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RESEARCH**

APPLICATION NUMBER:

22-437

OTHER ACTION LETTER(s)



NDA 22-437

COMPLETE RESPONSE

Watson Laboratories, Inc.
577 Chipeta Way
Salt Lake City, UT 84108

Attention: Kevin Barber, Ph.D., R.A.C., P.M.P.
Executive Director, Proprietary Regulatory Affairs

Dear Dr. Barber:

Please refer to your new drug application (NDA) dated September 12, 2008, received September 12, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trelstar® (triptorelin pamoate for injectable suspension), 22.5 mg.

We acknowledge receipt of your amendments dated October 6 and December 22, 2008; January 21, 30, March 24, May 4, and June 29, 2009.

We also acknowledge receipt of your amendment dated July 9, 2009 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 the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

1. For Study DEB-TRI6M-301, you have provided testosterone levels using two different assay methods, immunoassay and liquid chromatography/tandem mass spectroscopy (LC/MS). The result of the analysis of the co-primary endpoint, maintenance of castrate testosterone levels from Day 57 to Day 337, using testosterone levels derived from the immunoassay differs markedly from the result using testosterone levels derived from the assay using LC/MS. It is unclear whether the co-primary endpoint should be analyzed using the results of the immunoassay or of LC/MS.
 - a. Please provide your rationale for the use of testosterone levels from the LC/MS assay in your primary analyses. Please compare the testosterone assay used in your primary analyses to the methods used to assay testosterone levels in your own approved applications, in the approved applications of others (reviews available on the FDA website) and in published articles.

- b. Please provide references to support your contention that the LC/MS method is preferred for the assay of hypogonadal testosterone levels. This should include a comparison of the intra-assay and inter-assay coefficient of variation using both of these assay methods.
- c. Please provide information concerning the storage and shipment conditions used for the testosterone serum samples.

PRODUCT QUALITY

1. DMFs (b) (4), 8084 and (b) (4) have been reviewed and found deficient. Letters detailing the deficiencies have been sent to the designated agents for each DMF holder. This application cannot be approved until these deficiencies have been resolved.
2. Regarding the analytical method for drug substance testing:
 - a. Either revise the description of methods 02-002264 (peptide assay and identity) and 02-002878 (related substances) to indicate that the sample and reference standard solutions are to be used immediately or revise their method validation studies to address sample stability under room temperature and freezer conditions.
 - b. For method 02-002651 (pamoic acid assay and identity), describe the preparation of the drug sample for analysis.
 - c. For method 02-002878 (related substances), revise the validation study to address method robustness.
3. (b) (4) are stated to be part of an on-going extractables/leachables study of the proposed stopper with the proposed drug product. Explain what part of this study has yet to be completed and submitted to the application.
4. Regarding the proposed manufacturing and control sites:
 - a. (b) (4) is cited in the application as performing stability testing on Sterile Water for Injection (WFI) Syringes, and (b) (4). (b) (4) is cited as performing Water Content testing on drug product. Both sites have indicated to the Office of Regulatory Affairs that they do not perform these functions. Clarify the functions performed at these two sites and identify the sites which do perform these functions.
 - b. Identify the site for the secondary packaging of the vial-alone configuration.
5. Regarding the drug product manufacturing process:
 - a. Provide a list of manufacturing equipment for each processing step and include the intermediate storage containers.

- b. Describe the in-process control for determining completion of the [REDACTED] (b) (4) process.
 - c. For the manufacture of PLG [REDACTED] (b) (4) microgranules, either justify the proposed [REDACTED] (b) (4) maximum storage time or provide long term stability data supporting the proposed storage time and condition.
 - d. Verify that the procedures and parameters for the sterilization and depyrogenation of vials and stoppers in this application are the same as those validated and approved in NDA 20-715 and NDA 21-288.
 - e. For the filling and microgranule dispersion processes, specify the sampling frequency for weight checks, and describe the weight adjustment procedure used during microgranule dispersion.
 - f. Provide a brief description the WFI preparation process and controls, and include the sampling frequency.
6. Regarding the proposed analytical method for drug product testing:
- a. In the validation study for method 02-002236 (Triptorelin Identity, Assay and Content Uniformity), the acceptance criteria for the sample storage studies indicate that you are willing to accept a [REDACTED] (b) (4) assay loss for sample held at room temperature for 24 hours in addition to a potential [REDACTED] (b) (4) assay loss for sample held at -20°C for 10 days. This is a very large assay loss and a lot which fails assay after being held at -20°C then at room temperature cannot be re-tested or re-sampled. Justify the proposed acceptance criteria for the room temperature study. Also, address method specificity for samples held at -20°C and at room temperature.
 - b. Revise the validation study (validation report 02-002550/01) for related substances method 02-002232 to address the [REDACTED] (b) (4) impurity. For the specificity study, identify the peaks of each impurity and degradation product observed.
7. Provide a justification for the proposed criteria for Total Impurities, [REDACTED] (b) (4) Impurity and Individual Unspecified Impurities based on manufacturing capability and drug product quality with the impurity at the proposed limit.
8. Provide the specifications for the acceptance of vial, stoppers and overseals at the drug product manufacturing site.
9. There is only a limited amount of stability history for the proposed drug product. Therefore, the on-going studies for each of the five primary study lots and the five supportive study lots need to be completed. In addition, include the 3-month and 9-month sampling sites in the protocol for physical and chemical testing.

10. Regarding the submitted stability information:
 - a. There is insufficient data from the primary and supportive stability studies to support the proposed 36-month expiration dating period with storage at USP controlled room temperature. Either provide additional data from these studies or propose a reduced expiration dating period for the drug product.
 - b. In the Reconstituted Suspension Study, describe what the “peptide released” test is intended to measure, and how the samples were prepared.
11. Revise the proposed in vitro dissolution method and acceptance criteria as follow:
 - a. Add a sampling point between 1 and 24 hours.
 - b. Eliminate the (b) (4) sampling point, and replace with a sampling point at 96 hours.
12. Revise the dissolution sampling points and acceptance criteria as follow: 1 hr (b) (4), 12 hr (b) (4), 24 hr (b) (4), 96 hr (b) (4), and 168 hr (b) (4). Note that the 12-hour and 96-hour timepoints and acceptance criteria reflect interpolation, as no data were provided for the 12-hour and 96-hour sampling points.
13. The IVIVR is not acceptable because the formulations used to develop the relationships did not have different release rates, and the IVIVR did not predict the entire profile for the two phases of drug release. Additionally, the IVIVR did not meet the criteria for internal and external predictability. Therefore, this IVIVR can not be used to support any post-approval changes.

FACILITY INSPECTIONS

During a recent inspection of the Debio R.P.S.A manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Additionally, two other sites proposed in the application (b) (4) were given withhold recommendations. Satisfactory resolution of these deficiencies is required before this application may be approved.

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/oc/datacouncil/spl.html>.

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:
 - a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - b. Present tabulations of the new safety data combined with the original NDA data.
 - c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - d. 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 study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study 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.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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 Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.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 Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Robert Justice
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