of the first cycle application for the Follistim® AQ liquid formulation (review dated 16-May-01). In particular, there were:

- No new deaths
- No unexpected adverse events
- No substantive changes in the post-marketing adverse event reports that would indicate a trend since the previously submitted safety updates (See NDA 21-273 Medical Officer clinical reviews dated 16-Jul-03 and 13-May-05).

Overall, the post-marketing data reveal that there are no major safety issues to resolve with Follistim® AQ liquid formulation.

Brief Overview of the Clinical Program:

The original Follistim® freeze dried cake product (NDA 20-582) was approved by the Agency on 29-Sep-97 for the indications of development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program and induction of ovulation in the anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure.

On 18-Mar-99, a pre-NDA meeting was held with the Division to discuss a bioequivalence study as the basis of a new NDA submission. The Applicant proposed Follistim® AQ, a new presentation of the approved lyophilized product Follistim®. This liquid Follistim® AQ formulation, is a clear aqueous solution that does not require reconstitution, and would facilitate self-administration by patients. The Applicant subsequently requested a Biowaiver for Follistim® AQ liquid formulation (NDA 21-273) on 11-Jan-00. The Applicant felt that the concentration difference between the approved product and Follistim® AQ liquid formulation would not impact bioavailability. However, the Division had concerns that concentration differences caused by the various ways in which the different Follistim® products are handled and administered could impact bioavailability. Therefore, during a teleconference between DRUDP and Organon on 31-Mar-00 (minutes issued by the Division 28-Apr-00), a decision was reached that supportive data from in vitro tests to show volume/dose losses from liquid and cake formulations to support the waiver should be provided by the Applicant. Based on this decision, an in vitro study (Comparison of In Vitro Activity of FSH in Follistim® (lyophilized cake formulation) and Org 32489 Solution in Vial (Liquid) by EIA Method; (Document No. PDTSR-050.00) was submitted to substantiate the request for a Biowaiver (in vitro study contained in the original NDA submission for Follistim® AQ liquid dated 21-Jul-00).

Clinical Pharmacology and Biopharmaceutics section concluded this in vitro study was adequate to substantiate the Applicant's request for a Biowaiver submitted on 11-Jan-00. Because the bioequivalence study, referenced for the waiver of bioequivalence, was conducted following subcutaneous administration, the Applicant was also requested to provide information to show that subcutaneous equivalence can be extrapolated to intramuscular administration. In response the Applicant submitted synopses of 3 pharmacokinetic studies that supported bioequivalence of 150 IU/ml Follistim® by the intramuscular or subcutaneous route of administration in _____ total injections. A safety and efficacy study submitted to the original NDA for the approved lyophilized Follistim® product (NDA 20-582 approved on 29-Sep-97), also showed comparable safety and efficacy between the subcutaneous and intramuscular routes of administration. Based on this information, the bioequivalence via the subcutaneous route of administration can be extrapolated to the intramuscular route of administration.

The initial medical officer review of NDA 21-273 recommended an Approval action from a clinical perspective, based on acceptable demonstration of bioequivalence of the liquid formulation to the original approved and marketed Follistim® lyophilized cake formulation (review dated 16-May-01). The medical officer's review concurred with the recommendation by the Office of Clinical Pharmacology and Biopharmaceutics that bioequivalence between the approved Follistim® lyophilized cake and liquid Follistim® formulation had been demonstrated. However, deficiencies in the chemistry and manufacturing information resulted in NDA 21-273 receiving an Approvable action on 24-May-01.

The Applicant submitted the initial Complete Response to the first Approvable action letter for NDA 21-273 (submission dated 18-Oct-02) to address chemistry and microbiology deficiencies along with a clinical safety update. On 14-Apr-03, the Agency received additional chemistry data on two additional validation batches as requested by the Agency. The Medical Officer's Review of the first safety update in the 2002 Complete Response concurred with the original recommendation for Approval of Follistim® AQ from a clinical perspective (review of the Complete Response dated 16-Jul-03). However, the complete response submission for NDA 21-273 received a second Approvable Action letter on 17-Jul-03 after significant cGMP deficiencies in a manufacturing and testing were noted during an inspection (inspection date 26-Jul-03) of the manufacturing and testing facility in a West Orange, New Jersey facility. These deficiencies resulted in a WARNING letter and "Withhold" recommendation issued by the District on 27-Jun-03 for the West Orange facility, and concurrence from the Office of Compliance.

The Applicant submitted a second Complete Response (CDER stamp date 22-Nov-04) to the second Approvable action letter for NDA 21-273 dated 17-Jul-03. In the updated Complete Response, the Applicant submitted updated CMC information on the manufacturing, testing and packaging sites, container and closure information, analytical methods and specifications for the excipients, drug substance and drug product and included stability and methods validation information.

In addition, the Applicant reported in the November 2004 submission that manufacturing and testing operations for Follistim® AQ liquid were transferred from the West Orange, New Jersey facility to a facility in Dublin, Ireland. A routine inspection was scheduled for the new Ireland manufacturing facility. The inspection of the Dublin Ireland manufacturing facility (held between 25-Apr-05 through 03-May-05) demonstrated cGMP deficiencies (including deficiencies in stability program records and reports and inadequate laboratory controls) that resulted in a recommendation of "Withhold" from the Office of Compliance (issued 03-May-05). The "Withhold" recommendation resulted in a third Approvable Action letter (dated 17-May-05) for Follistim® AQ liquid. Subsequently, the Applicant's responses to the inspection findings were found to be satisfactory by the FDA District Office and the Office of Compliance. An overall recommendation "Acceptable" for the NDA was issued by the Office of Compliance on 11-Jul-05."

In the third Approvable Action letter, the Applicant was also asked to update available clinical safety information for Follistim® AQ liquid. In the third Approvable Action letter, the Applicant was asked to submit the following clinical safety information:

1. Any changes or findings in the safety profile.
2. Incorporate new safety data as follows:
 - New safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Tabulations of new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. A re-tabulation of reasons for premature study discontinuation.
4. Case report forms and narrative summaries for each patient who died during a study or did not complete a study because of serious adverse events. In addition, provide narrative summaries of any serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience with the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide an English translation of current approved foreign labeling not previously submitted.

The Applicant has addressed these seven clinical issues with a worldwide safety update for all Follistim® (follitropin beta) products from 2000 through 2005 (CDER stamp date 27-Jun-05) and a previous safety update for all Follistim® products from 1996 through 2004 (CDER stamp date 19-Nov-04). The 2005 safety update also contains a revised label for Follistim® AQ liquid and updated information on the Dublin manufacturing/testing and packaging site (CDER stamp date 27-Jun-05).

Efficacy

The efficacy of the new liquid formulation (NDA 21-273) is based on the assumption that Follistim® AQ liquid formulation was clinically equivalent to Follistim® lyophilized cake formulation-SRS, and a Biowaiver (requested on 11-Jan-00) was granted.

A single clinical trial, Protocol [REDACTED] was also submitted in support of the application for the Follistim® AQ liquid formulation. Protocol [REDACTED] was performed in 126 patients with 62 patients in the Follistim® AQ liquid formulation arm and 64 patients in the Follistim® lyophilized cake formulation-SRS (the original approved product).

Ovulation rate was the primary efficacy parameter. The original Medical Officer's Review of NDA 21-273 concluded that the difference between the Follistim® groups, in terms of overall ovulation, was not statistically or clinically significant (see original Medical Officer's Review of NDA 21-273 dated 16-May-01).

No new efficacy clinical study information was included in the current Complete Response to the third Approvable Action letter (letter dated 17-May-05). Efficacy claims for Follistim® AQ are based on the original granted Biowaiver and clinical data from Protocol [REDACTED] submitted in the original NDA 21-273 submission (CDER stamp date of original submission 21-Jul-00).

The indications claimed for Follistim® AQ liquid are: 1) induction of ovulation and 2) for use in assisted reproductive technologies, the same indications described for the original approved Follistim® cake product.

Safety

Follistim® AQ formulation differs from the approved Follistim® lyophilized cake formulation in pharmaceutical presentation only. Based on the accepted Biowaiver between Follistim® cake and Follistim® AQ liquid, the clinical safety profile for Follistim® AQ liquid was supported using clinical study data obtained from the original NDA 20-582 for the approved Follistim® cake product. The first periodic safety update for Follistim® AQ liquid was submitted in the first Complete Response dated 18-Oct-02 for NDA 21-273. The Medical Officer's review of subsequent submitted post-marketing clinical safety updates for Follistim® AQ concurred with the original Medical Officer's review that patient exposure for Follistim® AQ was adequate, and the safety profile for Follistim® AQ obtained from the limited post-marketing information did not reveal new safety issues or trends. (See Medical Officer's reviews of the safety updates contained in Complete Responses to Approvable Actions for NDA 21-273 dated 16-Jul-03, 13-May-05).

The current (third) Complete Response submission (CDER stamp date 27-Jun-05) contained a worldwide safety profile for all Follistim® products including Follistim® AQ liquid from the introduction of the original lyophilized Follistim® product in May 2000 through May 2005.

The Applicant also provided additional adverse event listing beginning on the date of the second safety update (November 2004) through the date of submission of the second (and current) Complete Response (June 2005) for comparison to previous safety updates.

The Applicant reported a total of 85 adverse events (both medically confirmed and unconfirmed) with 10 being classified as serious since the previous November 2004 safety update. No additional post-marketing deaths related to Follistim® products were reported since the original three reported deaths (these were previously evaluated by the Medical Officer in the first Complete Response submission dated 16-Jul-03). These three cases documented three individual reports of: a completed suicide, a ruptured ectopic pregnancy, and a fatal case of ovarian hyperstimulation syndrome that was complicated by the development of Adult Respiratory Distress Syndrome.

Reviewer's comments:

- 1. The reviewing medical officer evaluated the three deaths in her review of the first complete response submitted in October 2002 (see Medical Officer's Review dated 16-Jul-03). She concluded that the subject who committed suicide and the subject with the ectopic pregnancy had deaths that were not related to the follitropin beta products used. In the case of the fatal ovarian hyperstimulation, the reviewer concluded that although follitropin beta was indirectly related to the death, the case of ovarian hyperstimulation was a result of the medical management of this case.**
- 2. It is reassuring that no additional post-marketing deaths have been reported with Follistim® products since 2003 (over the last 2 years), despite continued worldwide use.**

The updated post-marketing adverse event reports contained in this third Complete Response does not appear to demonstrate new trends in the safety profile or new safety issues for Follistim® products and therefore, further supports the approval of Follistim® AQ liquid.

Dosing Regimen and Administration

A starting dose of 150 to 225 IU of Follistim® AQ liquid is recommended for at least the first four days of treatment for patients undergoing Assisted Reproductive Technology procedures. After this, the dose may be adjusted for the individual patient response until an adequate response is achieved. A maximum daily dose in clinical studies that has been used in patients undergoing Assisted Reproductive Technology procedures is 600 IU. In patients undergoing ovulation induction, the starting dose recommended is 75 IU of Follistim® AQ liquid for up to 14 days. After this, the dose may be increased by 37.5 IU at weekly intervals until an adequate response is achieved. The maximum daily dose that has been used in clinical studies of ovulation induction is 300 IU per day. The dosage regimen recommended for Follistim® AQ Liquid is identical to the dosage regimen described in the labeling for the currently approved Follistim® lyophilized cake formulation. This is acceptable based on the accepted Biowaiver.

Current Safety Update

In this submission, the primary clinical data source for this review was a post-marketing safety update submitted 24-Jun-05. This update reports the most recent safety data from the worldwide experience with Puregon® products (Puregon® is the European tradename for Follistim® in the United States). The most recent estimate provided by the Applicant reports that the total amount of follitropin beta for injection sold in between November 2004 and June 2005 is [REDACTED] units. A breakdown of these figures by product lyophilized cake, liquid and pen-injector device at in the past year revealed that approximately [REDACTED] of sales were in the liquid formulation (with [REDACTED] of sales being follitropin beta in the cartridge pen device) and approximately [REDACTED] were the lyophilized cake formulation.

Reviewer's comment: Given these estimates for all follitropin beta products, the current 5 year world-wide experience provided by the Applicant combined with the previous safety update (dated 22-Nov-04 for all follitropin beta products since 1996) appears adequate for the purposes of generating a safety profile for Follistim® AQ liquid, since the liquid (in vials and in the pen-injector) appears to represent a majority of the product currently sold overseas.

Most of the safety information contained in this safety update has already been submitted to the NDA and reviewed. The current update (dated 24-Jun-05) focuses on safety data for follitropin beta products from the previous five years of post-marketing information on the Follistim® AQ liquid formulation from 2000 through May 2005. In addition, the Applicant has also included summary tables of the adverse events (both medically confirmed and unconfirmed) from the previous safety update in November 2004 through the month of submission in June 2005. The Applicant also submitted current worldwide market authorization status and proposed labeling information.

Reviewer's comment: Previous post-marketing information (from prior to 2004) has been evaluated by this reviewer. Therefore, this review will focus on new post-marketing information received from the Applicant beginning November 2004.

