CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213953Orig1s000

PRODUCT QUALITY REVIEW(S)

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213953
Assessment 2

Drug Product Name	Kyzatrex™ (testosterone undecanoate)
Dosage Form	Capsules
Strength	100mg, 150mg, and 200mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Marius Pharmaceuticals, LLC
US agent, if applicable	Not applicable

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission of the Application	01/27/2022	All
Meeting Minutes	01/28/2022	All
Revised Reviewers Guide	02/09/2022	All
Correspondence Regarding Meeting	02/18/2022	All
Response to Clinical Information Request	03/18/2022	Clinical
General Correspondence	03/24/2022	Regulatory/Clinical
Response to Clinical Information Request	06/06/2022	Clinical
Container and Carton Labels	06/09/2022	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Jeffrey Medwid, Ph.D.	Donna Christner, Ph.D.
Drug Product	Venkateswara Pavuluri, Ph.D.	Wendy Wilson-Lee, Ph.D.
Manufacturing	Amit Kokate, Ph.D.	Vaikunth Prabhu, Ph.D.
Microbiology	Amit Kokate, Ph.D.	Vaikunth Prabhu, Ph.D.

Biopharmaceutics	Jia Yin, Ph.D.	Vidula Kolhatkar, Ph.D.
Regulatory Business Process Manager	Dahlia Walters, M.S., PMP	
Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	Venkateswara Pavuluri, Ph.D.	Wendy Wilson-Lee, Ph.D.

NDA Executive Summary

1. Application/Product Information

NDA Number.	213953
Applicant Name	Marius Pharmaceuticals, LLC
Drug Product Name	Kyzatrex™ (testosterone undecanoate)
Dosage Form.	Capsule
Proposed Strength(s)	100mg, 150mg and 200mg
Route of Administration	Oral
Maximum Daily Dose	(b) (4)
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of primary and secondary hypogonadism in adult males
Drug Product Description	Kyzatrex™ (testosterone undecanoate) capsules 100mg, 150mg, and 200mg for oral use is intended for the testosterone replacement therapy in treatment of primary and secondary hypogonadism. Kyzatrex™ is a solid oral dosage form consisting of a (b) (4) soft gelatin capsule. Each capsule contains 100mg, 150mg, or 200mg of testosterone undecanoate (TU) depending on strength as the active ingredient and the following inactive ingredients: propylene glycol monolaurate (b) (4), phytosterol esters (b) (4), polyoxyl 40 hydrogenated castor oil (b) (4), (b) (4), DL-α-tocopheryl acetate (Vitamin E) (b) (4). The capsule shells are composed of glycerin, gelatin (b) (4), sorbitol (b) (4), titanium dioxide, water and (b) (4) Red as imprinting ink. All the excipients are compendial (USP and/or NF) grade except phytosterol esters and (b) (4) Red Ink. Phytosterol is also a novel excipient. Adequate information regarding the non-compendial excipients is provided in the NDA. The use of the non-compendial excipients as well as the level of each

	excipient have been cleared through the Pharm/Tox review team. TU is a fatty acid ester prodrug of the androgen, testosterone and once it is absorbed, the ester is cleaved by nonspecific esterases. TU was first approved on March 5, 2014 as the active ingredient of AVEED for intramuscular injection under NDA 022219. Since the first approval, TU oral capsules have been approved under NDA 206089 and NDA 208088. Kyzatrex™ will be packaged and marketed as 90 capsules packaged in wide-mouth, round, white high-density polyethylene (HDPE) bottles with white, polypropylene, child resistant screw caps and induction-sealed liner.
Co-packaged product information	N/A
Device information:	N/A
Storage Temperature/ Conditions	Store at 20°C to 25ºC (68°F to 77ºF), with excursions permitted between 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature]. Store the capsules in a dry place avoiding exposure to excessive moisture and humid conditions.

Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Jeffrey Medwid, Ph.D.	Donna Christner, Ph.D.
	Drug Product/ Labeling	Venkateswara Pavuluri, Ph.D.	Wendy Wilson-Lee, Ph.D.
	Manufacturing	Amit Kokate, Ph.D.	Vaikunth Prabhu, Ph.D.
	Biopharmaceutics	Jia Yin, Ph.D.	Vidula Kolhatkar, Ph.D.
	Microbiology	Amit Kokate, Ph.D.	Vaikunth Prabhu, Ph.D.
	Other (specify):	N/A	N/A

	RBPM	Dahlia Walters,
	ATL	Hamid Shafiei, Ph.D.
Consults	None	

2. Final Overall Recommendation - *Approval*

This is a resubmission for this application. This application received a CR on October 22, 2021 due to clinically-related deficiencies and the labeling/label negotiations were not pursued during the first review cycle. Therefore, from the OPQ perspective, this application was not recommended for approval until the CMC labeling/label deficiencies are appropriately addressed. In this resubmission the CMC labeling/label deficiencies have been adequately addressed. No other CMC updates requiring the OPQ review except the revised labeling/labels were submitted in this resubmission. Also in this review cycle, the Office of Pharmaceutical Manufacturing Assessment (OPMA) has made the recommendation that the facilities involved in this application have remained adequate. This application is now recommended for approval from the OPQ perspective.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, testosterone undecanoate and the drug product, Kyzatrex™ (testosterone undecanoate) Capsules, 100mg, 150mg, and 200mg.
- The Office Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC issues on labels/labeling have been satisfactorily resolved.
- The applicant's request for the categorical exclusion from the preparation of the environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is recommended for **approval** with the expiration dating period of **24 months.**

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Yes

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

None

Hamid Shafiei

Digitally signed by Hamid Shafiei
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FDA U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs: Refer to the IQA 1 dated October 7, 2021

