CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

206089Orig1s000

Trade Name:	Jatenzo capsules, for oral use CIII
Generic or Proper Name:	Testosterone undecanoate
Sponsor:	Clarus Therapeutics, Inc.
Approval Date:	March 27, 2019
Indication:	for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone

CENTER FOR DRUG EVALUATION AND RESEARCH

206089Orig1s000

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206089

NDA APPROVAL

Clarus Therapeutics, Inc.
Attention: Robert E. Dudley, Ph.D.
President and CEO
555 Skokie Blvd., Suite 340
Northbrook, IL 60062

Dear Dr. Dudley:

Please refer to your New Drug Application (NDA) dated January 2, 2014, received January 3, 2014, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for testosterone undecanoate oral capsules.

We acknowledge receipt of your amendment dated September 27, 2018, which constituted a complete response to our March 22, 2018, action letter.

This new drug application provides for the use of Jatenzo (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 text.

WAIVER OF HIGHLIGHTS SECTION

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, text for the Medication Guide). 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*, available at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and the immediate container labels submitted on March 25, 2019, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the Guidance for Industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 206089**." Approval of this submission by FDA is not required before the labeling is used.

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 from birth to less than 17 years of age and males from birth to less than 14 years of age, because studies are impossible or highly impracticable. We are deferring submission of your pediatric trial for this application for males ages 14 years and older, because 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 according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. This required trial is listed below.

> A trial of testosterone replacement therapy in pediatric males ages 14 years and older 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, March 21, 2019, states that you will conduct this study according to the following schedule:
>
> | | |
> |---|---|
> | Draft Protocol Submission: | 01/2021 |
> | Final Protocol Submission: | 04/2021 |
> | Trial Completion: | 04/2026 |
> | Final Report Submission: | 10/2026 |

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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 unexpected serious risks of (1) patients not accurately understanding the serious risk of increased blood pressure due to Jatenzo that can increase the risk of major adverse cardiovascular events, (2) adrenal insufficiency with chronic Jatenzo therapy, and (3) Jatenzo acting as an inhibitor or inducer of drug metabolizing enzymes and transporters.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess the aforementioned unexpected serious risks.

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

3582-1: An appropriately designed label comprehension study that assesses patient understanding of key risk messages in the Medication Guide for Jatenzo. 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 Jatenzo. 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 patient understanding of important risks of Jatenzo.

The timetable in your electronic communication dated, March 21, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol	06/2019
Final Protocol Submission:	10/2019
Study Completion:	04/2020
Final Report Submission:	07/2020

3582-2: An appropriately designed one-year trial to evaluate for the development of adrenal insufficiency with chronic Jatenzo therapy. Assess adrenal function with Cosyntropin stimulation testing prior to starting Jatenzo, and again after six months and one year on Jatenzo. Test at earlier timepoints for subjects who demonstrate signs or symptoms consistent with adrenal insufficiency. Assess serum cortisol, adrenocorticotropic hormone, and corticosteroid binding globulin concentrations prior to Cosyntropin 0.25 mg injection and serum cortisol concentrations at 30

minutes and 60 minutes after the injection. Standardize the testing time to 8 AM and the route of Cosyntropin administration (intramuscular or intravenous). Perform hormonal analytical assays in a central laboratory on batched serum samples. Use appropriate serum cortisol criteria to interpret results as normal and provide an algorithm for managing abnormal test results.

The timetable in your electronic communication dated, March 21, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2019
Final Protocol Submission:	04/2020
Trial Completion:	04/2022
Final Report Submission:	10/2022

3582-3: Conduct *in vitro* studies to assess the potential of testosterone undecanoate to inhibit or induce drug metabolizing enzymes and transporters as outlined in the draft Guidance for Industry *In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies (available at:* https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf).
If *in vitro* studies suggest a potential for interaction, additional *in vivo* studies may be required.

The timetable in your electronic communication dated, March 21, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2019
Final Protocol Submission:	09/2019
Trial Completion:	06/2020
Final Report Submission:	09/2020

Submit all the clinical protocols to your IND 078104 with a cross-reference letter to this NDA.

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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, contact Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Prescribing Information
Medication Guide
Carton and Container Labeling

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/

HYLTON V JOFFE
03/27/2019 01:48:05 PM