As requested in the third Approvable Action letter (dated 17-May-05), the Applicant has submitted the following safety update information:

1. An updated safety profile of the post-marketing adverse event reports for all follitropin beta products from May 2000 thorough May 2005 (most reports previously reviewed in the 2004 update (See Medical Officer's Review dated 16-May-05). The Applicant noted that since the previous November 2004 safety update, an additional 85 spontaneous adverse events were reported with use of follitropin beta products, of which 10 were listed as serious (See summary in Table 1).
2. New safety data:
 - No new clinical studies for the proposed indications of multiple follicular development for Assisted Reproductive Technology therapy or ovulation

induction have been initiated by the Applicant since the previous safety update submitted in 2004. The Applicant provided a tabular descriptive overview of 28 previously completed clinical studies.

- Tabulations of the post-marketing events that occurred since the last safety update in November 2004 (See summary in Table 1) were provided by the Applicant. Ten new serious adverse events were reported in this timeframe.
 - The Applicant reported that follitropin beta products are approved overseas for the additional indication of deficient spermatogenesis due to hypogonadal hypogonadism (although not in the United States). Two medically confirmed adverse events in men have been reported in the post-marketing adverse event report period collected since May 2000 (one event of injection site pain, the other a generalized allergic reaction). No serious adverse events were reported to have occurred in men since the previous November 2004 safety update. As the Applicant does not wish to market this product for this indication in the United States, no clinical trial data for this indication was submitted.
3. Premature study discontinuations in new clinical studies were not included in this 2005 submission as no new clinical studies were conducted by the Applicant since the original NDA submission.
 4. The Applicant provided additional updated information on serious adverse events and deaths reported for follitropin beta.
 - a. Case report forms and summaries were previously provided for three patients who died after use of follitropin beta products. These three deaths were previously reported to the Division and reviewed by the Medical Officer including:
 - Case CNL-123581-NL – In case report, there is suspicion that suicide was the actual cause, and this is also the opinion of the reporting doctor. A 29 year old female patient was reported in Vietnam. The death occurred 14 days after receiving the last dose of Puregon® (European formulation of Follistim®) 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.
 - Case Report 2003-106353-NL – A 33 year old woman in the Philippines was brought to the emergency room in shock with a ruptured ectopic pregnancy. She had a history of previous ectopic pregnancies. She underwent controlled ovarian stimulation with Puregon® for an in vitro fertilization procedure. The subsequent ultrasound documented an intrauterine pregnancy. She subsequently died after a failed resuscitation in the Emergency Room.
 - Case Report 2003-103132-NL - A 32 year old woman in Ireland developed ovarian hyperstimulation syndrome after stimulation with the Puregon® in a pen-injector device. Thirty-two oocytes

were recovered during an in vitro fertilization procedure. She developed Adult Respiratory Distress Syndrome and was subsequently placed on a ventilator. She died 39 days after a dose of human chorionic gonadotropin to stimulate maturity of the oocytes.

- b. The Applicant provided narrative summaries of the ten new serious adverse events collected since the previous November 2004 safety update (See summary in Table 2).
5. The Applicant provided a summary of all non-serious reports from spontaneous medically confirmed reports for all follitropin beta products beginning in May 2000 through May 2005, and summary tables of non-serious and serious reports from November 2004 through June 2005.
6. The Applicant provided a summary of the worldwide experience with follitropin beta products by reporting that these products have been available since registration in May 1996 and are currently sold in over 93 countries including the United States (in the lyophilized cake formulation).

Reviewer's comment: The most recent submission by the Applicant stated that no actions for safety reasons were initiated by any regulatory authority or by the Applicant.

7. An English translation of a currently approved foreign label was included in this 2005 submission. The Applicant previously submitted ten foreign labels to the previous safety update (CDER stamp date 19-Nov-04) that were representative of the current approved foreign labeling in 25 European Union and 46 non-European Union countries.

Reviewer's comments regarding the November 2004- June 2005 post-marketing safety update:

- **In this reviewer's opinion, post-marketing data submitted for follitropin beta liquid is not adequate to determine the actual frequencies of adverse events (both serious and non-serious) for follitropin beta. To address this question, a controlled clinical study would need to be proposed, and based on the key adverse events known to occur with follitropin products would need to be powered appropriately. A study of these adverse events, including ovarian hyperstimulation syndrome would probably require several thousands patients. Furthermore, post-marketing tabulations are not useful as a comparator to frequencies of adverse events seen in the original follitropin beta clinical studies submitted to the NDA. However, post-marketing safety profiles are useful for examining rare events and safety trends. The reviews of the first and second safety updates submitted for Follistim® AQ (dated 16-Jul-03, 13-May-05), and the adverse event data from this safety update (letter date 24-Jun-05) compared to post-marketing data from the previous 6-months (May 2004 through November 2004 do not demonstrate new safety issues or trends.**

- **The 2005 safety update reported ten new serious adverse events (SAEs) since the previous 2004 safety update. The most frequently reported serious adverse event was severe ovarian hyperstimulation syndrome [(OHSS); 3 cases over approximately 11 months]. This update appears to present a similar frequency of serious OHSS cases to the Applicant's previous reported 11 serious OHSS cases between 2002 and 2004 (See Medical Officer's Review dated 16-May-05). These OHSS cases were reviewed (See Appendix – Table 3) and do not appear to represent evidence of an increasing rate of OHSS. These cases confirm that the rate of conception in cases severe OHSS is high and is an important risk factor¹, but pregnancy is of little predictive value as pregnancy is usually diagnosed after the symptoms of OHSS develop.² Unfortunately, although the literature reports several risk factors for severe OHSS (such as history of polycystic ovarian disease, high serum estradiol and/or high oocyte numbers)³, recommendations to prevent OHSS are not uniform. At this date, the only known prevention against severe OHSS is cycle cancellation, sometimes refused by patients. In this reviewer's opinion, it is difficult to determine an actual rate of severe ovarian hyper-stimulation syndrome for any gonadotropin as treatment termination criteria vary widely between practices), and furthermore, many severe cases are probably not reported.**
- **The total number of ovarian hyperstimulation cases was 28 over 5 years (between May 1999 and May 2004) while 8 cases were documented between November 2004 and June 2005 (over approximately 1 year). The actual rate of ovarian hyperstimulation with Follistim® AQ is unknown as no safety studies designed to look at this have been conducted to date. However, this reviewer notes that the increased reporting of ovarian hyperstimulation over time is expected as the number of ART treatment cycles being performed in the U.S. increases over time (— cycles in 1996 compared to — cycles in 2001). Therefore, an upward trend in OHSS may represent an increased use of gonadotropins (and ART) over time, not necessarily an increased rates of ovarian hyperstimulation from follitropin beta. In this reviewer's opinion, there is no clinical data at this time to suggest that follitropin liquid increases the absolute risk of ovarian hyperstimulation compared to other gonadotropin products.**

In summary, this reviewer concludes that the Applicant should continue to monitor OHSS yearly for trends for follitropin beta products in the U.S. and overseas for both serious OHSS cases and total OHSS cases in relation to the number of treatment cycles per year and report this in their Annual Report.

- **Other clinically significant new serious adverse events include:**
 - **Two cases of pulmonary embolism (CNL-125190 and 2004-117348): These cases both occurred after Puregon® treatment, and it is unknown whether these patients had underlying coagulation disorders such as Leiden factor abnormalities. Thromboembolism may present usually in association with gonadotropin use for assisted**

reproductive technology procedures, and are usually rare complications in patients who have developed moderate and severe ovarian hyperstimulation.⁴ The mechanism for development of thromboembolism may occur in the presence of high serum estradiol levels pre-and post-gonadotropin treatment. Additional previously submitted worldwide experience submitted in the second Complete Response (November 2004) for Follistim® AQ liquid revealed only 2 cases of deep vein thrombosis, 1 pulmonary embolism and two cases of deep vein thrombophlebitis were reported since May 1996 (the initial date of use of Follistim®).

This reviewer also notes that a recent publication suggested that recombinant gonadotropins do not appear to significantly alter the coagulation cascade. This published article further supports that the development of thromboembolism in cases of severe ovarian hyperstimulation stimulation is probably the end result of the addition of other clinical factors, such as ongoing pregnancy.⁵ In this reviewer's opinion, these rare reports of thromboembolism (including the Applicant's reported two new cases of pulmonary embolism), do not demonstrate a new safety trend for these products in terms of directly altering coagulation. The Applicant should continue to monitor the number of cases of thromboembolism through post-marketing surveillance.

- One case of generalized erythema subsequent to Puregon Pen® use (2005-128430): This patient developed a generalized rash and edema of her limbs within 24 hours after Puregon® use. A subject with an anaphylactic reaction to follitropin alfa has previously been reported in a recent clinical study for Menopur® (See Medical Officer's review of NDA 21-663/Study MFK/IVF/0399E dated 29-Oct-04). An additional report of an anaphylactic reaction after use of gonadotropins was also reported in the literature.⁶ In this reviewer's opinion, anaphylaxis appears to be a rare event, although it is difficult to determine whether this event was a result of the recombinant follicle stimulating hormone protein(s) or from an excipient.
- This reviewer also notes that a total of 11 additional subjects with clinically significant rashes (included one case each of erythema nodosum and erythema multiforme, respectively) were also reported by the Applicant, although none were listed as serious. In this reviewer's opinion, it is difficult to assess the actual incidence of clinically significant anaphylaxis to follitropin beta using the currently available post-marketing data. Allergic reaction warnings are described in the current (and proposed) labels for follitropin beta. This reviewer would strongly recommend the Applicant monitor for trends in anaphylactic and allergic reactions over time.
- One case of toxic hepatitis (2005-126489): This case was a patient treated with leuprolide acetate and Puregon® (formulation unknown) who noted itching, nausea and fever after beginning the Puregon® for

a third IVF cycle. The patient had an allergic reaction site at the injection site for Puregon® and was noted to have an SGOT of 230 U/L and a total bilirubin of 23 umol/L. Puregon® was discontinued and the patient's abnormal liver function tests (LFTs) resolved. Reports of increased LFTs have been reported previously with use of follitropin beta products (including 3 post-marketing reports in the past 5 years, although none reported as serious). In addition, clinically significant LFTs were seen in two subjects in the previously conducted ovulation induction study for Follistim® AQ solution (See Medical Officer's Safety review of Study 058004 dated 20-Jan-03). This reviewer notes that all of these LFT abnormalities resolved without further complications. Also, gonadotropins (including follitropin beta) are often given with gonadotropin-hormone releasing agonists (which have also been shown to occasionally cause liver toxicity). The clinical reports are usually unclear what the presumed etiology of the LFT abnormalities are for an individual patient. Of note, this post-marketing case report also noted that patient was taking leuprolide acetate (a gonadotropin-releasing hormone agonist). In this reviewer's opinion, leuprolide probably contributed to this toxicity. The Applicant should monitor for any reports of subjects with LFT abnormalities and attempt to identify which formulation was used.

- This reviewer also notes that the Applicant has not been able to totally separate the collected post-marketing adverse event reports by indication (use in ART procedures or ovulation induction) as this information has not been consistently reported or available to the Applicant.

In summary, this reviewer recommends that Applicant:

1. determine trends in safety for follitropin beta by indication and formulation, and specifically target case reports associated with OHSS, allergic and/or anaphylactic reactions, toxic hepatitis and/or deaths.
2. monitor OHSS yearly for trends in the U.S. and overseas for both serious OHSS cases and total OHSS cases in relation to the number of treatment cycles per year.

PREGNANCY OUTCOME INFORMATION

The very limited pregnancy outcome information from follow-up of patients enrolled in study 058007 and six additional post-marketing case reports provided in submission that encompasses the past 5 years of follitropin beta use does not demonstrate new trends in miscarriage, intra-uterine death or congenital anomalies.

Reviewer's comments:

- No definitive conclusions on the effects of Follistim® products during pregnancy and lactation can be made with these few post-marketing case reports. Current literature evidence suggests that there are increases seen in

the risks of multiple gestation, chromosomal abnormalities, low birth weight infants and preterm delivery in children conceived with ART. Of the six case reports of actual follitropin beta exposure during pregnancy, only one patient experienced a miscarriage, and one case of autism was reported. It is unknown whether these adverse events that occurred with use of follitropin beta during pregnancy are a direct result of ART treatment, gonadotropin use, some other factor related to the parent's underlying infertility problem, or occurred by chance. However, the 5-year worldwide post-marketing reports do not appear to demonstrate any new trends or safety issues in pregnant patients.

- **In addition, it is unlikely that routine clinical practice in the United States would expose embryos to follitropin beta. Therefore, this reviewer would agree that the follitropin beta products should continue to be labeled as contraindicated during pregnancy.**
- **Since the amount of Follistim® excreted in breast milk is unknown, (and therefore, the risks are unknown). No adverse events associated with follitropin beta products during lactation have been reported in any of the clinical studies or safety updates. The Applicant has recommended in labeling that a practitioner should consider whether discontinuation of nursing should occur if the patient wishes to proceed with a treatment cycle. This reviewer concurs with this labeling statement.**

ADDITIONAL CLINICAL ISSUES

Drug-Drug Interactions:

No drug-drug interaction studies have been performed with any of the Follistim® products. In this clinical reviewer's opinion, this is acceptable as it is unlikely that a recombinant follicle stimulating hormone product would cause significant drug interactions in the indicated young, healthy infertile female population

Special Populations:

Safety and effectiveness in geriatric patients have not been established. This is acceptable given the indications of this product.