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
	II					

B. OTHER DOCUMENTS: Refer to the IQA 1 dated October 7, 2021

Document	Application Number	Description

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **06-JUL-2022**

From: **Venkateswara R. Pavuluri, Ph.D., R. Ph.**
Drug Product Reviewer
DNDP II
Office of New Drug Products

Through: **Hamid Shafiei, Ph.D.**
SPQA, Br4 /DNDP II
Office of New Drug Products

To: **CMC Labeling Review of NDA 213953 for KYZATREX®**
Subject: Final Recommendation APPROVAL

At the time when initial Labeling Review of NDA 213953 was completed on 19-09-2021, this NDA was not recommended for approval 21 CFR 314.125(b)(6) from the CMC labeling/labels perspective due to deficiencies listed below. The NDA for this drug product was otherwise complete and adequate from the drug product perspective, per the review dated 21-SEP-2021. This labeling memo is based on the resubmission (SN 0037, dated 27-JAN-2022) and subsequent amendments through 28-JUN-2022.

Labeling/Label Deficiencies identified in CMC Labeling review as of 19-SEP-2021:

A. Prescribing Information

Full Prescribing Information:

DOSAGE FORMS AND STRENGTHS

1. *Text may be simplified as follows*:

"Capsules:
-100 mg, opaque, white, oval, imprinted with "MP100" in red ink.
-150 mg, opaque, white oblong, imprinted with "MP150" in red ink.
-200 mg, opaque, white oblong, imprinted with "MP200" in red ink."

Information as in the resubmission:

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

Reviewer Assessment: Adequate.

DESCRIPTION

2. *The text in 3rd and 4th paragraphs may be rewritten as follows, with listing of inactive ingredients in alphabetical order in both fill* (b) (4) *and capsule shell composition. Vitamin E may be described with given name followed by general descriptor (Vitamin E) in parenthesis as: DL-alpha-tocopheryl acetate (Vitamin E).*

"KYZATREX (testosterone undecanoate) capsules for oral use are available in three strengths, 100 mg, 150 mg, and 200 mg. The 100 mg strength is an opaque white capsule is imprinted with "MP100" in red ink. The 150 mg strength is an opaque white capsule is imprinted with "MP150" in red ink. The 200 mg strength is an opaque white capsule imprinted with "MP200" in red ink. All capsule strengths also contain polyoxyl 40 hydrogenated castor oil, phytosterol esters, propylene glycol monolaurate, and DL-α-tocopheryl acetate (Vitamin E) as inactive ingredients."

Deficiency conveyed to Applicant upon resubmission: *We advise you to list all inactive ingredients in alphabetical order by name, for both fill* (b) (4) *and capsule shell compositions separately, per USP <1091> recommendations. Vitamin E is available in multiple forms and thus it shall be described with given name of the form used in formulation followed by general descriptor in parenthesis, i.e., DL-alpha-tocopheryl acetate (Vitamin E).*

Information as in the Amendment:

(b) (4)

Reviewer Assessment: Adequate.

HOW SUPPLIED/STORAGE AND HANDLING

3. *How Supplied: section may be simplified as*:

"KYZATREX capsules are available in three strengths of 100 mg, 150 mg, and 200 mg, packaged as 90 units in wide-mouth, round, white HDPE bottles with white, polypropylene, child resistant caps and induction-sealed liner.

- 100 mg: Oval, opaque white capsules imprinted with “MP100” in red ink; NDC 80603-101-11.
- 150 mg: Oblong, opaque white capsules imprinted with “MP150” in red ink; NDC 80603-103-11.
-200 mg: Oblong, opaque white capsules imprinted with “MP200” in red ink; NDC 80603-105-11.”

Information as in the resubmission:

(b) (4)

Reviewer Assessment: Adequate.

4. *Storage statements shall be revised as follows*:

“Store at 20°C to 25ºC (68°F to 77ºF), excursions permitted between 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature]. Store the capsules in a dry place, avoiding exposure to excessive moisture and humid conditions.”

Information as in the resubmission:

(b) (4)

Reviewer Assessment: Adequate.

B. Container Labels

Though no deficiencies were identified in the original review cycle for container labels, a typographical error was noticed in the storage statement resubmission for all container labels, i.e., *Store at: 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C to 30°C (59°C to 86°F)”*. The following deficiency was conveyed to Applicant and container labels with correction of “C” to “F” were submitted on 09-JUN-2022.

Deficiency to be conveyed to Applicant: *Revise the storage statement on container labels as “Store at: 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C to 30°C (59°F to 86°F)”.*

This CMC labeling addendum was prepared to document the most updated information in relevant sections of prescribing information as submitted on 27-JAN-2022 and revised subsequently on 28-JUN-2022. The labeling changes are acceptable from the CMC labeling perspective.

Recommendation:

The CMC label/labeling issues identified in the labeling review have been satisfactorily resolved, as reproduced in attachment below. This application is recommended for APPROVAL from the CMC labeling/label perspective.

