CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209863Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209863

COMPLETE RESPONSE

Antares Pharma, Inc.
Attention: Nader Fotouhi, Ph.D.
Director, Regulatory Affairs
100 Princeton South, Suite 300
Ewing, NJ 08628

Dear Dr. Fotouhi:

Please refer to your New Drug Application (NDA) dated and received December 20, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for testosterone enanthate subcutaneous injection.

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.

CLINICAL

1. Based on the findings in Studies QST13-003 and QST15-005, we are concerned that your testosterone enanthate product could cause a clinically meaningful increase in blood pressure. For example, your ambulatory blood pressure monitoring (ABPM) assessments, which were conducted in patients without pre-existing hypertension, showed mean increases in systolic and diastolic blood pressure of approximately 4 mmHg and 2 mmHg, respectively. In addition, cumulative distribution function curves generated from these ABPM data demonstrated that approximately 60% of the patients had an increase in systolic blood pressure, with increases of up to 20 mmHg. Approximately 9.5% of patients in the study required initiation or adjustment of antihypertensive medications in order to maintain their blood pressures in the normal range. We are concerned that these unexpected findings based on data from a largely normotensive population may underestimate the effects of your drug on blood pressure in the real world setting, where many patients have co-existing hypertension, with the potential to increase the risk for adverse cardiovascular outcomes.

2. There were two cases of suicide attempt (including one completed suicide) and two cases of depression in your development program. We are unable to exclude drug causality.

Information Needed to Resolve the Deficiencies

Further characterize the effects of your product on blood pressure and the impact on cardiovascular risk in the hypogonadal population anticipated to use your product. One approach is to conduct a new ABPM study to assess blood pressure effects in a population more consistent with real-world use of testosterone replacement as opposed to a normotensive study population. This ABPM study would collect key blood pressure data at steady state for your product within the normal range to evaluate the magnitude of effect in the intended population. Collecting data on other parameters that may influence cardiovascular risk (e.g., hematocrit, hemoglobin, cholesterol parameters) in this ABPM study could, together with the blood pressure assessment, facilitate better characterization of the impact of your product on cardiovascular risk with use in a real world setting.

Propose a plan to address the suicidality signal. One approach is to include prespecified, periodic, validated psychiatric evaluations to monitor and assess for the occurrence of depression and suicidality in the ABPM study mentioned above.

We are open to considering other scientifically valid approaches for addressing the identified concerns.

On the next review cycle, we anticipate convening a meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee to obtain expert advice on whether the demonstrated benefit of treatment with testosterone enanthate injection outweighs the potential of increased cardiovascular and suicidality risks with its use in the real world setting.

PRESCRIBING INFORMATION

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

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the 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.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

ADDITIONAL COMMENTS

We have the following comment/recommendation regarding your Information for Use (IFU) that are not approvability issues:

> The results of your patient and caregiver validation study (CLS-1022-R1) and healthcare provider validation study (HSS-1088-R1A) show use errors with the critical task of uncapping the device before the user is ready to inject. We are concerned with these use errors because they may lead to infection and unintended exposure. We have the following recommendation to further optimize the Instructions for Use (IFU), which does not require additional validation:
>
> As currently presented in the IFU, the statement, 'Do not remove cap until ready to inject', is located above the diagram of the device instead of in close proximity to the corresponding use task. The removal of the cap prior to use poses risk of medication error of wrong technique which may result in contamination or infection. Based on the errors noted in the HF validation study and the participant subjective feedback, we recommend adding the same statement to the section titled, "Inspect Autoinjector", to call the user's attention that they should not remove the cap until they are ready to inject.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling based on our proposed revisions dated May 18, 2017.

PROPRIETARY NAME

Please refer to correspondence dated, March 16, 2017, which addresses the proposed proprietary name, Xyosted. This name was found acceptable pending approval of the application in the current review cycle. Please 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 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. 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 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 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.

You may request a meeting or teleconference 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 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, please contact Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

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
10/20/2017