Pediatrics:

Safety and effectiveness in pediatric patients have not been established. This is acceptable given the indications of this product.

Conclusions

This clinical reviewer concurs with the original Medical Officer's review that Follistim®-AQ liquid formulation differs from the original formulation in pharmaceutical

presentation only. This reviewer concludes that the benefits of taking Follistim® AQ outweigh the risks.

Recommendation on Regulatory Action

Approval of this application for Follistim® AQ is recommended as resolution of the recommendation of “Withhold” from Compliance has occurred.

Recommendation on Postmarketing Actions

No additional recommendations necessary.

Risk Management Activity

This reviewer recommends that the Applicant:

1. continue to monitor safety for follitropin beta by indication and formulation, and specifically target case reports associated with OHSS, allergic and/or anaphylactic reactions, toxic hepatitis and/or deaths.
2. monitor OHSS yearly for trends in the U.S. and overseas for both serious OHSS cases and total OHSS cases. These OHSS reports should also be analyzed in relation to the number of ART treatment cycles per year for the U.S. as well as overseas in the Annual Report.

Required Phase 4 Commitments

None.

Labeling Review

47 Page(s) Withheld

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Draft Labeling

Deliberative Process

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/s/

Audrey Gassman
8/24/2005 04:21:04 PM
MEDICAL OFFICER

Shelley Slaughter
8/25/2005 10:12:31 AM
MEDICAL OFFICER

I concur with the Medical Officer's assessment of the
submitted safety update and recommendation for approval for
the application.

Daniel A. Shames
8/25/2005 12:12:59 PM
MEDICAL OFFICER

**Follistim®-AQ
Team Leader Review**

NDA: 21-273
2nd Resubmission (November 19, 2004)

Drug: Follistim®-AQ (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 aqueous solution for subcutaneous or intramuscular injection; each vial contains 75 IU, 150 IU, ██████████ FSH per 0.5 ml

Applicant: Organon, Inc.

Original Resubmission Date: November 19, 2004

Primary Clinical Review Completed: May 13, 2005

Date of Memorandum: May 16, 2005

Background

NDA 20-582 for 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 lyophilized cake formulation for reconstitution with sterile water.

NDA 21-273 for Follistim®-AQ was submitted on July 21, 2000. Evidence for safety and efficacy were to be based on a waiver of bioequivalence based on a previous bioequivalence trial of Follistim®-AQ Cartridge vs. Follistim® submitted to NDA 21-211. This trial was a comparative open-label bioavailability study comparing a single dose of Follistim®-AQ (150 IU) Cartridge with Follistim® (reconstituted 150 IU). Follistim®-AQ Cartridge resulted in a 20% higher AUC and Cmax than Follistim® 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, Follistim®-AQ Cartridge administered with the Pen-Injector was bioequivalent to Follistim®. The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) accepted this approach to demonstrate that the drug product in Follistim® and Follistim®-AQ are bioequivalent and are expected to result in the same blood levels when delivered by the conventional syringe and needle. Therefore, based on the bioequivalence study from NDA 21-211 and the in vitro comparative data on loss of dose during handling and injection, the request for waiver of a bioequivalence study for the Follistim-AQ liquid formulation for NDA 21-273 was acceptable to OCPB. Because the bioequivalence study, referenced for the waiver of bioequivalence, was conducted following subcutaneous administration, the Sponsor was requested to provide information to show that subcutaneous equivalence can be extrapolated to intramuscular administration. In response the Sponsor submitted synopses of 3 pharmacokinetic studies that supported bioequivalence of 150 IU/ml Follistim® by the intramuscular or subcutaneous route of administration in total injections. A safety and efficacy study submitted to the original NDA, 20-582, also showed comparable safety and efficacy between the subcutaneous and intramuscular routes of administration. Based on this information, the bioequivalence via the subcutaneous route of administration could be extrapolated to the intramuscular route of administration.

Several Chemistry, Manufacturing and Control (CMC) and Microbiology deficiencies were identified and communicated to Organon. On October 30, 2000, the Office of Compliance issued a "Withhold" recommendation following a WARNING LETTER issued on September 19, 2000 by the New Jersey District after inspection of the West Orange, NJ manufacturing plant between July 17 and August 23, 2000. From a CMC perspective, the NDA was considered approvable pending satisfactory resolution of CMC and Microbiology deficiencies and satisfactory inspection reports from the Office of Compliance. NDA 21-273 receive an approvable recommendation on May 24, 2001.

Another "Withhold" recommendation was issued on April 16, 2002 because the firm was not ready for re-inspection. Following an inspection on August 23, 2002, the District again issued a "Withhold" recommendation due to inadequate quality assurance (QA) functions, and the Office of Compliance concurred. A Complete Response addressing CMC and Microbiology deficiencies was received on October 18, 2002. To address the issue of inadequate QA functions and deficiencies found in executed batch records, the Sponsor was requested to manufacture two additional batches of drug product (see March 04, 2003 and March 28, 2003 amendments) and to submit these to the NDA (see April 11, 2003 and April 30, 2003 amendments). On April 14, 2003, the Agency received additional CMC data comprised of the executed batch records on two addition validation batches requested by the Agency. The submitted executed batch records were reviewed and found to be acceptable. In addition, the certificate of analysis for the two batches show that the drug product complied with all test attributes. No new clinical trial results were submitted with this resubmission. A safety update to the resubmission was submitted January 29, 2003. There were no new concerns for safety raised with this update. On June 26, 2003, the West Orange, NJ manufacturing facility was inspected and a WARNING letter and "Withhold" recommendation were issued on June 27, 2003. The Office of Compliance concurred with the "Withhold" recommendation. The District also stated that Organon had shut down the manufacturing facility and was implementing corrective actions. A second Approvable action was taken on July 17, 2003. The Approvable letter had a single deficiency, the "Withhold" recommendation from the Office of Compliance for the West Orange, NJ manufacturing site.

Organon submitted a second Complete Response (CDER stamp date November 22, 2004) to the second Approvable action letter for NDA 21-273 dated July 17, 2003. In the updated Complete Response, the Applicant has submitted updated CMC information on the manufacturing, testing and packaging sites, container and closure information, analytical methods and specifications for the excipients, drug substance and drug product and included stability and methods validation information. In the 2nd Complete Response Organon withdraws the West Orange, New Jersey facility and submits a new manufacturing and testing facility for Follistim® AQ liquid, Organon Ireland, LTD in Swords, County Dublin, Ireland. With the Complete Response Organon also submits the updated available clinical safety information for Follistim® AQ liquid.

Clinical Efficacy and Safety

Efficacy and safety of NDA 21-273 for Follistim®-AQ are based on bioequivalence of the liquid drug product formulation of Follistim®-AQ to the reconstituted lyophilized cake drug product formulation of Follistim® when both are delivered by conventional syringe and needle. During the original review cycle, the Sponsor requested a biowaiver for bioequivalence based on a bioequivalence study comparing Follistim®-AQ Cartridge with Follistim® and an in vitro comparative study on loss of dose during handling and injection, a biowaiver was granted. In the original review cycle application, the Sponsor also submitted a supportive clinical trial (Protocol ██████████) for ovulation induction. As a stand-alone study this study would not have provided sufficient evidences for efficacy and safety, however, it was supportive to the bioequivalence study for the indication of ovulation induction. A safety update to the first resubmission was submitted January 29, 2003. There were no new concerns for safety raised with the first Resubmission Safety Update update.

No new efficacy clinical study information was included in the current Complete Response to the second Approvable Action letter (dated November 18, 2004). Efficacy claims for Follistim® AQ are based on the original granted Biowaver and clinical data from Protocol ██████████ submitted in the original NDA 21-273 submission (dated July 21, 2000). The current (second) Complete Response submission (dated November 19, 2004) contained a worldwide safety profile for all Follistim® products including Follistim® AQ liquid from May 1996 through November 2004. No new safety issues or trends were identified from this information (see Medical Officer Review dated May 13, 2005)

The indications claimed for Follistim® AQ liquid are the same as in the original approved Follistim® cake product (NDA 20-582; approved September 29, 1997). These are:

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.

Chemistry, Manufacturing and Controls

As noted above the Approvable letter of July 17, 2003 had a single deficiency, the "Withhold" recommendation fro the Office of Compliance for the West Orange, NJ manufacturing site. All Chemistry and Microbiology deficiencies noted in the original Approvable action on May 24, 2001 were satisfactorily addressed with the first resubmission (please refer to Chemistry and Microbiology reviews for second review clock). On May 3, 2005 the inspection of the manufacturing site of the drug product, Organon Ireland, Swords, Dublin County Ireland, was

concluded and the site was found to be in violation of cGMP. On May 5, 2005 the Office of Compliance issued an overall recommendation of "Withhold" for the NDA.

Conclusions and Recommendations:

An approvable action was taken during the original review period because of Chemistry and Microbiology deficiencies as well as a non-acceptable inspection of one of the manufacturing sites. All Chemistry and Microbiology deficiencies were satisfactorily addressed with the first complete response of October 18, 2002. However, major manufacturing site deficiencies remained and another Approvable was taken on July 17, 2003. With the current (2nd) Complete Response, the Sponsor withdrew the West Orange, NJ manufacturing site and submitted a new site in Swords, Dublin County Ireland. The Office of Compliance has issued a "Withhold" approval recommendation for this site.

I agree with the Chemistry and Medical Officer recommendations that this application can be approved pending a satisfactory recommendation from the Office of Compliance. The Sponsor's Swords, Dublin County Ireland facility will need to be in cGMP compliance before an Approval recommendation can be issued. In addition, all relevant facilities in the application need to remain in cGMP compliance.

Shelley R. Slaughter, M.D., Ph.D.

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/s/

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5/17/05 01:50:43 PM
MEDICAL OFFICER

Daniel A. Shames
5/17/05 02:21:45 PM
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CLINICAL REVIEW

Application Type NDA 21-273
Submission Number N-000
Submission Code AZ

Letter Date November 19, 2004
Stamp Date November 22, 2004
PDUFA Goal Date May 20, 2005

Reviewer Name Audrey Gassman, MD
Review Completion Date May 13, 2005

Established Name Follitropin beta for injection
(Proposed) Trade Name Follistim® AQ
Therapeutic Class Infertility
Applicant Organon, Inc.

Priority Designation S

Formulation Sterile aqueous solution
Dosing Regimen 150 to 225 IU of follitropin beta
for the first four days of treatment.
After this, the dose is adjusted for
the individual patient response.

- 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

Intended Population Infertility patients

Appears This Way
On Original

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective approval of this application is recommended based on: 1) An acceptable complete response with respect to clinical issues to the Approvable Action dated 17-Jul-03 and 2) the acceptable demonstration of bioequivalence of this drug to that of the previously approved follitropin beta drug product, Follistim®. This recommendation from a clinical perspective is in concurrence with the previous Medical Officer reviews which found the supportive clinical efficacy, safety and post-marketing data acceptable in terms of risk/benefit ratio (See NDA 21-273 Medical Officer clinical reviews dated 16-May-01 and 16-Jul-03).

1.2 Recommendation on Postmarketing Actions

Phase 4 studies are not recommended.

1.2.1 Risk Management Activity

As a part of risk management, the Applicant should continue to submit individual adverse event reports of post-marketing experience obtained from all countries where the drug is currently marketed and monitor these reports for safety trends.

1.2.2 Required Phase 4 Commitments

No additional phase 4 studies are necessary.

1.3 Summary of Clinical Findings

There is no evidence in the two clinical safety updates submitted by the Applicant (19-Nov-04 and 08-Feb-05) of any new efficacy or safety concerns with Follistim® AQ liquid since the original Medical Officer's review of the first cycle application for the Follistim® AQ liquid formulation (dated 16-May-01). In particular, there were:

- No new deaths
- No unexpected adverse events
- No substantive changes in the post-marketing adverse event reports that would indicate a trend since the previous safety update submitted in 2003.

Overall, the post-marketing data reveal that there are no major safety issues to resolve with Follistim® AQ liquid formulation.

1.3.1 Brief Overview of Clinical Program

The original Follistim® freeze dried cake product (NDA 20-582) was approved by the Agency on 29-Sep-97 for the indications of development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program and induction of ovulation in the anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure.

On 18-Mar-99, a pre-NDA meeting was held with the Division to discuss a bioequivalence study as the basis of a new NDA submission. The Applicant proposed Follistim® AQ, a new presentation of the approved lyophilized product Follistim®. This liquid Follistim® AQ formulation, is a clear aqueous solution that does not require reconstitution, and would facilitate self-administration by patients.