Venkateswara R. Pavuluri, Ph. D., R. Ph.,
Drug Product Reviewer
DNDP II, ONDP

Hamid Shafiei, Ph. D.,
SPQA, Branch 4, DNDP II, ONDP

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Venkateswara Pavuluri

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Hamid Shafiei

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/s/

HAMID R SHAFIEI
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Office of Pharmaceutical Quality

New Drug Application (NDA)

Integrated Quality Assessment

Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 213953
Assessment 01

Drug Product Name	Kyzatrex™ (testosterone undecanoate) capsules
Dosage Form	Capsules
Strength	100 mg, 150 mg, 200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	MARIUS PHARMACEUTICALS LLC
US agent, if applicable	Not applicable

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission (0000)	12/31/2020	All
Amendment (0002)	01/08/2021	Labeling; OPMA
Amendment (0012)	03/25/2021	OPMA; DP
Amendment (0017)	06/11/2021	DP
Amendment (0019)	06/15/2021	OPMA; DP
Amendment (0020)	06/25/2021	DP; OPMA
Amendment (0022)	07/09/2021	DP; OPMA
Amendment (0023)	07/26/2021	OPMA
Amendment (0025)	09/03/2021	DP
Amendment (0026)	09/13/2021	DP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Jeffrey Medwid	Donna Christner
Drug Product	Venkateswara Pavuluri	Wendy Wilson-Lee
Manufacturing	Amit Kokate	Vaikunth Prabhu
Microbiology	Amit Kokate	Vaikunth Prabhu
Biopharmaceutics	Jia Yin	Vidula Kolhatkar
Regulatory Business Process Manager	Marquita Burnett	

Application Technical Lead	Hong Cai, Ph.D.	
Laboratory (OTR)	na	na
Environmental	Venkateswara Pavuluri	Wendy Wilson-Lee

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	09/24/2019	See Chapter 1 for the drug substance review
	III *(packaging)*			--		Adequate information provided in submission. Used in other approved drugs
	III *(packaging)*			--		Adequate information provided in submission. Used in other approved drugs
	III *(packaging)*			--		Adequate information provided in submission. Used in other approved drugs
	III *(packaging)*			Adequate	Jul 7, 2010	None of the annual reports or DMF amendments filed thereafter affected (b) (4) . Also used in bottles for packaging other approved drugs.
	III (packaging)			--		Adequate information provided in submission. Used in other approved drugs.

(b) (4)	III	(b) (4)		Adequate information provided in submission. Used in other approved drugs.
	III		Sept 7, 2010	used in bottles for packaging other approved drugs
	III			Liners used in packaging other approved capsules
	III			used in bottles for packaging other approved drugs
	IV			Adequate information included in submission
	IV *(Excipient)*			Meets compendial (USP) standard
	III *(*(b) (4)*)*		Dec 11, 2013	used in bottles for packaging other approved drugs

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	118675	Testosterone undecanoate soft gelatin capsules

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	na			
Pharmacology/Toxicology	na			
CDRH	na			
Clinical	na			
Other	na			

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

In its present form, Marius Pharmaceutical's 505(b)(2) New Drug Application #213953 for Kyzatrex™ (testosterone undecanoate) capsules, 100 mg, 150 mg, and 200 mg, submitted on December 31, 2020, is not ready for APPROVAL from the OPQ perspective. Labeling (package insert, container/carton) negotiations have not been completed, and in its present form, the labeling does not comply with the requirements under 21 CFR 201.

Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product.

The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status.

A 24-month expiration dating period for the drug product when stored at 20ºC to 25ºC has been granted.

The request for a categorical exclusion from an environmental assessment (EA), is accepted.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The Sponsor Marius Pharmaceutical submitted 505 b2 NDA 213953 of Kyzatrex™, for testosterone undecanoate (TU) as Testosterone Replacement Treatment (TRT) for primary and secondary hypogonadism. In this document Kyzatrex™ is also referred to as SOV2012-F1. Kyzatrex™ is an oral formulation for testosterone undecanoate, an ester prodrug of testosterone. Kyzatrex™ capsules are available in three strengths of 100 mg, 150 mg, and 200 mg of TU.

Testosterone undecanoate (TU) is a fatty acid ester of testosterone, an androgen. Once TU is absorbed, the ester is cleaved by nonspecific esterases. Testosterone undecanoate is poorly soluble (less than 50 µg/mL) in water.
Two NDAs for oral TU have been approved or conditionally approved for TRT. Kyzatrex™ will be the third oral formulation of TU for TRT. TU was first approved in the U.S. as AVEED, an injection for intramuscular administration, on March 5, 2014 (see NDA 022219). The first oral TU

product, Clarus' JATENZO, was approved under NDA 206089 on March 27, 2019. Subsequently Lipocine (NDA 208088) was tentatively approved on December 8, 2020; final approval is subject to expiration of a period of patent protection and/or exclusivity.

Kyzatrex™, an immediate-release drug product, is prepared as a [redacted] soft gelatin capsules. The capsule contains the following excipients: propylene glycol monolaurate ([redacted], phytosterol esters [redacted], polyoxyl 40 hydrogenated castor oil [redacted], DL-α-tocopheryl acetate (Vitamin E) as the [redacted]. The formulation is a [redacted]. The soft gelatin capsule shells are composed of glycerin, gelatin, sorbitol [redacted], titanium dioxide, and water. [redacted]. It is worth noting that [redacted] is a novel excipient and the applicant has provided adequate information to support its use in Kyzatrex™. The level of the [redacted] (propylene glycol monolaurate) is above the levels listed in the IID for the FDA approved oral products. However, all the excipients and impurities are acceptable from the PharmTox review team perspective.

Kyzatrex™ capsules are packaged as 90 units in wide-mouth, round, white high-density polyethylene (HDPE) bottles with white, polypropylene, child resistant screw caps and induction-sealed liner. The drug product is manufactured, packaged and labeled at [redacted].

Kyzatrex™ is manufactured by [redacted].

A total of eight registration batches with the bracket strategy (three batches each from the lowest and highest strengths (100mg and 200mg)

and two batches from the middle strength (150mg) are provided in the application. The data support a 24-monthshelf life when stored as labeled: "Store at 20°C to 25ºC (68°F to 77ºF), with excursions permitted between 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature]. Store the capsules in a dry place avoiding exposure to excessive moisture and humid conditions."

