CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

213953Orig1s000

Trade Name:	KYZATREX capsules, for oral use, CIII
Generic or Proper Name:	testosterone undecanoate
Sponsor:	Marius Pharmaceuticals, LLC
Approval Date:	July 27, 2022
Indication:	For testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone

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213953Orig1s000

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 213953

NDA APPROVAL

Marius Pharmaceuticals, LLC
Attention: Om Dhingra
Regulatory Affairs
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 (FDCA) for Kyzatrex (testosterone undecanoate) oral capsules.

We acknowledge receipt of your amendment dated January 27, 2022, which constituted a complete response to our October 22, 2021, action letter.

This NDA provides for the use of Kyzatrex (testosterone undecanoate) oral capsules for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Prescribing Information, and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CONTAINER LABELING

We acknowledge your June 9, 2022, submission containing final printed carton and container labeling.

DATING PERIOD

Based on the stability data submitted to date, the expiration dating period for Kyzatrex shall be 24 months from the date of manufacture when stored at 20°C to 25ºC (68°F to 77ºF), with excursions permitted between 15ºC to 30ºC (59ºF to 86ºF).

ADVISORY COMMITTEE

Your application for Kyzatrex was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a drug in thisclass.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for all females and for males from birth to less than 12 years of age, because necessary studies are impossible or highly impracticable.

We are deferring submission of your pediatric trial for this application for males ages 12 years to less than 18 years of age, since this product is ready for approval for use in adults and the pediatric trial has not been completed. Your deferred pediatric trial required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing trial. The status of this postmarketing trial must be reported annually

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

according to 21 CFR 314.81 and section 505B(a)(3)(C) of the Federal Food, Drug, and Cosmetic Act (FDCA). This required trial is listed below.

#4313-1 A trial of testosterone replacement therapy in pediatric males ages 12 years to less than 18 years of age for conditions associated with a deficiency or absence of endogenous testosterone due to primary hypogonadism or hypogonadotropic hypogonadism.

The timetable in your electronic communication dated, July 13, 2022, states you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2024
Final Protocol Submission:	08/2024
Study/Trial Completion:	08/2029
Final Report Submission:	02/2030

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of patients not accurately understanding the serious risk of increased blood pressure due to Kyzatrex that can increase the risk of major adverse cardiovascular events.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

#4313-2 An appropriately designed label comprehension study that assesses patients' understanding of key risk messages in the Medication Guide for testosterone replacement therapy. The primary objective of this study is to assess patient comprehension of materials related to increases in blood pressure that can increase the risk of major adverse cardiovascular events with testosterone replacement therapy. Include men representative of those who use prescription testosterone therapy with a range of cardiac risk factors, a range of education levels, and various literacy levels. The study findings may result in revisions to the

Medication Guide to optimize patients' understanding of important risks of testosterone replacement therapy.

The timetable in your electronic communication dated, July 13, 2022, states you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2022
Final Protocol Submission:	06/2023
Study/Trial Completion:	12/2023
Final Report Submission:	03/2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocols to your IND 118675 with a cross-reference letter to this NDA 213953. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jeannie Roule, Chief, Project Management Staff, at 301-796-3993.

Sincerely,

{See appended electronic signature page}

Catherine Sewell, MD, MPH
Deputy Director (Acting)
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic, And Reproductive Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Container Labeling

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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/

CATHERINE A SEWELL
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