The Applicant subsequently requested a Biowaiver for Follistim® AQ liquid formulation (NDA 21-273) on 11-Jan-00. The Applicant felt that the concentration difference between the approved product and Follistim® AQ liquid formulation would not impact bioavailability. However, the Division had concerns that concentration differences caused by the various ways in which the different Follistim® products are handled and administered could impact bioavailability. Therefore, during a teleconference between DRUDP and Organon on 31-Mar-00 (minutes issued by the Division 28-Apr-00), a decision was reached that supportive data from in vitro tests to show volume/dose losses from liquid and cake formulations to support the waiver should be provided by the Applicant. Based on this decision, an in vitro study (Comparison of In Vitro Activity of FSH in Follistim® (lyophilized cake formulation) and Org 32489 Solution in Vial (Liquid) by EIA Method; (Document No. PDTSR-050.00) was submitted to substantiate the request for a Biowaiver (in vitro study contained in the original NDA submission for Follistim® AQ liquid dated 21-Jul-00). Clinical Pharmacology and Biopharmaceutics section concluded this in vitro study was adequate to substantiate the Applicant's request for a Biowaiver submitted on 11-Jan-00. Because the bioequivalence study, referenced for the waiver of bioequivalence, was conducted following subcutaneous administration, the Applicant was also requested to provide information to show that subcutaneous equivalence can be extrapolated to intramuscular administration. In response the Applicant submitted synopses of 3 pharmacokinetic studies that supported bioequivalence of 150 IU/ml Follistim® by the intramuscular or subcutaneous route of administration in total injections. A safety and efficacy study submitted to the original NDA for the approved lyophilized Follistim® product (NDA 20-582 approved on 29-Sep-97), also showed comparable safety and efficacy between the subcutaneous and intramuscular routes of administration. Based on this information, the bioequivalence via the subcutaneous route of administration can be extrapolated to the intramuscular route of administration.

The initial medical officer review of NDA 21-273 recommended an Approval action from a clinical perspective, based on acceptable demonstration of bioequivalence of the liquid formulation to the original approved and marketed Follistim® lyophilized cake formulation (review dated 16-May-01). The medical officer's review concurred with the recommendation by the Office of Clinical Pharmacology and Biopharmaceutics that bioequivalence between the approved Follistim® lyophilized cake and liquid Follistim® formulation had been demonstrated.

However, deficiencies in the chemistry and manufacturing information resulted in NDA 21-273 receiving an Approvable action on May 24, 2001.

The Applicant submitted the initial Complete Response to the first Approvable action letter for NDA 21-273 (complete response submission dated 18-Oct-02) that addressed chemistry and microbiology deficiencies. On 14-Apr-03, the Agency received additional chemistry data on two additional validation batches as requested by the Agency. The Medical Officer's Review of the first safety update in the Complete Response concurred with the original recommendation for Approval of Follistim® AQ from a clinical perspective (review of the Complete Response dated 16-Jul-03). However, the complete response submission for NDA 21-273 received a second Approvable Action letter on 17-Jul-03 after significant cGMP deficiencies in a manufacturing and testing were noted during an inspection (inspection date 26-Jul-03) of the manufacturing and testing facility in a West Orange, New Jersey facility. These deficiencies resulted in a WARNING letter and "Withhold" recommendation issued by the District on 27-Jun-03 for the West Orange facility, and concurrence from the Office of Compliance.

The Applicant submitted a second Complete Response (CDER stamp date 22-Nov-04) to the second Approvable action letter for NDA 21-273 dated 17-Jul-03. In the updated Complete Response, the Applicant has submitted updated CMC information on the manufacturing, testing and packaging sites, container and closure information, analytical methods and specifications for the excipients, drug substance and drug product and included stability and methods validation information. In addition, the Applicant reported in the November 2004 submission that all manufacturing and testing operations for Follistim® AQ liquid have been transferred from the West Orange, New Jersey facility to a facility in Dublin, Ireland.

In the second Approvable Action letter (dated 17-Jul-03), the Applicant was asked to update available clinical safety information for Follistim® AQ liquid. In the second Approvable Action letter, the Applicant was asked to submit the following clinical safety information:

1. Any changes or findings in the safety profile.
2. Incorporate new safety data as follows:
 - New safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Tabulations of new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. A re-tabulation of reasons for premature study discontinuation.
4. Case report forms and narrative summaries for each patient who died during a study or did not complete a study because of serious adverse events. In addition, provide narrative summaries of any serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience with the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide an English translation of current approved foreign labeling not previously submitted.

The Applicant has addressed these seven clinical issues with a worldwide safety update for all Follistim® products from 1996 through 2005 in two submissions dated 19-Nov-04 and 08-Feb-05. In addition, a revised label for Follistim® AQ liquid and information on the Dublin manufacturing/testing and packaging site was included in the 19-Nov-04 submission.

1.3.2 Efficacy

The efficacy of the new liquid formulation (NDA 21-273) is based on the assumption that Follistim® AQ liquid formulation was clinically equivalent to Follistim® lyophilized cake formulation-SRS, and a Biowaiver (requested on 11-Jan-00) was granted. A single clinical trial, Protocol [REDACTED] was also submitted in support of the application for the Follistim® AQ liquid formulation. Protocol [REDACTED] was performed in 126 patients with 62 patients in the Follistim® AQ liquid formulation arm and 64 patients in the Follistim® lyophilized cake formulation-SRS (the original approved product). Ovulation rate was the primary efficacy parameter. The original Medical Officer's Review of NDA 21-273 concluded that the difference between the Follistim® groups, in terms of overall ovulation, was not statistically or clinically significant (see original Medical Officer's Review of NDA 21-273 dated 16-May-01).

No new efficacy clinical study information was included in the current Complete Response to the second Approvable Action letter (dated 19-Nov-05). Efficacy claims for Follistim® AQ are based on the original granted Biowaiver and clinical data from Protocol [REDACTED] submitted in the original NDA 21-273 submission (dated 21-Jul-00).

The indications claimed for Follistim® AQ liquid are: 1) induction of ovulation and 2) for use in assisted reproductive technologies, the same indications described for the original approved Follistim® cake product.

1.3.3 Safety

Follistim® AQ formulation differs from the approved Follistim® lyophilized cake formulation in pharmaceutical presentation only. Based on the accepted Biowaiver between Follistim® cake and Follistim® AQ liquid, the clinical safety profile for Follistim® AQ liquid was supported using clinical study data obtained from the original NDA 20-582 for the approved Follistim® cake product. The first periodic safety update for Follistim® AQ liquid was submitted in the first Complete Response dated 18-Oct-02 for NDA 21-273. The Medical Officer's review of submitted post-marketing clinical safety data for Follistim® AQ concurred with the original Medical Officer's review that patient exposure for Follistim® AQ was adequate, and the safety profile for Follistim® AQ obtained from the limited post-marketing information did not reveal new safety issues or trends. (See Medical Officer's review of the first Complete Response to NDA 21-273 (review dated 16-Jul-03).

The current (second) Complete Response submission (dated 19-Nov-2004) contained a worldwide safety profile for all Follistim® products including Follistim® AQ liquid from May 1996 through November 2004.

The Applicant was also asked to provide a revised periodic update with safety information beginning on the date of the first safety update (submitted 17-Oct-02) through the date of submission of the second (and current) Complete Response (19-Nov-04). This focused update was submitted on 08-Feb-05 to further evaluate the most recent safety Follistim® worldwide data available. The Applicant reported a total of 418 adverse events (both medically confirmed and unconfirmed) with fifty seven being classified as serious. Three reported post-marketing deaths related to Follistim® products were previously evaluated by the Medical Officer in the first Complete Response submission (19-Nov-02). These three cases included a suicide, a ruptured ectopic pregnancy, and a fatal case of ovarian hyperstimulation syndrome that was compounded with Adult Respiratory Distress Syndrome.

Reviewer's comment: This reviewer notes that the case report of the patient who successfully committed suicide occurred 2 weeks post-treatment and was not likely to be associated with short-term gonadotropin treatment. The second patient death was secondary to a ruptured ectopic pregnancy after an in vitro fertilization procedure. Although rare, ectopic pregnancies are more common in patients who undergo in vitro fertilization. In this reviewer's opinion, the ruptured ectopic pregnancy was most likely related to use of the in vitro technology. The third death of a patient with ovarian hyperstimulation syndrome (OHSS) had secondary Adult Respiratory Distress, a very unusual complication of OHSS. Adult Respiratory Distress syndrome has been reported secondary to OHSS in a few literature reports with use of gonadotropins. However, in this reviewer's opinion, this case of ovarian hyperstimulation was likely related to the medical management of this case.

Also reassuring is that no deaths from the original Follistim® product have been reported in the United States since introduction in 1997, and no post-marketing deaths have been reported with Follistim® products since 2003 (over the last 2 years), despite continued worldwide use.

The updated post-marketing adverse event data contained in this second Complete Response does not appear to demonstrate new trends in the safety profile or new safety issues for Follistim® products and therefore, further supports the approval of Follistim® AQ liquid.

1.3.4 Dosing Regimen and Administration

A starting dose of 150 to 225 IU of Follistim® AQ liquid is recommended for at least the first four days of treatment for patients undergoing Assisted Reproductive Technology procedures. After this, the dose may be adjusted for the individual patient response until an adequate response is achieved. A maximum daily dose in clinical studies that has been used in patients undergoing Assisted Reproductive Technology procedures is 600 IU.

In patients undergoing ovulation induction, the starting dose recommended is 75 IU of Follistim® AQ liquid for up to 14 days. After this, the dose may be increased by 37.5 IU at weekly intervals until an adequate response is achieved. The maximum daily dose that has been used in clinical studies of ovulation induction is 300 IU per day.

The dosage regimen recommended for Follistim® AQ Liquid is identical to the dosage regimen described in the labeling for the currently approved Follistim® lyophilized cake formulation. This is acceptable based on the accepted Biowaiver.

1.3.5 Drug-Drug Interactions

Formal drug-drug interaction studies were not conducted or required for this recombinant follicle stimulating hormone (FSH) product.

1.3.6 Special Populations

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

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Follistim® AQ is a sterile aqueous solution with recombinant follicle stimulating hormone that is administered via subcutaneous or intramuscular injection. Each vial of Follistim® AQ solution contains 75 IU or 150 IU FSH per 0.5ml.

2.2 Currently Available Treatment for Indications

Follistim® AQ liquid formulation is one of two recombinant follicle stimulating hormone products in the United States marketplace. Seven additional purified urinary gonadotropin products are available and approved for use in patients undergoing Assisted Technology therapy. All but one of these urinary gonadotropin products are also approved for use in oligo-ovulatory patients undergoing ovulation induction.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in Follistim® AQ, follitropin beta was originally approved in a lyophilized cake formulation on 29-Sep-97. Follitropin beta in solution in a pen-injector device (NDA 21-211) was approved on 23-Mar-04. Follitropin beta in solution in vials for self-injection has not been approved.

The Applicant states that this ready to use Follistim® AQ formulation will be more convenient than previous cake formulations since it requires less patient handling prior to injection.

2.4 Important Issues With Pharmacologically Related Products

A majority of the serious adverse events associated with gonadotropin therapy result from ovarian stimulation, follicular development and ovulation, although allergic reactions and injection site reactions have also been reported. The two most concerning serious adverse events are ovarian hyperstimulation syndrome, thromboembolism and multiple birth rate.

Ovarian hyperstimulation syndrome is the least common complication of gonadotropin therapy, but the most serious one. The underlying pathophysiology is unknown, but results in increased vascular permeability. Published literature report that ovarian hyperstimulation may occur in 0.5 to 5% of women that receive gonadotropin therapy.¹ The treatment for this ovarian hyperstimulation is usually conservative, with management of the increased vascular permeability. Deaths have been reported after the occurrence of severe ovarian hyperstimulation in the literature.^{2,3} The incidence of ovarian hyperstimulation syndrome using the original approved Follistim® product was previously reviewed and found to be similar to other published studies (See the original Medical Officer's Review of NDA 20-582 dated 18-Mar-97). In addition, a reexamination of the limited ovarian hyperstimulation clinical data submitted in the supportive ovulation induction study for Follistim® AQ did not reveal a rate significantly different from that seen in the published literature for other gonadotropins. (See Medical Officer's Safety Update of NDA 21-273 dated 28-Jan-03). In addition, in the most recent submitted safety update, only 14 cases of ovarian hyperstimulation syndrome were reported to the Applicant over the approximately 2 and a half year period of the post-marketing safety update.

Reviewer's comment: The actual rate of serious ovarian hyperstimulation syndrome of Follistim® AQ is unknown. The Applicant provided 12 narrative reports during the 2 year safety update period (2002 through 2004) – of which a majority of the follitropin beta (over 80%) used worldwide is the liquid formulation. These twelve cases do not appear excessive as a conservative estimate would approximate at least 200,000 follitropin beta treatment cycles per year (which would translate to less than a 1% serious ovarian hyperstimulation rate worldwide). Unfortunately, post-marketing data is extremely limited in determining the actual rates of these serious adverse events as many post-marketing events are not reported. In addition, there are concerns that the reporting of certain adverse events may be biased even in countries where the surveillance systems are more aggressive as the adverse event was determined by the physician to be not related or not significant. Therefore, continued monitoring of post-marketing events is warranted, as new trends may be noted.