Proposed Indication(s) including Intended Patient Population	for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
Duration of Treatment	as needed
Maximum Daily Dose	400 mg twice daily (800 mg total per day)
Alternative Methods of Administration	Not applicable

B. Quality Assessment Overview

Drug Substance: Adequate

The chemistry, manufacturing, and controls of testosterone undecanoate are documented in Type II DMF (b) (4). The DMF (b) (4) was last reviewed by Jeffrey B. Medwid, PhD and found adequate on September 24, 2019. There have been no updates to the DMF since the last review. A letter of authorization to reference the DMF (b) (4) is located in Module 1, Section 1.4.2.

The drug substance reviewer Dr. Jeffrey B. Medwid finds the information on the drug substances testosterone undecanoate is adequate to support the approval of the NDA. See IQA Chapter I, Drug Substance for details.

Drug Product: Adequate

Kyzatrex™ is a solid oral dosage form consisting of a (b) (4) soft gelatin capsule. In addition to the active ingredient TU, the (b) (4) fill also contains the following excipients: propylene glycol monolaurate (b) (4), phytosterol esters (b) (4), polyoxyl 40 hydrogenated castor oil (b) (4), DL-α-tocopheryl acetate (Vitamin E) as the (b) (4). The active ingredient TU is insoluble in water (b) (4). The capsule shells are composed of glycerin, gelatin (b) (4), sorbitol (b) (4), titanium dioxide, water and (b) (4) Red as imprinting ink. All the excipients are compendial (USP and/or NF) grade except phytosterol esters and (b) (4) Red Ink. Adequate quality information is provided in the NDA for those two non-compendial excipients. Therefore, DMF (b) (4) for phytosterol esters was not reviewed. It is noted that phytosterol esters is

a novel excipient and that the level of [redacted] used is above the IID limits for the oral route. However, all the excipients are acceptable from a PharmTox perspective via email communications with Dr Yangmee Shin, the PharmTox reviewer, dated September 13, 2021.

Kyzatrex™ capsules are available in three strengths of TU, 100 mg, 150 mg and 200 mg. The three strengths are [redacted]. The 100 mg capsules are oval, opaque, white and imprinted with “MP100” in red ink; the 150 mg capsules are oblong, opaque, white and imprinted with “MP150” in red ink; the 200 mg capsules are oblong, opaque, white and imprinted with “MP200” in red ink. Kyzatrex™ capsules are packaged as 90 units in wide-mouth, round, white high-density polyethylene (HDPE) bottles with white, polypropylene, child resistant screw caps and induction-sealed liner.

The drug product specification includes required tests for oral solid dosage form per ICH Q6A guideline and USP general chapter <2> for oral drug product. The acceptance criteria is supported by the primary batch results at release and in stability. Although the drug load of TU in each capsule is [redacted]% w/w of the total fill and less than [redacted]% of the total weight of the capsule, TU is [redacted]. Therefore, uniformity of dosage units (UDU) test will be performed [redacted] per USP <905> and this is acceptable. This approach is further confirmed by the comparability study data for UDU via [redacted]. Refer to the OMPA review chapter for further information. It is noted that the appearance tested include “the aged capsules may often [redacted]. There is no effect on dissolution and most importantly those capsule batches with the [redacted] observed were used in the Phase 3 studies. Water content control for this soft gel capsule product is included in the drug product specification. The biopharmaceutics team has found that the dissolution test method and acceptance criteria proposed is adequate. The higher than ICH Q3B (R2) recommended limits for four specified impurities /degradants in drug product are acceptable based on the supporting nonclinical safety studies, as confirmed by the PharmTox reviewer, Dr Yangmee Shin. The risk assessments of the elemental impurity (EI) per ICHQ3D and the [redacted] supports the omission of the routine testing for EI and the [redacted]. The various analytical methods listed in the product specification are deemed suitable for intended purposes. The test of the content (assay) of [redacted] DL-alpha-tocopheryl acetate is recommended by the Agency because the

[redacted] over stability was observed.
The applicant provided the following justification for the omitting of the control of DL-alpha-tocopheryl acetate: [redacted]. This is acceptable. Microbial limits proposed for TAMC, TYMC and E.coli are as recommended in USP<1111>. It is acceptable to the OPMA review team. Stability data on all three product strengths have been provided. The data support the applicant's proposed expiration dating period of 24 months when stored at 20-25ºC with excursions permitted [redacted] 15ºC -30ºC (59ºF-86ºF).
The request for categorical exclusion from filing an environmental impact assessment under 21 CFR § 25.31(b) is acceptable based on the review by Dr. Pavuluri.

[redacted]

The drug product reviewer Dr. Venkateswara Pavuluri finds the information on the drug product Kyzatrex™ is adequate to support the approval of the NDA. See IQA Chapter II, Drug Product for details.

Labeling: Inadequate

During the initial assessment of the labeling (prescribing information (PI), and container/carton labels), several deficiencies were identified. The deficiencies will be conveyed to the Applicant. Labeling negotiations were not completed at the time of this review.
Therefore, as of this review, this application is not deemed ready for approval in its present form per 21 CFR 314.125(b)(6) from the CMC labeling/labels perspective until the remaining deficiencies are satisfactorily resolved.
Refer to IQA Labeling Chapter IV by Dr. Venkateswara Pavuluri for the detailed review and the list of the deficiencies.

