CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201110Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201110

COMPLETE RESPONSE

Ferring Pharmaceuticals, Inc.
Attention: Giselle Rose
Director, US Regulatory Affairs
100 Interpace Parkway
Parsippany, NJ 07054

Dear Ms. Rose:

Please refer to your New Drug Application (NDA) dated and received on April 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for progesterone vaginal ring.

We acknowledge receipt of your amendment dated February 26, 2016, which constituted a complete response to our February 28, 2011, action letter.

We acknowledge receipt of your major amendment dated June 27, 2016, which extended the goal date by three months.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

DEVICE

1. Your to-be-marketed combination drug-device product, progesterone vaginal ring, contacts the skin and mucosal surface for a permanent contact duration (cumulative single, multiple or repeated long-term use or contact exceeds 30 days), and you provided insufficient biocompatibility information to support this contact duration. To address biocompatibility, you must provide acceptable data on cytotoxicity, sensitization, irritation, genotoxicity, and sub-acute toxicity to support permanent contact duration of use, and thus safety of your to-be-marketed product. You have provided acceptable data on irritation. However, the remaining biocompatibility tests (cytotoxicity, sensitization, genotoxicity, and sub-acute toxicity) are still needed to support your to-be-marketed product.

    - We do not agree that biocompatibility testing may be performed on the progesterone-free vaginal ring (placebo) only. This determination is based on our concern that the base (b) (4) progesterone vaginal ring silicone material plus drug (progesterone) could interact with each other, likely resulting in release of different types and quantities of residuals and leachable substances for the final

to-be-marketed combination product compared to the progesterone-free (placebo) vaginal ring product. Additionally, the process of application of the drug onto the vaginal ring product could result in alteration of surface properties and chemical characteristics of the (b) (4) vaginal ring silicone material, leading to changes in the biocompatibility response. To meet the biocompatibility requirements and adequately evaluate and support safety of the to-be-marketed progesterone vaginal ring product, satisfactorily address the following testing paradigm:

- For products that are inherently cytotoxic or products that demonstrate cytotoxicity, perform additional testing using several dilutions of the extracts derived from the final, finished, to-be-marketed combination progesterone vaginal ring product to determine the level at which cytotoxicity no longer occurs.
- A chemical characterization followed by a toxicological risk assessment on extracts derived from the final, finished, to-be-marketed combination progesterone vaginal ring product will provide the overall leachable profile of the progesterone vaginal ring product and will be necessary to understand the breakdown products that result from progesterone vaginal ring silicone material and progesterone interaction. The toxicological risk assessment can serve as an alternative to the chronic systemic toxicity and genotoxicity testing requirements for the to-be-marketed progesterone vaginal ring.
- Sensitization testing that fulfills the principles outlined in the Center for Devices and Radiological Health (CDRH) G95-1 guidance document, "Use of International Standard ISO 10993-10, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing."

CLINICAL

2. You have not established an adequate clinical safety bridge between your legacy progesterone vaginal ring used in the phase 3 clinical trials and your new progesterone vaginal ring product. We recommend you conduct a study to evaluate the clinical safety of the new progesterone vaginal ring. The study should include women who are undergoing Assisted Reproductive Technology (ART) procedures, which is the intended population. This study should evaluate the safety and tolerability of the to-be-marketed ring over the entire duration of treatment (up to 10 weeks post-embryo transfer). In addition, collect data on women who discontinue use of the new progesterone ring. Data collected in this study should include:

    - Adverse events (AEs) such as pain, vaginal bleeding, vaginal irritation, vaginal infection, and other more serious adverse events that may be related to the progesterone vaginal ring
    - Adverse events related to pregnancy outcomes, including miscarriage and ectopic pregnancy.

3. We remind you of the deficiency in our Complete Response letter dated February 28, 2011, that you have not provided sufficient evidence of efficacy for the progesterone vaginal ring in the subgroup of women 35-42 years of age. To address this concern, we continue to recommend that you conduct, prior to approval of your product, a randomized, active-controlled clinical trial to evaluate the efficacy of your product in women 35-42 years of age. The trial should be adequately powered to demonstrate sufficient retention of efficacy in the progesterone vaginal ring arm when compared to the active comparator. Details of the trial should be agreed upon with the Agency prior to the conduct of the study. We also stated in the February 28, 2011, Complete Response letter that a possible alternative approach would be appropriate labeling, which would include a statement on limitation of use along with a post-marketing commitment to conduct the clinical trial described above.

PRESCRIBING INFORMATION

4. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

   If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR: 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

5. Refer to our correspondence dated, June 10, 2016, which addresses the proposed proprietary name, MILPROSA. This name was found acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug/product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
    - Present tabulations of the new safety data combined with the original application data.
    - Include tables that compare frequencies of adverse events in the original application with the retabulated 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. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for 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 application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug/product. Include an updated estimate of use for drug/product marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following additional comments and recommendations:

1. Address the following items in future biocompatibility testing:

    A. In your preliminary biocompatibility assessment, you state that you initiated a 14-day intraperitoneal (IP) study in female rates for sub-chronic toxicity testing. A 14-day IP study does not represent an acceptable sub-chronic systemic toxicity testing scenario. For sub-chronic systemic toxicity testing, a 28-day intravenous (IV) and/or 90-day IP study should be conducted to demonstrate potential systemic toxicity concerns following exposure to device extracts over a duration of time that is considered to be greater than that for a typical sub-acute systemic

toxicity test study. The duration of the study should not exceed 10% of the animal species's life span. Provide justification for selection of the 14-day duration of time.

