CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213953Orig1s000

OTHER ACTION LETTERS

NDA 213953

COMPLETE RESPONSE

Marius Pharmaceuticals, LLC
Attention: Om Dhingra, CEO
8601 Six Forks Road, Suite 630
Raleigh, NC 27615

Dear Mr. Dhingra:

Please refer to your new drug application (NDA) dated and received December 31, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for testosterone undecanoate.

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/Clinical Pharmacology

Approvability of your NDA depends on reliable evidence that the proposed dose and dosage regimen for your product restore testosterone (T) concentrations to the normal range (C_{avg}) and avoid unacceptably high T peak concentrations (C_{max}). Therefore, reliable measurement of T concentrations in pharmacokinetic (PK) samples collected in your single efficacy and safety trial (MRS-TU-2019EXT) is critical to the acceptability of the PK data forming the basis of the efficacy and safety of your product.

Multiple subjects at Site 104 (Manhattan Medical Research Practice, LLC, Jamaica, NY) had NaF/EDTA plasma T concentrations paradoxically higher than serum T concentrations obtained at the same timepoint. You stated a post-study interview with the site coordinator indicated PK sample handling/processing deviations from instructions in the central laboratory manual as the cause of these aberrant findings. As such, you requested to exclude Site 104 from the efficacy analysis of C_{avg} and C_{max}. Although the C_{avg} efficacy endpoint was achieved with or without Site 104, the key secondary C_{max} endpoints were achieved only after excluding Site 104.

During the Agency's inspection of Site 104 to determine whether excluding this site was justified, the site personnel were unable to provide documentation on PK blood sample processing and handling. Based on the findings at Site 104, the Agency conducted an inspection of Site 107 (South Florida Medical Research, Maitland, FL). Similar to Site 104, multiple subjects at Site 107 had NaF/EDTA plasma T concentrations paradoxically higher than serum T concentrations obtained at the same timepoint and there was no documentation to support that the PK blood sample handling and

processing were carried out properly. In addition, review of your responses to the Agency's information requests revealed lack of documentation for PK sample handling and processing in the other clinical study sites of MRS-TU-2019EXT.

Without documentation of PK sample handling and processing at Sites 104 and 107, we do not know the cause of the aberrant results at that site and, therefore, cannot agree to exclude data from Site 104. Your product does not achieve any of the key secondary C_{max} endpoint targets with the inclusion of data from Site 104. More importantly, absent contemporaneous documentation for PK sample handling and processing at all clinical sites of MRS-TU-2019EXT calls into question how the PK samples were processed and handled and poses significant uncertainties about the reliability of the PK data of the entire study.

As the integrity and reliability of the PK data from MRS-TU-2019EXT cannot be assured, we cannot conclude that MRS-TU-2019EXT provides substantial evidence of effectiveness for your product.

Information Needed to Resolve the Deficiency

Conduct a new phase 3, efficacy and safety trial with adequate number of hypogonadal subjects treated with your product. This trial needs to have reliable data to demonstrate that your drug is safe and effective with your proposed dose, dosing regimen, and dose titration scheme. You need to have adequate documentation of PK sample collection, handling, processing, and storage to verify these steps are carried out according to the prespecified procedures, ensuring the reliability of the PK results. If you choose to rely on plasma T concentrations (e.g., NaF/EDTA tubes) for dose titration and safety and efficacy assessments in this new trial, but intend to label for serum T concentrations (i.e., plain tubes) in clinical practice, we strongly recommend you measure T concentrations in both plasma and serum from all PK blood samples in your trial to inform serum-based dose titration thresholds for labeling purposes.

We recommend you submit the phase 3 protocol for our review and concurrence prior to conducting the study.

PRESCRIBING INFORMATION

We reserve further comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] 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.

CARTON AND CONTAINER LABELING

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

We reserve further comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, March 31, 2021, which addresses the proposed proprietary name, Kyzatrex. 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.

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[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

(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 guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

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 Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, M.D.
Director
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTINE P NGUYEN
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