Manufacturing: Adequate

The drug product is manufactured by [redacted]

(b) (4)

Microbial limits testing is conducted in accordance with USP <61> and USP <62>. The acceptance criteria are consistent with USP <1111>.
The commercial drug product manufacturer is (b) (4) which is the same manufacturing site for the drug product batches used for Phase II & III clinical studies.
The drug product and drug substance manufacturing facilities and external testing facilities are recommended for approval based on compliance history, acceptable profile codes and experience in the proposed responsibilities.
The OPMA reviewer Dr. Amit Kokate finds the information on the manufacturing process, the facilities and the microbiology controls are adequate to support the approval of the NDA.

(b) (4)

(b) (4)

See IQA Chapter V Manufacturing from Dr. Kokate for detailed assessment.

Biopharmaceutics: Adequate

Kyzatrex™ is an immediate release (IR) soft gelatin capsule product. The proposed three strengths (100 mg, 150 mg, and 200 mg) are (b) (4), and all three strengths have been studied in phase 3 clinical studies. The formulation used in the pivotal clinical batches are identical to the proposed commercial batches. No biowaiver request was submitted.
The dissolution test method and acceptance criteria below were found adequate.

Approved dissolution method and acceptance criterion

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance Criterion
II (Paddle)	75	0.01N HCl with 0.5% Triton-X 100/ 37°C ± 0.5°C	900	Q = (b) (4)% in 30 min

As the phase 3 formulation (SOV2012-F1) is the same as the commercial formulation, no in vivo formulation bridging study is needed.

The Biopharmaceutics reviewer Dr. Jia Yin finds the information on the Biopharmaceutics is adequate to support the approval of the NDA.. Refer to the review by Dr. Yin in IQA Biopharmaceutics Chapter for details.

Microbiology (if applicable): Adequate

See Manufacturing Section.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Appearance	Process Stability	L	(b) (4)	Acceptable	None
Identification	CGMP	L		Acceptable	None
Assay	Formulation Raw Materials Process	M		Acceptable	None
Related Substances Impurities/Degradants	Formulation Raw Materials Process Container Closure System	M		Acceptable	None
Water Contents	Raw Materials Process Container Closure System	L		Acceptable	None
Uniformity of Dosage Units	Formulation Process	H		Acceptable	None
Dissolution	Formulation Raw Materials Process	M		Acceptable	None
Micro limits	Raw Material Process	L		Acceptable	None

*Risk ranking applies to product attribute/CQA

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

na

2. Drug Substance Deficiencies

na

3. Drug Product Deficiencies

na

4. Labeling Deficiencies

na

5. Manufacturing Deficiencies

na

6. Biopharmaceutics Deficiencies

na

7. Microbiology Deficiencies

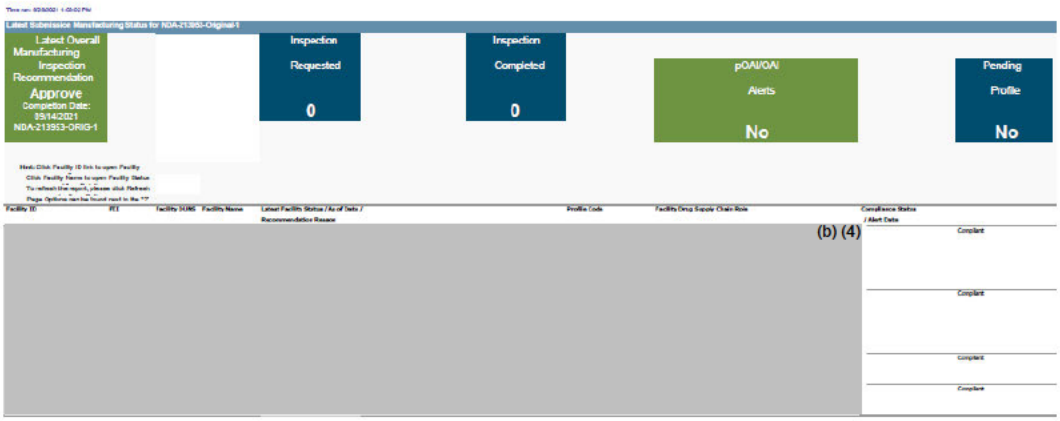
na

8. Other Deficiencies *(Specify discipline, such as Environmental)*

na

E. The Facility Status:

The drug substance, drug product manufacturers and external testing facilities are recommended for approval based on compliance history, acceptable profile codes and experience in the proposed responsibilities to support this application at this time (See the screen capture of the "Submission facility Status View" from Panorama).



Application Technical Lead Name and Date:

Hong Cai, Ph.D.
September 28, 2021

Hong Cai

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: as submitted in eCTD SN 0010 Date: 13-03-2021

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	KYZATREX	**Deferred to DMEPA**
Established name(s)	Testosterone undecanoate	Acceptable.
Route(s) of administration	for oral use	Acceptable.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s)	Capsules available in the following strengths:	Acceptable.

in metric system.	100 mg, 150 mg, 200 mg	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not a tablet.	Not Applicable.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not an injectable.	Not Applicable.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Not Applicable.	Not Applicable.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

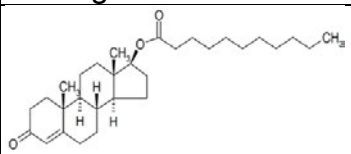
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Capsule	Acceptable.
Strength(s) in metric system	100 mg, 150 mg and 200 mg.	Acceptable.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	*Dose of testosterone undecanoate expressed in ester form.*	Acceptable. *Note: testosterone undecanoate is an ester of testosterone and undecanoic acid. USP salt policy doesn't apply.*
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	(b) (4)	**Acceptable,** However, text in product description section may be simplified as: Capsules: *100 mg, opaque, white, oval, imprinted with "MP100" in red ink *150 mg, opaque, white oblong, imprinted with "MP150" in red ink *200 mg, opaque, white oblong, imprinted with "MP200" in red ink
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not a tablet.	Not Applicable.