Thromboembolism may present with or without ovarian hyperstimulation, and is usually a rare complication in patients who have developed moderate and severe ovarian hyperstimulation.⁴ The mechanism for development of thromboembolism may occur in the presence of high serum estradiol levels pre-and post-gonadotropin treatment.

Additional worldwide experience submitted in this second Complete Response for Follistim®-AQ liquid reveals only 2 cases of deep vein thrombosis, 1 pulmonary embolism and two cases of deep vein thrombophlebitis were reported since May 1996 (the initial date of use of Follistim®).

Reviewer's comment: Cases of deep venous thromboembolism have been previously reported as a result of controlled ovarian hyperstimulation.⁵ A recent publication reported that gonadotropins do not appear to significantly alter the coagulation cascade, supporting the theory that the development of thromboembolism in cases of gonadotropin stimulation is probably secondary to other additional factors (in this reviewer's opinion, probably significant elevations in serum estradiol levels).⁶ In this reviewer's opinion, rare reports of thromboembolism (including the Applicant's five reported post-marketing cases) do not demonstrate a new trend for these products in terms of alteration of coagulation.

The potential of an increased risk of multiple births after gonadotropin stimulation for Assisted Reproductive Technology procedures in the United States has been well documented in the literature.⁷ In 2001, it was estimated that the multiple infant rate from ART procedures was 53%.⁸ The original NDA submission for Follistim® (NDA 20-582) reported rates of multiple gestations of 31% and 8% for ART and ovulation induction patients, respectively. These rates were acceptable to the original clinical review team.

Reviewer's comment: Limited information on the multiple birth rate after ovulation induction using Follistim® AQ can be derived from Study 058007 which presents the follow-up pregnancy information from Study 058004. In Study 058004, 62 patients were randomized and treated with Follistim® AQ solution. Study 058007 reported 6 multiple deliveries (a rate of approximately 10%), which is a similar multiple pregnancy rate to that (approximately 8%) reported in a recent published ovulation induction study using a urinary gonadotropin, Repronex®.⁹ The multiple birth rate with Follistim® cake (3%) was lower than that (10%) with Follistim® AQ solution, but study 058007 was not powered to show a difference in clinical or multiple pregnancy rate.

The actual multiple birth rate after use of follitropin beta liquid for controlled ovarian hyperstimulation for ART procedures cannot be derived from post-marketing data, as multiple births are not routinely reported as adverse events. The multiple birth rate data for controlled ovarian hyperstimulation for ART procedures with Follistim® AQ is derived from the original randomized, controlled studies using the European formulation of the currently approved Follistim®. In one of those controlled clinical studies, Follistim® did not show a statistically significant difference from an approved urofollitropin (Metrodin®) in terms of multiple birth rates. A more recent non-comparative, open-label, multicenter study of ovulation induction in women with WHO group II anovulation described a multiple pregnancy rate of less than 1% of treatment cycles (presumably using the new Puregon® solution).¹⁰

In this reviewer's opinion, there is no current clinical evidence to suggest that Follistim® AQ solution has a clinically different multiple birth rate when compared to the original Follistim® cake formulation.

2.5 Presubmission Regulatory Activity

Not applicable for this resubmission.

2.6 Other Relevant Background Information

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 from human menopausal urine was first introduced in 1982. In the 1990's, Chinese Hamster Ovary (CHO) cells were developed that were capable of producing biologically active follicle stimulating hormone (FSH) in culture. This recombinant derived FSH from *in vitro* cultured cells does not appear to be different from native human FSH clinically.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

In the previous review cycle, a "Withhold" was recommended by the Office of Compliance on 30-Oct-00 after an inspection (conducted between 17-Jul-00 and 23-Aug-00) of the manufacturing plant at the Applicant's West Orange, New Jersey facility revealed sterility assurance issues. From a Chemistry, Manufacturing and Controls perspective, the NDA was approvable if the issues at the New Jersey facility could be resolved.

Another "Withhold" recommendation was issued on 16-Apr-000 because the firm was not ready for inspection. Following a second inspection on 23-Aug-02, the District again issued a "Withhold" recommendation due to inadequate quality assurance functions and the Office of Compliance concurred. To address the issues of inadequate quality assurance functions, two batches were manufactured and the executed batch records and release data were submitted to the NDA (see 11-Apr-03 and 30-Apr-03 Amendments). No significant deficiencies were noted during review of these Amendments. However, a follow-up inspection of the West Orange, New Jersey facility was conducted on 26-Jun-03, and a WARNING LETTER and "Withhold" recommendation were issued by the District.

The Office of Compliance concurred with the "Withhold" recommendation. From a chemistry, manufacturing and controls perspective, the West Orange site would need to be in cGMP compliance before an Approval recommendation could be issued.

In the resubmission of this NDA, the West Orange, New Jersey facility was withdrawn from the application and a new manufacturing and testing site for the follitropin beta drug product in Ireland was added. Methods validation of two batches of Follistim® manufactured at the site in September 2004 with analytic data was submitted to this Complete Response. An inspection of this overseas site on April 2005 also yielded a "Withhold" recommendation from the Office of Compliance.

3.2 Animal Pharmacology/Toxicology

The original Pharmacology/Toxicology Reviewer concluded that the composition of Follistim® AQ did not significantly differ from the original approved Follistim® in terms of toxicological significance (review dated 14-May-01). Therefore, no pharmacology/toxicology studies in animals were performed or required for the Follistim® AQ (follitropin beta injection) NDA submission. Previously performed carcinogenicity studies using the original approved Follistim® (follitropin beta for injection) product was not mutagenic in the Ames test using *S. typhimurium* and *E. coli* tester strains and did not produce chromosomal aberrations in an in vitro assay using human lymphocytes.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

This review was conducted from the updated post-marketing clinical information contained in this submission from by the Applicant. Data quality and integrity was previously reviewed (see Medical Officer Reviews for NDA 20-582 and 21-273) and found acceptable.

4.1 Sources of Clinical Data

This application was submitted in paper only. This review also contains excerpts from the original Medical Officer's review of Follistim® dated March 18, 1997, the original Medical Officer's review of Follistim® AQ dated 16-May-01, a Medical Officer's review of a safety update for Follistim® AQ on 14-May-97 and the Medical Officer's review of the Complete Response to the first Approvable action letter for Follistim® AQ (review dated 17-Jul-03). Additional information for this review was derived from published literature and a two current periodic safety updates (dated 19-Nov-04 and 08-Feb-05).

4.2 Tables of Clinical Studies

The tables listing the original clinical trials for follitropin beta products are contained in previous reviews of NDA 20-582 and NDA 21-273 and are incorporated into this review by cross-reference.

4.3 Review Strategy

This review was conducted from the worldwide post-marketing information provided by the Applicant in two safety updates submitted by the Applicant on 19-Nov-04 and 08-Feb-05.

4.4 Data Quality and Integrity

Data quality and integrity for Follistim® and Follistim® AQ were previously reviewed (see Medical Officer Reviews for NDA 20-582 and 21-273) and found acceptable. The appropriate DSI audits conducted during the initial review of clinical data to NDA 21-273 did uncover some violations at one of the clinical sites.

Reviewer's comment: However, the Medical Team concluded during the original review of Follistim® AQ that the violations at the clinical site did not warrant exclusion of the data from the site for the purposes of demonstrating bioequivalence. No new clinical study data was submitted with this Amendment, and therefore new DSI audits are not necessary.

4.5 Compliance with Good Clinical Practices

Informed consent forms were not evaluated for this post-marketing safety update.

4.6 Financial Disclosures

The financial disclosure statements (FDA 3454) for Follistim® AQ liquid were reviewed previously (see original Medical Officer Review of NDA 21-273 dated 16-May-01) and found to be acceptable. An updated financial disclosure is not required for this Complete Response since no new clinical studies for Follistim® AQ were requested or submitted.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics and Pharmacodynamics

The main difference between the original approved Follistim® formulation and the current proposed formulation is in the concentration of follitropin beta.

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

The Applicant determined that the conventional syringe delivered a lower amount than the nominal dose, and calculated a correction factor to the AUC and C_{max} for Follistim® concluding that the Pen-Injector with Follistim® AQ was bioequivalent to the approved Follistim® product.

The bioequivalence study from NDA 21-211, (with additional in vitro comparative data using the correction factor on loss of dose during handling), was acceptable to the Office of Clinical Pharmacology and Biopharmaceutics to support the Applicant's request for a Biowaiver submitted 11-Jan-00. The bioequivalence study submitted in NDA 21-211 was referenced for the waiver of bioequivalence between the original approved Follistim® lyophilized cake formulation and Follistim® AQ liquid, was conducted following subcutaneous administration, the Applicant was requested to provide information to show that subcutaneous equivalence can be extrapolated to intramuscular administration. In response the Applicant submitted synopses of 3 pharmacokinetic studies that supported bioequivalence of 150 IU/ml Follistim® by the intramuscular or subcutaneous route of administration in total injections.

A safety and efficacy study previously submitted to the original Follistim® NDA (20-582) also showed comparable safety and efficacy between the subcutaneous and intramuscular routes of administration. The Clinical Pharmacology and Biopharmacology concluded that the bioequivalence of Follistim® and therefore, Follistim® AQ via the subcutaneous route of administration could be extrapolated to the intramuscular route of administration.

No additional biopharmaceutical studies were necessary for this Complete Response.

6 INTEGRATED REVIEW OF EFFICACY

6.1 First Indication:

Follistim® AQ (follitropin beta injection) is indicated for the development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology.

6.16 Efficacy Conclusions

This reviewer concurs with the previous Medical Officer's conclusion that efficacy for the indication of Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology procedure is based primarily on the bioequivalence of Follistim® AQ liquid formulation to the approved Follistim® lyophilized cake formulation-SRS.

6.2 Second Indication:

Follistim® AQ is also 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.

6.16 Efficacy Conclusions

This reviewer concurs with the previous Medical Officer's conclusion that efficacy for induction of ovulation in the anovulatory infertile patient is also based primarily on the bioequivalence of Follistim® AQ liquid formulation to the approved Follistim® lyophilized cake formulation.

The Applicant conducted a single supportive open-label clinical trial (Protocol █████) that provided some additional data for one of the two proposed indications, ovulation induction.

Reviewer's comment: This reviewer concurs with the original Medical Officer's review that the supportive clinical trial (Protocol █████) alone does not provide substantial evidence of efficacy upon which approval could be based. However, the results of clinical Protocol █████ were supportive to the bioequivalence study for the indication of ovulation induction.

INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety of this drug is based primarily on data from the clinical studies reviewed in the original NDA (20-582) for Follistim® lyophilized cake formulation approved on 29-Sep-97. The overall adverse event data for the original approved Follistim® lyophilized cake formulation-SRS product with the additional supportive ovulation induction study (Protocol █████) conducted with Follistim® AQ liquid formulation were previously reviewed and found clinically acceptable. (See Medical Officer's original review of Follistim® lyophilized cake (NDA 20-582) dated 18-Mar-97, a Medical Officer's safety update of NDA 20-582 dated 11-Sep-97, the Medical Officer's original review of 21-273 dated 16-May-01, a secondary safety review of NDA 21-273 dated 30-Jan-03, and a review of the initial safety update for NDA 21-273 dated 16-Jul-03.) Additional post-marketing overseas safety data was collected by the Applicant and submitted in this Complete Response. In this reviewer's opinion, the post-marketing data in the safety update did not demonstrate new safety trends or issues.

7.1.7.5 Special assessments

ODS conducted a post-marketing safety review of the literature for an association between gonadotropins and a variant of Creutzfeldt-Jacob disease (vCJD) dated 20-Mar-03. The ODS reviewer concluded that there were no confirmed cases of vCJD after use of urinary or recombinant derived products. At this time, there is no evidence of a link between vCJD and any recombinant gonadotropin product, although surveillance should continue.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There have been no reports of abuse or dependence with any Follistim® product (follitropin beta for injection) or any of the gonadotropin products during clinical studies or in the post-marketing adverse event reports submitted by the Applicant.

7.1.14 Human Reproduction and Pregnancy Data

The Applicant provided a summary of pregnancy outcomes (Study 058007) collected from the supportive ovulation induction study (058004) originally submitted to this NDA. These pregnancy outcomes are listed in Table 1.

Reviewer's comment: In this reviewer's opinion, the pregnancy outcome data from open-label Study 058004 (listed in Table 1) is of limited use. The numbers of miscarriages are similar between Follistim® cake and Follistim® AQ solution.

It is noted that there were numerically a greater number multiple deliveries in the Follistim® AQ solution group (six) compared to the Follistim® cake group (two). Also of note was that a larger number of neonates in the Follistim® AQ solution group had abnormalities (six) compared to the Follistim® cake group (one). This was an open-label study and the total numbers of multiple births are too small to draw any conclusion about the risk of multiple births with use of Follistim® AQ solution. In addition, the increased rate of neonatal abnormalities seen in the Follistim® AQ group is most likely secondary to the higher rate of multiple births (with multiple births having an increased rate of congenital anomalies).