B. On page 4 of your October 14, 2016, correspondence, you state that the progesterone dose-exposure calculation in rats is based on (b) (4) progesterone by the IP route of administration. However, as the maximum injection dose volume limit via IP in rat species is 20 ml per kg, it is unclear how the dosage volume that is (b) (4) times lower than the maximum recommended injection dose is representative of an exaggerated exposure dose for a systemic toxicity study. Additionally, the frequency of dose exposure is not clear (i.e., single, multiple, repeat, etc.). Provide justification for the dosage volume used in this study. Also, address whether there are any adjustment factors such as surface area-to-body weight and/or exaggerated exposure conditions, for example, dose, duration, frequency, route of exposure, physical-chemical and biological properties of the test sample, animal strain, etc., that make up for the lower limit of the maximum dosage volume selected for test sample administration.

C. In the information provided, the exposure dosing is based on the drug potency of progesterone, rather than the overall leachability profile of the final, to-be-marketed combination product. The objective of a sub-chronic systemic toxicity study is to evaluate the potential of leachable chemicals to induce systemic toxicity effects. Therefore, exposure dosing should be based on the leachability profile of the to-be-marketed product.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

We strongly recommend that you request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. Submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Nikia Morris, Regulatory Project Manager, at (240) 402-6625.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

AUDREY L GASSMAN
11/23/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201110

COMPLETE RESPONSE

Teva Women's Health, Inc.
Attention: Jennifer Norman, R.Ph.
Director, Regulatory Affairs
425 Privet Road
Horsham, PA 19044

Dear Ms. Norman:

Please refer to your New Drug Application (NDA) dated and received on April 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for progesterone vaginal ring.

We acknowledge receipt of your amendments dated May 7 and 20, August 13 and 19, September 13, October 5, November 10 and 30, December 9 and 17, 2010, and January 31, 2011.

We also acknowledge receipt of your amendment dated February 18, 2011, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. During the prior approval inspection (PAI) of your facility, foreign particulate contaminations were found in all five site transfer batches manufactured at the future commercial site. Conduct a thorough investigation to identify the root cause. Propose corrective measures and demonstrate that the root cause has been corrected by producing three production batches which show no particulates.
2. The progesterone vaginal ring contains (b) (4) % w/w concentration of progesterone dispersed evenly within the ring. The particle size distribution of progesterone is considered to be critical for the consistent release of progesterone. Amend your application to include a test for particle size distribution with acceptance criteria in the specification for the drug substance.

Reference ID: 4601440

3. The drug product specification is incomplete. Revise the "Description" of the drug product specification by adding "Free of particulates by visual inspection" and revise the "Microbiological Examination" of the drug product specification to include "The absence of (b) (4) ."
4. Analytical methods for the drug product are inadequate. To address this deficiency:
   - Validate the accuracy of the HPLC test method for detection of impurity/degradation products in the drug substance.
   - Validate the repeatability and intermediate precision of the drug product impurity test using samples spiked with the four known impurities at quantitation levels (QL).
   - Revise the acceptance criteria of the relative standard deviation (RSD) (b) (4) for establishing the system suitability of the HPLC method.

CLINICAL

You have not provided sufficient evidence of efficacy for the progesterone vaginal ring in the subgroup of women 35-42 years of age. This subgroup represents approximately 50% of the infertile women for whom your drug is intended for use as part of an Assisted Reproductive Technology (ART) treatment program. In general, the subgroup of infertile women 35-42 years of age has diminished ovarian reserve relative to women under the age of 35. You have not demonstrated that information obtained from the subgroup of women less than 35 years of age can be extrapolated to women in the older subgroup.

To address this concern, we continue to recommend that you conduct, prior to approval of your product, a randomized, active-controlled clinical trial to evaluate the efficacy of your product in women 35-42 years of age. The trial should be adequately powered to demonstrate sufficient retention of efficacy in the progesterone vaginal ring arm when compared to the active comparator. Details of the trial should be agreed upon with the Agency prior to the conduct of the study.

It is also possible that appropriate labeling, which would include a statement on limitation of use, and a postmarketing commitment to conduct the clinical trial described above would be sufficient to support approval of the progesterone vaginal ring for use in women less than 35 years of age.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

FACILITY INSPECTIONS

During recent inspections of the Northvale, NJ, testing facility and the Cincinnati, OH, manufacturing facility, our field investigator(s) conveyed deficiencies to the representatives of

the facilities. Satisfactory resolution of these deficiencies is required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated 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. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for 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 updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

In addition to the above deficiencies, the following issues should be addressed in your response to this letter:

PRODUCT QUALITY

1. (b) (4)

2.

3.

MICROBIOLOGY

1. The method validation studies for total yeast and mold count included an incubation temperature of (b) (4) C, while the proposed test method has an incubation temperature of (b) (4) C. This appears to be an error based on information found later in the method validation package. The error occurs in section 5.2.1(i) and the correct temperature is listed in section 5.3. Revise ARD_RPT-5064 version 2.0 accordingly.
2. Submit the results from microbial enumeration studies on the stability and site transfer batches using the revised test methods.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have

such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

SCOTT E MONROE
02/28/2011