For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Not injectable.	Not Applicable.

1.2.3 Section 11 (DESCRIPTION)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	KYZATREX, testosterone undecanoate.	Acceptable.
Dosage form(s) and route(s) of administration	Capsule,	Acceptable, but the route of administration is not included in the section 11. The text in 3rd and 4th paragraphs may be rewritten as follows, with listing of inactive ingredients in alphabetical order in both fill (b) (4) and capsule shell composition: KYZATREX (testosterone undecanoate) capsules for oral use are available in three strengths of 100 mg, 150 mg, and 200 mg. The 100 mg strength is an opaque white capsule is imprinted with "MP100" in red ink. The 150 mg strength is an opaque white capsule is imprinted with "MP150" in red ink. The 200 mg strength is an opaque white capsule imprinted with "MP200" in red ink. All capsule strengths also contain polyoxyl 40 hydrogenated castor oil, phytosterol esters, propylene glycol monolaurate, and DL-α-tocopheryl acetate (Vitamin E) as inactive ingredients.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	testosterone undecanoate	Acceptable. *Note: testosterone undecanoate is an ester and USP salt policy doesn't apply.*

List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	propylene glycol monolaurate, polyoxyl 40 hydrogenated castor oil, vitamin E, and phytosterol esters as inactive ingredients. Gelatin capsule shells are composed of the following inactive ingredients: gelatin, sorbitol, glycerin, purified water, and titanium dioxide.	**Acceptable.** However, inactive ingredients shall be listed in alphabetical order, for both fill (b) (4) and gelatin shell compositions. Vitamin E may be described with given name followed by general descriptor (Vitamin E) in parenthesis as: DL-alpha-tocopheryl acetate (Vitamin E).
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Not injectable.	Not Applicable.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	No Alcohol present	Not Applicable.
Statement of being sterile (if applicable)	Not sterile.	Not Applicable.
Pharmacological/ therapeutic class	The active moiety, testosterone, is an Androgen.	Acceptable.
Chemical name, structural formula, molecular weight	 17β-hydroxyandrost-4-en-3-one undecanoate. $C_{30}H_{48}O_3$; 456.7 g/mol.	Acceptable.
If radioactive, statement of important nuclear characteristics.	Not radioactive.	Not Applicable.
Other important chemical or physical properties (such as pKa or pH)	None	Not Applicable.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	No Gluten statement.	Not Applicable
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None.	Not Applicable.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Capsule	Acceptable.
Strength(s) in metric system	100 mg, 150 mg, and 200 mg	Acceptable.
Available units (e.g., bottles of 100 tablets)	90 units	Acceptable.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	Acceptable. However, the text may be simplified as: KYZATREX capsules are available in three strengths of 100 mg, 150 mg, and 200 mg, packaged as 90 units in wide-mouth, round, white HDPE bottles with white, polypropylene, child resistant caps and induction-sealed liner. 100 mg: Oval, opaque white capsules imprinted with "MP100" in red ink; NDC 80603-101-11. 150 mg: Oblong, opaque white capsules imprinted with "MP150" in red ink; NDC 80603-103-11. 200 mg: Oblong, opaque white capsules imprinted with "MP200" in red ink; NDC 80603-105-11.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not a tablet.	Not Applicable.

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not an injectable.	Not Applicable.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	(b) (4) [redacted]	**Acceptable**. However, the text may be revised as: Store the capsules in a dry place, avoiding exposure to excessive moisture and humid conditions.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	No Desiccant was included.	Not Applicable.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25ºC (68°F to 77ºF), excursions permitted (b) (4) 15ºC to 30ºC (59ºF to 86ºF).	**Not Acceptable.** Second sentence shall be revised as "Excursions permitted between 15°C-30°C (59°C-86°F) [see USP Controlled Room Temperature].
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid	Not Applicable.	Not Applicable.

statements such as “latex-free.”		
Include information about child-resistant packaging	Information on child resistant caps included. (b) (4)	Acceptable.

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

Not Applicable.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Marketed by: Marius Pharmaceuticals 8601 Six Forks Road, Suite 630 Raleigh, NC 27615	Acceptable.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Medication Guide: The established and proprietary names in Medication Guide submitted in eCTD SN# 0021 Dt. 13-MAR-2021 are same as in the PI. Inactive listed in the Medication Guide are also same as listed in section 11 of PI. The inactive ingredients may be listed in alphabetical order, in both fill (b) (4) and shell compositions. Vitamin E may be described with given name followed by general descriptor (Vitamin E) in parenthesis as: DL-alpha-tocopheryl acetate

(Vitamin E). No other CMC relevant information included in the Medication Guide.

3.0 CARTON AND CONTAINER LABELING

Information reviewed is as submitted in eCTD SN 0000, Date: 14-09-2021

3.1 Container Label

Start of Applicant material

(b) (4)

End of Applicant material

Item	Information Provided in the NDA	Assessor's Comments about Container Labels for 100 mf, 150 mg and 200 mg capsules
Proprietary name, established name, and dosage form (font size and prominence	(b) (4)	Acceptable
Dosage strength	100 mg, 150 mg, or 200 mg as applicable	Acceptable.
Route of administration	Not included.	Acceptable. *Not required for oral dosage forms per 21 CFR 201.100(b)(3).*
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not Applicable. *Note: testosterone undecanoate is an ester and USP salt policy doesn't apply.*	Acceptable. .
Net contents (e.g. tablet count)	90 Capsule	Acceptable.
"Rx only" displayed on the principal display	(b) (4)	Acceptable.
NDC number	100 mg: NDC 80603-101-11 150 mg: NDC 80603-103-11 200 mg: NDC 50603-105-11	Acceptable.
Lot number and expiration date	(b) (4)	Acceptable. Applicant confirmed that 7-digit lot number generated will be compliant with 21 CFR 201.18 and Expiration date format acceptable per 21 CFR 201.17
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at: 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to-30°C (59°C to86°F).	Acceptable.