Follistim® products (follitropin beta) are contraindicated during pregnancy, and therefore, assessments of the risks of use in pregnancy are unnecessary. Since the amount of Follistim® excreted in breast milk is unknown, (and therefore, the risks are unknown) the Applicant has recommended that a practitioner should consider whether discontinuation of nursing should occur if the patient wishes to proceed with a treatment cycle.

In this Amendment, the Applicant has documented seven post-marketing reports of Follistim® use during pregnancy or lactation. One of these seven reports contained information of a 42v year old patient who miscarried after follitropin beta treatment during pregnancy. In addition, the post-marketing data had reports of 4 congenital, familial and genetic disorders reported to the Applicant since the initial marketing of Follistim® in 1996.

7.1.15 Assessment of Effect on Growth

Follistim® AQ is not for use in the pediatric patients, and therefore, no studies of growth in infants or children was necessary.

7.1.16 Overdose Experience

Aside from the possibility of Ovarian Hyperstimulation Syndrome and multiple births (as discussed previously), there are no additional known risks concerning the consequences of acute overdosage with Follistim® (follitropin beta for injection) or any other gonadotropin product.

7.1.17 Postmarketing Experience

In this submission, the primary clinical data source for this review was a post-marketing safety update submitted 19-Nov-04. This update reports the most recent safety data from the worldwide experience with Puregon® products (tradename Follistim® in the United States). The most recent estimate provided by the Applicant reports that the total amount of follitropin beta for injection sold worldwide in 2004 to be [REDACTED] international units sold. The Applicant reported that a breakdown of these figures by product lyophilized cake, liquid and pen-injector device at in the past year revealed that approximately [REDACTED] of sales were in the liquid formulation (with over [REDACTED] of sales being follitropin beta in the cartridge pen device) and approximately [REDACTED] were the lyophilized cake formulation.

For the year 2004, it is estimated that if all the distributed vials were used for Assisted Reproductive Technology procedures, this would have resulted in a maximum of [REDACTED] cycles or for ovulation induction, a maximum of [REDACTED] cycles.

Reviewer's comment: Given these estimates for all follitropin beta products, the current 2004 world-wide experience provided by the Applicant combined with the safety update for all follitropin beta products since 1996 appears adequate for the purposes of generating a safety profile for Follistim® AQ liquid, since the liquid (in vials and in the pen-injector) appears to represent a majority of the product currently sold overseas.

7.2 Adequacy of Patient Exposure and Safety Assessments

Safety data has been collected since 1997 when the original formulation of Follistim® lyophilized cake formulation-SRS was approved in the United States and in Europe since 1999 when Follistim® AQ liquid formulation was introduced. Patient exposure is adequate as evidenced by the previously reviewed clinical studies as well as current estimate of patient usage in 2004 reported in the 08-Feb-05 post-marketing safety update. Therefore, the safety profile for Follistim® products (and therefore, Follistim® AQ) appears adequate and well defined.

7.2.2.1 Other studies

The Applicant has indicated that no new clinical studies are in progress or planned for Follistim® AQ.

7.2.2.3 Literature

The Applicant indicated that since the Follistim® AQ was introduced in overseas in 1999, a total of 33 clinical studies were completed, although a complete listing of all published literature was not included in the submission. However, since the re-submission of the this NDA for Follistim® AQ liquid in November 2004, the Applicant reported that no new studies for safety were conducted, and no relevant new safety information emerged from non-clinical, clinical or epidemiologic studies.

In response to a request from the Division to provide a tabular overview of published literature reports since the previously submitted safety update, the Applicant provided eight references of published adverse events after gonadotropin use. Three published adverse event case reports were included in the submission, although the gonadotropin(s) used were not identified in the publications.^{11,12,13} These three published serious adverse events all occurred after controlled ovarian hyperstimulation. All three patients had significant ovarian hyperstimulation syndrome associated with a subsequent secondary complication (myocardial infarction, massive unilateral hydrothorax and a perforated duodenal ulcer), although all patients recovered. An additional publication was included on a clinical pregnancy with Triple Y syndrome after Puregon® use.

Reviewer's comments: Published literature indicates that ovarian hyperstimulation syndrome (OHSS) after controlled ovarian hyperstimulation can lead to life-threatening complications and several deaths. The fluid redistribution in OHSS leads to many of the reported complications including pleural effusion, hemoconcentration, hypercoagulability and electrolyte imbalance. These changes rarely results in more serious adverse events such as thrombosis resulting in clots or stroke, myocardial infarction and liver and renal dysfunction requiring medical intervention, Unfortunately, the majority of these publications do not identify the gonadotropin used, although several occurred prior to the use of recombinant gonadotropins. Therefore, in this reviewer's opinion, although these are serious adverse events, there is no evidence that these complications are secondary to one particular brand of gonadotropin, but may be a rare class effect. The literature appears to support that although OHSS may result from gonadotropin stimulation, death after gonadotropin-induced OHSS is very rare. In addition, it does not appear that any particular gonadotropin (including follitropin beta products) results in a significant number or type of complications after ovarian hyperstimulation syndrome. Therefore, no specific changes to the warnings or adverse events section of the label are indicated by these post-marketing reports.

Congenital abnormalities after intracytoplasmic treatment have been noted in previous literature reports, and have lead to concerns about the technique.¹⁴ However, in this reviewer's opinion, there is no evidence that use of any gonadotropin increases the risk of any specific type of congenital or genetic abnormalities. However, continued monitoring of post-marketing adverse event reports is warranted.

7.2.3 Adequacy of Overall Clinical Experience

Safety data has been collected since 1997 when the original formulation of Follistim® lyophilized cake formulation-SRS was approved and overseas since 1999 when the liquid formulation was first introduced to the overseas market. The overall clinical experience with the original approved Follistim® product is adequate, and the safety profile is well defined. There is no clinical evidence that the experience with Follistim® AQ formulation will be significantly different from the original Follistim® product.

7.2.9 Additional Submissions, Including Safety Update

Most of the safety information submitted by the Applicant has already been submitted to the NDA previously. The current update (dated 19-Nov-04) contained safety data on follitropin beta products from the first introduction of the Follistim® AQ liquid formulation in 1999 up to the month of the submission in November 2004. Additional tabulations of the post-marketing safety data were requested by the Medical Reviewer on 23-Dec-04 to examine serious adverse events and individual case reports since the previous post-marketing safety update submitted in the Follistim® AQ submission dated 17-Oct-02. In response to the most recent (and second) Approvable letter (dated 17-Jul-03), the Applicant submitted current post-marketing and overseas labeling information.

1. The overall safety profile of the post-marketing adverse event reports from the initial launch of follitropin beta liquid in 1999 through 2004 is summarized in Table 2. The Applicant also reported that since the previous safety update in 2002, there were a total of 208 spontaneous adverse events reported with use of follitropin beta products, of which 38 were serious.
2. New safety data:
 - No safety data for the proposed indications is included in this post-marketing safety update. The Applicant reports that no new clinical studies for the proposed indications of multiple follicular development for Assisted Reproductive Technology therapy or ovulation induction have been conducted by the Applicant since the previous safety update submitted in 2002.
 - Summary tabulations of selected adverse event data from prior to 1999 (pre-launch of follitropin beta liquid) is compared to the recent post-marketing adverse event reports for follitropin beta from 1999 through 2004 (See summary of this tabulation in Table 3).
 - The Applicant reported that follitropin beta products are approved overseas for the additional indication of deficient spermatogenesis due to hypogonadal hypogonadism. One medically confirmed adverse event (injection site pain) was reported in the post-marketing adverse event reports collected since the 1999 launch date of follitropin beta liquid and no serious adverse events were reported to have occurred in men since the previous 2002 safety update.
3. No new data was obtained from premature study discontinuations by the Applicant since the previous safety update in 2002 as no new studies were conducted.
4. The Applicant provided additional updated information on serious adverse events reported for follitropin beta.
 - a. Case report forms and summaries were previously provided for three patients who died after use of follitropin beta products. These three deaths were previously reported to the Division and reviewed by the Medical Officer including:
 - Case CNL-123581-NL – In case report, there is suspicion that suicide was the actual cause, and this is also the opinion of the reporting doctor. A 29 year old female patient was reported in Vietnam. The death occurred 14 days after receiving the last dose of Puregon® (European formulation of Follistim®) 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.

- Case Report 2003-106353-NL – A 33 year old woman in the Philippines was brought to the emergency room in shock with a ruptured ectopic pregnancy. She had a history of previous ectopic pregnancies. She underwent controlled ovarian stimulation with Puregon® for an in vitro fertilization procedure.

The subsequent ultrasound documented an intrauterine pregnancy. She subsequently died after a failed resuscitation in the Emergency Room.

- Case Report 2003-103132-NL - A 32 year old woman in Ireland developed ovarian hyperstimulation syndrome after stimulation with the Puregon® in a pen-injector device. Thirty-two oocytes were recovered during an in vitro fertilization procedure.

She developed Adult Respiratory Distress Syndrome and was subsequently placed on a ventilator. She died 39 days after a dose of human chorionic gonadotropin to stimulate maturity of the oocytes.

- b. The applicant provided a narrative summary of serious adverse events that were reported in clinical studies since the initial marketing of the liquid follitropin beta (See summary in Table 4). In addition, the applicant also provided a narrative summary of serious adverse events collected since the previous 2002 safety update (See summary in Table 5).

Reviewer's comment: Of the serious adverse events (SAEs) reported, the most frequently reported was ovarian hyperstimulation syndrome. From the case reports provided by the Applicant, it appears that there were 4 cases in 2002, 4 cases in 2003 and 3 cases in the 11 months reported in 2004. These reports do not appear to indicate an increased trend in ovarian hyperstimulation cases with use of follitropin beta, and no trends in other serious adverse events were seen in these adverse event case reports. Additionally of note is that none of the fatalities were reported with use of the Follistim® cake formulation currently marketed in the United States.

5. The Applicant provided a summary of all non-serious reports for all follitropin beta products beginning in 1999 (the initial marketing of follitropin beta liquid). The Applicant divided these events by reporting period so that a comparison between the previous post-marketing data on the liquid could be compared to more current post-marketing data. (See summary of common adverse events seen previous to the liquid introduction in 1999 compared to more recent safety data using common adverse events derived from the original Follistim® label in Table 3).
6. The Applicant provided a summary of the worldwide experience with follitropin beta products by reporting that these products have been available since registration in May, 1996 and are currently sold in over 64 countries including the United States (in the lyophilized cake formulation) in Table 6. In addition, the most recent submission by the Applicant stated that no actions for safety reasons were initiated by any regulatory authority or by the Applicant.

7. English translations of ten versions of foreign labels were included in the recent submission. The Applicant reports that these ten labels are representative of the current approved foreign labeling in 25 European Union and 46 non-European Union countries. The Applicant reported that no boxed or major safety warnings were added to any follitropin beta labels.

Reviewer's comments:

1. **In this reviewer's opinion, post-marketing data submitted for follitropin beta liquid is not adequate to determine the actual frequencies of adverse events for these products, and are not useful for comparison to those seen in the original clinical studies. However, post-marketing safety profiles are useful for examining rare events and trends. In addition, the safety profiles obtained (see Table 2 and Table 3), a tabulation of serious adverse events obtained from more recent clinical studies (Table 4), and a review of the most recent post-marketing safety reports (Table 5) do not demonstrate new safety issues or trends.**
2. **It is important to note that the number of reports of ovarian hyperstimulation syndrome appears to have increased significantly over the timeframe of introduction of follitropin beta liquid (3 in the initial reporting period prior to 1999 compared to 28 post 1999). In this reviewer's opinion, the increased reporting of ovarian hyperstimulation over time is probably secondary to the increased number of ART treatment cycles (64,724 cycles in 1996 compared to 107,587 cycles in 2001) being performed in the U.S.¹⁵. In this reviewer's opinion, there is no clinical data to suggest that follitropin liquid increases the absolute risk of ovarian hyperstimulation compared to other gonadotropin products.**
3. **The Applicant was unable to separate post-marketing adverse event reports by indication (use in ART procedures or ovulation induction) as this information was not readily reported or available to the Applicant in the majority of reported adverse events. In this reviewer's opinion, the post-marketing data is too limited to further determine an actual adverse event rate for each individual indication. Therefore, the Applicant should continue to attempt to determine the indication of use for all reported adverse events if possible, especially in cases of severe ovarian hyperstimulation syndrome or deaths.**
4. **No additional deaths were reported with follitropin beta products in 2004. However, the rates of ectopic pregnancies [approximately 3% in a study of the approved Follistim® product (37608) from NDA 20-582] and OHSS [approximately 5.2% in a study of the approved Follistim® product (37608) from NDA 20-582] were previously documented in controlled clinical studies. Death after severe ovarian hyperstimulation syndrome¹⁶ and ruptured ectopic pregnancies¹⁷ have been reported in the literature, although not in any controlled clinical study of follitropin beta to date.**

In this reviewer's opinion, the occurrence of these post-marketing deaths, although rare, emphasize the need for continued monitoring of serious adverse events after use of follitropin beta products.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The very limited pregnancy outcome information from follow-up of patients enrolled in study 058007 and additional post-marketing information provided in this submission does not demonstrate new trends in miscarriage, intra-uterine death or congenital anomalies. However, this reviewer notes that no definitive conclusions on the effects of Follistim® during pregnancy and lactation can be made with these few case reports. Current literature evidence suggests that there are increases seen in the risks of multiple gestation, chromosomal abnormalities, low birth weight infants and preterm delivery in children conceived with ART.¹⁸

It is unknown whether the risks with use prior to or during pregnancy are a direct result of ART treatment, the gonadotropin used, or whether these effects are attributable to the parent's underlying infertility problem. However, the worldwide post-marketing reports provided by the Applicant does not appear to demonstrate any new trends or safety issues and further supports the approval of this product. In addition, there is no evidence of any additional clinical safety issues with Follistim® AQ since the original submitted application for the Follistim® AQ liquid formulation.