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Not Injectable.	Not Applicable.
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	Not Applicable.	Not Applicable.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	No alcohol is present in the drug	Not Applicable.
Bar code	(b) (4)	Acceptable.

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	(b) (4)	Acceptable. Per 21 CFR Part 201.1(a) name, place of business of the manufacturer / packer /distributor present on the container label.
Medication Guide (if applicable)	Provided	Acceptable, except for the comment above under PI
No text on Ferrule and Cap overseal	Not an Injectable	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	Not a USP monograph product.	Acceptable.
And others, if space is available		

Assessment of Carton and Container Labeling: Adequate

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies:

A. Full Prescribing Information:

1. DOSAGE FORMS AND STRENGTHS

i. Text may be simplified as follows:

"Capsules:
-100 mg, opaque, white, oval, imprinted with "MP100" in red ink.
-150 mg, opaque, white oblong, imprinted with "MP150" in red ink.
-200 mg, opaque, white oblong, imprinted with "MP200" in red ink."

2. DECRIPTION

ii. The text in 3rd and 4th paragraphs may be rewritten as follows, with listing of inactive ingredients in alphabetical order in both fill (b) (4) *and capsule shell composition. Vitamin E may be described with given name followed by general descriptor (Vitamin E) in parenthesis as: DL-alpha-tocopheryl acetate (Vitamin E).*

"KYZATREX (testosterone undecanoate) capsules for oral use are available in three strengths, 100 mg, 150 mg, and 200 mg. The 100 mg strength is an opaque white capsule is imprinted with "MP100" in red ink. The 150 mg strength is an opaque white capsule is imprinted with "MP150" in red ink. The 200 mg strength is an opaque white capsule imprinted with "MP200" in red ink. All capsule strengths also contain polyoxyl 40 hydrogenated castor oil, phytosterol esters, propylene glycol monolaurate, and DL-α-tocopheryl acetate (Vitamin E) as inactive ingredients."

3. HOW SUPPLIED/STORAGE AND HANDLING

iii. The text :How Supplied: section may be simplified as:

"KYZATREX capsules are available in three strengths of 100 mg, 150 mg, and 200 mg, packaged as 90 units in wide-mouth, round, white HDPE bottles with white, polypropylene, child resistant caps and induction-sealed liner.

- 100 mg: Oval, opaque white capsules imprinted with "MP100" in red ink; NDC 80603-101-11.
- 150 mg: Oblong, opaque white capsules imprinted with "MP150" in red ink; NDC 80603-103-11.
-200 mg: Oblong, opaque white capsules imprinted with "MP200" in red ink; NDC 80603-105-11."

iv. Storage statements shall be revised as follows:

"Store at 20°C to 25ºC (68°F to 77ºF), excursions permitted between 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature]. Store the capsules in a dry place, avoiding exposure to excessive moisture and humid conditions."

B. Container Labels: None

Overall Assessment and Recommendation:

As of this review, this application is not deemed ready for approval in its present form per 21 CFR 314.125(b)(6) from the CMC labeling/labels perspective until the remaining deficiencies delineated in the **List of Deficiencies** (for PI only) above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Venkateswara R. Pavuluri, Ph. D., R. Ph.
Chemist, CDER/OPQ/ONDP/DNDPII/Br4;
19-09-2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Wendy Wilson-Lee, Ph. D.,
Division Director, DNDPII/ONDP/OPQ/CDER
-09-2021

Venkateswara Pavuluri

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Wendy Wilson- Lee

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BIOPHARMACEUTICS

NDA: 213953 (Associated IND 118675)
Submission Type: 505(b)(2)
Drug Product Name / Strength: Kyzatrex® Testosterone Undecanoate Capsule/100 mg, 150 mg, 200 mg
Dosage Form: Immediate Release Capsule
Route of Administration: Oral
Applicant: Marius Pharmaceuticals, LLC
Indication: Primary and secondary hypogonadism in adult males
Submission Date: 12/31/2020
Primary Reviewer: Jia Yin, Ph.D.
Secondary Reviewer: Vidula Kolhatkar, Ph.D.

Background: The Applicant seeks approval for Kyzatrex® (Testosterone Undecanoate, TU) via 505(b)(2) pathway for the treatment of primary and secondary hypogonadism in adult males. The proposed TU capsule is soft gelatin, immediate-release (IR) capsule containing (b) (4) . The proposed three strengths (100 mg, 150 mg, and 200 mg) are (b) (4) . All three strengths have been studied in phase 3 clinical studies. No biowaiver request was submitted.

REVIEW SUMMARY

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting **1)** formulation bridging between the pivotal clinical batch and the commercial batch, and **2)** the proposed dissolution method and acceptance criterion. The key review findings are summarized as follows:

Formulation Bridging: Adequate

As the phase 3 formulation (SOV2012-F1) is the same as the commercial formulation, no in vivo formulation bridging study is needed.

Dissolution Method: Adequate

The selection of dissolution parameters is reasonable. The selection of the critical quality parameters and the variation range of the parameters (±(b) (4)% of the reference value) for evaluation of the discriminating ability of the dissolution method is acceptable. However, as the difference in dissolution is only observed at the early time point (5 minutes) and the dissolution of tested batches reaches 85% and above by 15 minutes, the dissolution method is not considered as discriminating.