In conclusion, this Medical Reviewer concurs with the previous clinical review for Follistim® AQ that there are no new safety issues to resolve with Follistim® AQ liquid formulation.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

A starting dose of 150 to 225 IU of Follistim® AQ (follitropin beta injection) is recommended for at least the first four days of treatment for patients undergoing Assisted Reproductive Technology procedures. After this, the dose may be adjusted for the individual patient based upon their ovarian response.

The starting dose suggested for patients undergoing ovulation induction is 75 IU of Follistim® AQ for up to 14 days. The dose should then be increased by 37.5 IU of Follistim® AQ at weekly intervals until follicular growth and/or serum estradiol levels indicate an adequate response.

This is identical to the dosage regimens recommended for the original approved Follistim® product, and is acceptable.

8.2 Drug-Drug Interactions

No drug-drug interaction studies have been performed with any of the Follistim® products. In this clinical reviewer's opinion, this is acceptable as it is unlikely that a recombinant follicle stimulating hormone product would cause significant drug interactions in the indicated young, healthy infertile female population

8.3 Special Populations

Safety and effectiveness in geriatric patients have not been established. This is acceptable given the indications of this product.

8.4 Pediatrics

Safety and effectiveness in pediatric patients have not been established. This is acceptable given the indications of this product.

8.5 Advisory Committee Meeting

An Advisory Committee meeting is not recommended for this submission (Complete Response) as an Amendment to a 505b (2) application.

8.6 Literature Review

The Applicant provided a list of summaries of 34 relevant clinical studies that included published literature from original clinical studies of the original lyophilized Follistim® product through the present day. These brief summaries reported on the design and description of follitropin beta use for the indications of multiple follicular development and ovulation induction, although no study results were reported. The Applicant reported that in these studies over 2500 subjects were exposed to follitropin beta products.

Reviewer's comments:

- 1. None of the additional listed study outlines would meet the Division's criteria to support additional efficacy claims for the liquid formulation of follitropin beta.**
- 2. The Applicant provided a table with outlines of 34 relevant clinical studies. The Applicant also provided clinical data from a study that compared the local tolerance of follitropin beta solution with the cake formulation (E1616) in patients undergoing ART procedures. The protocol and results of this study were not previously reviewed by the Division. Study E1616 was an open-label, randomized, cross-over, multicenter study that had a primary objective of comparing local tolerance (using both a diary card and Visual Analogue Scale [VAS]) for Follistim® AQ solution compared to Follistim® in five centers in the European Union. This study treated 182 women undergoing IVF or IVF/ICSI with follitropin beta solution (89 subjects) or cake (93 subjects) for up to two treatment cycles. The Applicant concluded that no large treatment differences were observed for the different types of local reactions (itching, pain, bruising, swelling, and redness) between the two treatment groups. No significant clinical differences were seen in the number of oocytes retrieved or clinical pregnancies in first treatment cycle (defined as at least one fetal heart confirmed on ultrasound) as seen in Table 7. In addition, no differences in the number of patients who had ovarian hyperstimulation syndrome or serious adverse events were noted in comparing the two treatment groups as seen in Table 7.**

Although this study would not be adequate for additional efficacy or safety claims, (and this study was performed using a European formulation of follitropin beta), study E1616 appears to be supportive of the Applicant's position that there is no evidence of significant differences between the Follistim® cake formulation and the solution.

8.7 Postmarketing Risk Management Plan

None required.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

This clinical reviewer concurs with the original Medical Officer's review that Follistim®-AQ liquid formulation differs from the original formulation in pharmaceutical presentation only. This reviewer concludes that the benefits of taking Follistim® AQ outweigh the risks.

9.2 Recommendation on Regulatory Action

Approval of this application for Follistim® AQ is recommended pending resolution of outstanding cGMP manufacturing and testing issues based on the recommendation by "Withhold" from Compliance after plant inspection in April 2005.

9.3 Recommendation on Postmarketing Actions

No additional recommendations necessary.

9.3.1 Risk Management Activity

The Applicant should continue to monitor all adverse event reports and any safety trends.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

The proposed label was submitted for review. Clinical safety and efficacy data included in the labeling for Follistim® AQ liquid formulation are identical to the labeling for the approved Follistim® lyophilized cake formulation.

The Division of Medication Errors and Technical Support (DMETS) accepted the use of the proprietary name of Follistim AQ on 25-Mar-03. In addition, DMETS also re-reviewed the proposed container, carton and insert labels for Follistim® AQ liquid formulation on 11-Feb-05. DMETS made several recommendations to the container label, carton, and insert label.

Reviewer's response to February 2005 DMETS comments:

- 1. This reviewer disagrees that the abbreviation for international units (IU) would be confused with intravenous (IV). There is no intravenous use of any gonadotropin product, and most practicing physicians use international units to determine therapeutic dosage regimes.**
- 2. This reviewer disagrees that a different recommendation for the dosage and administration section for Follistim® AQ is necessary. This reviewer notes that the recommended dosage and administration section for ovulation induction for Follistim® AQ relies on clinical study information obtained from the original clinical studies for Follistim® cake formulation. Therefore, the ovulation induction dosage and administration sections for Follistim® and Follistim® AQ would be identical.**

The Division of Drug Marketing, Advertising and Communications (DDMAC) also reviewed the proposed label on 02-Mar-05. The DDMAC reviewer recommended two minor changes to the package insert. These comments on the label will be considered after resolution of the "Withhold" issued by the Office of Compliance during future labeling negotiations with the Applicant.

9.5 Comments to Applicant

No additional comments to the Applicant from the Clinical Reviewer.

10 APPENDICES

10.1 Line-by-Line Labeling Review

Label not included. Labeling negotiations are pending the Office of Compliance determining a withdrawal of the "Withhold" recommendation.

10.2 Tables

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Table 1 – Pregnancy outcome data from Study 058007 (Follow-up information from ovulation induction study 058004)

Adverse Event	Follistim cake formulation	Follistim® AQ solution formulation
Total number of patients treated	64	62
Miscarriage	0	0
Singleton delivery	10	7
Multiple delivery	2	6
Premature delivery*	8	9
Number of neonates with a congenital abnormality	0	2**

*Delivery before 37 weeks

** One neonate had bradycardia, the other neonate had Down's syndrome and a heart malformation.

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Table 2 - Summary Table comparing selected serious and non-serious (combined) adverse events per MedRA system organ class, preferred term*

Adverse Event	Number of Adverse Event Reports
Miscarriage	2
Ovarian Hyperstimulation Syndrome	28
Ectopic Pregnancy	2
Abdominal Pain	2
Injection Site Pain	30
Vaginal Hemorrhage	0
Hemoperitoneum	0
Adnexal Torsion	0
Dizziness	2
Tachycardia	0
Dyspnea	3
Tachypnea	0
Fever	2**
Chills	0
Musculoskeletal aches	0
Joint Pain	0
Nausea	3
Headache	8
Malaise	2
Breast Tenderness/Pain	1
Dry Skin	0
Body Rash	5
Hair loss	3
Hives	0
Ovarian neoplasm	1

*Selection of adverse events derived from list of Adverse Reactions section in the label for the current approved Follistim® lyophilized product.

** Listed as pyrexia

Table 3 – Summary Table comparing selected serious and non-serious (combined) adverse events per MeDRA system organ class, preferred term*

Adverse Event	Post-marketing Adverse Event Reports since 1999	Post-marketing Adverse Event Reports from 1999-2004
Miscarriage	0	2
Ovarian Hyperstimulation Syndrome	3	28
Ectopic Pregnancy	1	2
Abdominal Pain	6	2
Injection Site Pain	33	30
Ovarian Cyst	1	1

*Selection of adverse events derived from list of Adverse Reactions section in the label for the current approved Follistim® lyophilized product.

Table 4 – Summary Table of selected serious adverse events per MeDRA system organ class, preferred term for clinical studies reported between 1999 and 2004

Serious Adverse Event	Adverse event reports
Fetal Reduction	2
Ectopic Pregnancy	1
Ovarian Hyperstimulation Syndrome	29
Ovarian Cyst	1
Ovarian torsion	2
Asthma attack	1
Deep venous thrombosis	1

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Table 5– Summary Table of selected serious adverse events from post-marketing data per MedDRA between 2002 (previous safety update) and 2004

Serious Adverse Event	Adverse event reports
Joint effusion	1
Ectopic Pregnancy	1
Ovarian Hyperstimulation Syndrome	12
Sex chromosome abnormality (infant)	1
Epilepsy	1
Hypersensitivity/Hives	1
Loss of consciousness	1
Autism (infant)	1
Pulmonary embolism	1
Ischemic stroke	1
Parathyroid adenoma	1
Abdominal distention	1

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On Original

Table 6 – Total amount of follitropin beta sold, per reporting country in 100 IU recombinant follicle stimulating hormone

Country	Total amount since May 1999 through November 2004
Australia	
Canada	
Chile	
Czech Republic	
Denmark	
Finland	
France	
Germany	
Greece	
Italy	
Netherlands	
New Zealand	
Norway	
Philippines	
Sweden	
Switzerland	
Turkey	
United Kingdom*	
United States**	
Vietnam	
Other***	
Total	

* United Kingdom includes sales figures for Ireland

** In the US, Follistim® is sold as a kit containing three vials of 75 IU Follistim® with Antagon®

*** Sales in countries where follitropin beta was sold, but no reports on follitropin beta were received

Table 7 – Summary Table derived from study E1616

Secondary efficacy outcomes in the first treatment cycle	Follitropin beta solution	Follitropin beta cake
Total subjects treated	89	93
Total subjects with embryo transfer	76	76
Mean number of oocytes retrieved	9.7	9.0
Mean number of obtained embryos	7.1	6.8
Clinical pregnancy rate per started cycle (with at least one fetal heartbeat)	26.8%	26.1%
Ovarian hyperstimulation syndrome	3	2

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/s/

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Shelley Slaughter
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I concur.

**Follistim®-AQ
Team Leader Review**

NDA: 21-273
Resubmission (October 18, 2002)

Drug: Follistim®-AQ (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 aqueous solution for subcutaneous or intramuscular injection; each vial contains 75 IU, 150 IU, FSH per 0.5 ml

Applicant: Organon, Inc.

Original Resubmission Date: October 18, 2002

Primary Clinical Review Completed: July 14, 2003

Date of Memorandum: July 16, 2003

Background

NDA 20-582 for Follistim® was approved by the Agency on 9/29/97 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 lyophilized cake formulation for reconstitution with sterile water.

NDA 21-273 for Follistim®-AQ was submitted on July 21, 2000. Evidence for safety and efficacy were to be based on a waiver of bioequivalence based on a previous bioequivalence trial of Follistim®-AQ Cartridge vs. Follistim® submitted to NDA 21-211. This trial was a comparative open-label bioavailability study comparing a single dose of Follistim®-AQ (150 IU) Cartridge with Follistim® (reconstituted 150 IU). Follistim®-AQ Cartridge resulted in a 20% higher AUC and Cmax than Follistim® 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 [REDACTED] 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 Cmax values for Follistim® delivered with the conventional syringe and with this correction factor, Follistim®-AQ Cartridge administered with the Pen-Injector was bioequivalent to Follistim®. The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) accepted this approach to demonstrate that the drug product in Follistim® and Follistim®-AQ are bioequivalent and are expected to result in the same blood levels when delivered by the conventional syringe and needle. Therefore, based on the bioequivalence study from NDA 21-211 and the in vitro comparative data on loss of dose during handling and injection, the request for waiver of a bioequivalence study for the Follistim-AQ liquid formulation for NDA 21-273 was acceptable to OCPB. Because the bioequivalence study, referenced for the waiver of bioequivalence, was conducted following subcutaneous administration, the Sponsor was requested to provide information to show that subcutaneous equivalence can be extrapolated to intramuscular administration. In response the Sponsor submitted synopses of 3 pharmacokinetic studies that supported bioequivalence of 150 IU/ml Follistim® by the intramuscular or subcutaneous route of administration in [REDACTED] total injections. A safety and efficacy study submitted to the original NDA, 20-582, also showed comparable safety and efficacy between the subcutaneous and intramuscular routes of administration. Based on this information, the bioequivalence via the subcutaneous route of administration can be extrapolated to the intramuscular route of administration.

The Office of Compliance issued a "Withhold" recommendation on October 30, 2000 following a WARNING letter issued on September 19, 2000 by the New Jersey District after inspection of the West Orange, NJ manufacturing plant between July 17 and August 23, 2000. From a Chemistry, Manufacturing and Controls perspective, the NDA was considered approvable pending satisfactory resolution of CMC and Microbiology deficiencies and satisfactory inspection reports from the Office of Compliance.

NDA 21-273 receive an approvable recommendation on May 24, 2001. A complete response addressing chemistry and microbiology deficiencies was received on October 18, 2002. On April 14, 2003, the Agency received additional chemistry data comprised of the executed batch records on two additional validation batches requested by the Agency. The receipt of the data was within 3 months of the user fee goal date and the review clock was extended by ninety days to July 18, 2003.

Clinical Efficacy and Safety

Efficacy and safety of NDA 21-273 for Follistim®-AQ are based on bioequivalence of the liquid drug product formulation of Follistim®-AQ to the reconstituted lyophilized cake drug product formulation of Follistim® when both are delivered by conventional syringe and needle. During the original review cycle, the Sponsor requested a biowaiver for bioequivalence based on a bioequivalence study comparing Follistim®-AQ Cartridge with Follistim® and an in vitro comparative study on loss of dose during handling and injection, a biowaiver was granted. In the original review cycle application, the Sponsor also submitted a supportive clinical trial (Protocol [REDACTED]) for ovulation induction. As a stand-alone study this study would not have provided sufficient evidences for efficacy and safety, however, it was supportive to the bioequivalence study for the indication of ovulation induction. No new clinical trial results were submitted with this resubmission. A safety update was submitted January 29, 2003. There were no new concerns for safety raised with this update. There were two foreign deaths reported with the use

of Follistim®. One of these was a suicide. The other death occurred 14 days after last administration of Follistim® but autopsy results were not released and treating officials were unwilling to discuss the case.

Chemistry, Manufacturing and Controls

All Chemistry and Microbiology deficiencies noted in the May 24, 2001 Approvable letter were satisfactorily addressed. Please refer to Chemistry and Microbiology reviews.

As discussed above in this review, because of cGMP issues that were noted during the inspection in July and August 2000, the District issued a "Withhold" recommendation for the West Orange, NJ drug product manufacturing facility. Based on the District's recommendation, the Office of Compliance issued a "Withhold" recommendation on October 30, 2000. Another "Withhold" recommendation was issued on April 16, 2002 because the firm was not ready for re-inspection. Following an inspection on August 23, 2002, the District again issued a "Withhold" recommendation due to inadequate quality assurance (QA) functions, and the Office of Compliance concurred. To address this issue of inadequate QA functions and deficiencies found in executed batch records, the sponsor was requested to manufacture two additional batches of drug product (see 3/4/03 and 3/28/03 amendments). After the batches were manufactured the District would re-inspected the West Orange facility and confirm that past GMP deficiencies have been resolved. In addition, the executed batch records, along with batch release data, would be submitted to the NDA (see 4/11/03 and 4/30/03 amendments). The submitted executed batch records were reviewed and found to be acceptable. No glaring deficiencies were noted during review. In addition, the certificate of analysis for the two batches show that the drug product complied with all test attributes.

A WARNING letter and "Withhold" recommendation were issued by the District on June 27, 2003 for the West Orange, NJ facility following inspection on June 26, 2003. The Office of Compliance has concurred with the "Withhold" recommendation. The District also stated that Organon has shut down the manufacturing facility and is implementing corrective actions.

From chemistry, manufacturing, and controls point of view, this NDA is Approvable. The Sponsor's West Orange, NJ facility will need to be in cGMP compliance before an Approval recommendation can be issued. In addition, all relevant facilities in the application need to remain in cGMP compliance.

Conclusions and Recommendations:

After adjusting for losses in the handling and preparation for injection with the syringe and needle for the reconstituted lyophilized cake formulation, it was accepted that the drug product in Follistim®-AQ Cartridge and Follistim® were bioequivalent. Both the liquid formulation and the reconstituted lyophilized cake formulation when administered by conventional syringe and needle should provide the same bioavailability. In the original review cycle a biowaiver for bioequivalence for Follistim®-AQ and Follistim® was accepted based on the original bioequivalence study and the in vitro comparative data on loss of dose during handling and injection for Follistim® solution formulation versus Follistim® cake formulation. An Approvable action was taken during the original review period because of Chemistry and Microbiology deficiencies as well as a non-acceptable inspection of one of the manufacturing sites. All Chemistry and Microbiology deficiencies were satisfactorily addressed. However, major manufacturing site deficiencies remain and the Office of Compliance has issued a "Withhold" approval recommendation.

I agree with the Chemistry and Medical Officer recommendations that this application receive an Approvable action. The Sponsor's West Orange, NJ facility will need to be in cGMP compliance before an Approval recommendation can be issued. In addition, all relevant facilities in the application need to remain in cGMP compliance.

Shelley R. Slaughter, M.D., Ph.D.

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Follistim®-AQ liquid formulation

NDA 21-273

CLINICAL REVIEW

Medical Officer's Review
NDA 21-273/N-000-AZ.

Date NDA Submitted: December 23, 2002
Date NDA Received: December 29, 2002
Review Finalized: July 14, 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 liquid formulation
Chemical: recombinant human follicle stimulating hormone (r-hFSH)

Pharmacologic category: Infertility

Dosage/Strength: Sterile aqueous solution for subcutaneous or intramuscular injection: each vial contains 75IU, 150IU, ~~300IU~~ FSH per 0.5ml.

Dosages Regime:

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 with patients who are responding, 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. However, in patients that were low or poor responders, maintenance doses of 375 to 600 IU were administered according to individual response. This later category comprised approximately 10% of evaluated women. The maximum, individualized, daily dose of Follistim®-AQ liquid formulation 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®-AQ liquid formulation therapy; this will reduce the chance of developing OHSS.

CLINICAL REVIEW

Ovulation Induction:

Treatment usually starts with a 75 IU daily dose of Follistim®-AQ liquid formulation that is continued for up to 14 days. If there is no ovarian response, the daily dose will then be increased by 37.5 IU of Follistim®-AQ liquid formulation at weekly intervals until follicular growth and/or serum estradiol levels indicate an adequate response. The maximum, individualized, daily dose of Follistim®-AQ liquid formulation 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 preovulatory 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®-AQ liquid formulation therapy, hCG must be withheld during this course of treatment; this will reduce the chances of developing OHSS. During treatment with Follistim®-AQ liquid formulation 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®-AQ liquid formulation 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.

Proposed indications:

Women: Follistim®-AQ liquid formulation 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 liquid formulation 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 21-211

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 liquid dated July 21, 2000, Original Medical Officer's Review dated May 14, 2001, Teleconference dated March 31, 2000 (Minutes dated April 28, 2000), Biopharmacologist's Review dated May 16, 2001, Team Leader Review dated May 16, 2001, Approvable Letter dated May 14, 2001, Sponsor's Response to Approvable letter dated October 18, 2002, Medical Officer's Safety Review dated January 29, 2003,

CLINICAL REVIEW

Related documents
(continued):

ODS/DMETS Consult dated March 19, 2003, DDMAC Review dated March 20, 2003, Extension of Goal date letter dated April 22, 2003.

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Clinical Review for NDA 21-273

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Approval of the submission for Follistim®-AQ liquid formulation is recommended from a clinical perspective in concurrence with the original Medical Officer review which found the clinical efficacy and safe data acceptable (see review dated May 14, 2001). The original application received an approvable letter dated May 24, 2001 because of chemistry, microbiology and manufacturing site deficiencies.

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

The sponsor has submitted additional Phase 4 post-marketing studies from the worldwide experience with this product as requested by the previous medical officer. These studies did not reveal any new safety or efficacy issues. No additional phase 4 studies are necessary.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The original Follistim® lyophilized cake formulation-SRS (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.

A pre-NDA meeting March 18, 1999 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 Follistim®, Follistim®-AQ Cartridge (NDA 21-211). Follistim®-AQ Cartridge contained a liquid formulation that would be injected using a pre-filled pen injector. The sponsor had completed a single bioequivalence study that compared the original formulation of Follistim® with the new liquid filled pen injector, Follistim®-AQ Cartridge.

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Organon requested a Biowaiver for Follistim®-AQ liquid formulation (NDA 21-273) that was contained in the Follistim®-AQ Cartridge. The biowaiver was submitted with data presented for Follistim®-AQ Cartridge on January 11, 2000. The sponsor felt that the concentration difference between the approved product and Follistim®-AQ liquid formulation would not impact bioavailability. However, the Division had concerns that concentration differences caused by the various ways in which the different Follistim® products are handled and administered could impact bioavailability.

Therefore, during a teleconference between DRUDP and Organon on March 31, 2000 (minutes issued by the Division April 28, 2000) a decision was reached that supportive data from in vitro tests to show volume/dose losses from liquid and cake formulations to support the waiver should be provided. Based on this decision, an in vitro study was submitted to substantiate the request for a biowaiver. Clinical Pharmacology and Biopharmaceutics section reviewed the studies and concluded that the in vitro studies of Follistim®-AQ liquid formulation would support a biowaiver.

The initial medical officer review was dated May 14, 2001. Approval of the NDA 21-273 was primarily based on acceptable demonstration of bioequivalence of the liquid formulation to the original approved and marketed Follistim® lyophilized cake formulation-SRS. The medical officer accepted the recommendation by the Office of Clinical Pharmacology and Biopharmaceutics that bioequivalence was demonstrated. Based on bioequivalence of the liquid formulation to the approved reconstituted lyophilized cake and a supportive clinical trial for ovulation induction, the medical officer recommended that Follistim®-AQ liquid formulation was approvable.

A GMP and pre-approval inspection revealed deficiencies that resulted in NDA 21-273 to receive an Approvable action on May 24, 2001. The sponsor submitted an additional amendment on October 18, 2002 for NDA 21-273. In addition, the sponsor submitted two additional validation batches as agreed upon at a teleconference between the Chemistry Team Leader and the Sponsor. The amendments include a response to the deficiencies and additional tabulations of clinical safety data. No new clinical studies are included in the amendment

B. Efficacy

The new liquid formulation (NDA 21-273) was based on the assumption that Follistim®-AQ liquid formulation was clinically equivalent to Follistim® lyophilized cake formulation-SRS, and a biowaiver was granted. A single supportive clinical trial, Protocol [REDACTED], was also submitted in the application for the Follistim®-AQ liquid formulation.

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The clinical study was performed in 126 patients with 62 patients in the Follistim®-AQ liquid formulation arm and 64 patients in the Follistim® lyophilized cake formulation-SRS (the original approved product). Ovulation rate was the primary efficacy parameter, and the difference between the Follistim® groups for overall ovulation was not statistically significant.

The indications claimed are: 1) induction of ovulation and 2) for use in assisted reproductive technologies, the same indications for the original approved product.

C. Safety

Follistim®-AQ liquid formulation differs from the approved Follistim® lyophilized cake formulation-SRS in the pharmaceutical presentation only. Data on clinical safety contained in NDA 20-582 for the original approved product Follistim® lyophilized cake formulation-SRS, pertinent annual reports for Follistim® lyophilized cake formulation-SRS, a supportive clinical study (Protocol [REDACTED]), and a periodic safety update submitted on October 18, 2002 are the basis for the determination of safety of Follistim®-AQ liquid formulation. The safety data included in the labeling for Follistim® lyophilized cake formulation-SRS is identical data in the draft labeling for Follistim®-AQ liquid formulation. The additional supportive study, Protocol [REDACTED] also included additional safety and local tolerance data on Follistim®-AQ liquid formulation. No deaths were noted during the study, and seven serious adverse events were noted. All subjects that experienced adverse events completed treatment and recovered from the serious events.

The safety update (Amendment N-000-AZ to NDA 21-273) submitted by the sponsor contained additional worldwide experience for all Follistim® products from May 1997 through May 2002. The sponsor reported a total of two hundred nineteen reports that included three hundred and eight serious adverse events.

D. Dosing

Subjects in protocol [REDACTED] received 75 IU of Follistim®-AQ liquid formulation or the original Follistim® lyophilized cake formulation-SRS each day for up to seven days. If there was ovarian response, as defined by an increase in follicle size over baseline as measured by ultrasound, the dose was continued. If there was no ovarian response (any follicular growth), then the dose was increased to 150 IU for seven additional days. If no response was noted by day 15, then the dose was increased to 225 IU. 225 IU was considered the maximal allowable dose, and the maximum treatment period was 21 days. The sponsor felt that they could demonstrate an acceptable "step up" dose regimen of administration. This differs slightly from the sponsor's recommended dose increase schedule of 37.5 IU at weekly intervals until follicular growth and/or serum estradiol levels indicated an adequate response.

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The label for the dosing of Follistim®-AQ liquid formulation is identical to the label for the original Follistim® lyophilized cake formulation-SRS.

E. Special Populations

This drug is being approved for conditions that occur only in women. The studied indications for gonadotropin treatment for Follistim®-AQ liquid formulation 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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