However, considering this is an immediate release formulation with (b) (4) the dissolution medium, the demonstration of the discriminating ability of the dissolution method is challenging. Additional factors taken into consideration are: 1) the formulation is a (b) (4) , 2) (b) (4) , 3) the variation of the amount of (b) (4) could be detected by the appearance test, 4) according to Clinical Pharmacology reviewer, the post-dose Tmax is around 3 – 5 hours. Based on above considerations, Biopharmaceutics accepts that the proposed dissolution method.

Overall, the proposed dissolution method is adequate

Dissolution Acceptance Criterion: Acceptable

Based on the provided dissolution profile data of all clinical and registration batches, the proposed dissolution acceptance criterion of Q = (b) (4)% in 30 minutes is acceptable.

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 213953 for Kyzatrex® (Testosterone Undecanoate) Immediate Release Capsule is deemed adequate for APPROVAL.

Approved dissolution method and acceptance criterion

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance Criterion
II (Paddle)	75	0.01N HCl with 0.5% Triton-X 100/ 37°C ± 0.5°C	900	Q = (b) (4)% in 30 min

BIOPHARMACEUTICS ASSESSMENT

List Submissions Being Reviewed

Received Date	Submission
12/31/2020	Original submission

Physiochemical Property of Drug Substance

Testosterone Undecanoate (TU) is insoluble in water. The key physicochemical character of TU is its high lipophilicity, with estimated log P = 6.5. Therefore, according to the applicant, TU is absorbed through the lymphatic system, rather than through the portal vein circulatory system.[1]

Formulation Bridging

Reviewer's Assessment: ***Adequate***

As the phase 3 formulation (SOV2012-F1) is the same as the commercial formulation, no in vivo formulation bridging study is needed.

Formulation SOV2012-F1 (selected from study SOV-TU-BA2012) was used in all pivotal studies (definitive phase 1 studies and phase 3 studies) and is the proposed commercial formulation. In addition, The SOV2012-F1 100 mg, 150 mg and 200 mg strengths are (b) (4) (**Table 1**).

Table 1 Composition for SOV2012-F1 formulation

Component	Function	(b) (4)	Unit Dose (mg) 200 mg capsule	Unit Dose (mg) 150 mg	Unit Dose (mg) 100 mg
Testosterone Undecanoate	Active ingredient		200.0	150.0	100.0
Polyoxyl-40 hydrogenated castor oil ((b) (4))	(b) (4)				
Propylene glycol monolaurate ((b) (4))					
Phytosterol Esters ((b) (4))					
DL-alpha-tocopherol acetate ((b) (4) vitamin E (b) (4))					
Total fill (b) (4)	-	(b) (4)	(b) (4)		
Soft gelatin capsule	Capsule	1 capsule shell			
Total drug product (mg)	-	1 capsule			

[1] \\CDSESUB1\evsprod\nda213953\0000\m3\32-body-data\32p-drug-prod\sov2012-f1\32p2-pharm-dev\p22-pharm-dev-dp.pdf

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

Dissolution Method: ***Adequate***

The selection of dissolution parameters is reasonable. The selection of the critical quality parameters and the variation range of the parameters (±(b) (4)% of the reference value) for evaluation of the discriminating ability of the dissolution method is acceptable. However, as stated by the Applicant, the difference in dissolution is only observed at the early time point (5 minutes). By 15 minutes, the dissolution of all tested batches (reference and aberrant) has reached 85% and above. Therefore, the calculation of f2 values for dissolution profile comparison is not applicable in this situation. The dissolution method is not considered as discriminating.

However, considering this is an immediate release formulation with (b) (4) the dissolution medium, the demonstration of the discriminating ability of the dissolution method is challenging. Additional factors taken into consideration are: 1) (b) (4) , 4) Per discussion with Clinical Pharmacology reviewer, the post-dose Tmax is around 3 – 5 hours. Based on above considerations and available dissolution data, Biopharmaceutics accepts that the proposed dissolution method lacks discriminating ability.

Overall, the proposed dissolution method is adequate.

Dissolution Acceptance Criterion ***(Acceptable)***

The proposed drug product is a soft gelatin capsule (b) (4) . Based on the provided dissolution profile data, (b) (4) , as the detection of the API started at 5 minutes time point. Based on the provided dissolution data of the clinical and registration batches, very high variability in dissolution is observed at 5 minutes, which is expected. At later time points (15 minutes and later), the variability in dissolution is within 10% RSD, which is acceptable. By 30 minutes, the mean dissolution of all batches has reached 85% and above. The proposed dissolution acceptance criterion of Q = (b) (4)% in 30 minutes is acceptable.

Proposed Dissolution Method and Acceptance Criterion

Table 2 Proposed dissolution method and acceptance criterion

Parameter	Proposed value
Apparatus	USP<711> Apparatus 2 (paddles)
Volume	900 mL
Rotation speed	75 RPM
Media	0.5% Triton X-100 / 0.01N HCl
Specification	Q= (b)(4)% at 30 minutes

Dissolution Method Development

(b) (4)

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(b) (4)

2) Evaluation of the Discriminating Ability of the Dissolution Method

The Applicant evaluated the discriminating ability of the dissolution method against two critical quality parameters: (b) (4) content and (b) (4), variation of which may cause dissolution failure.

(b) (4)

(b) (4), is shown in a formulation robustness study to have a statistically significant negative effect on TU solubility. Thus, (b) (4) is expected to increase the risk of (b) (4) (this failure mode could also be detected by the appearance test). Additionally, variation in (b) (4) content might also affect the ability of the formulation to (b) (4) in the dissolution test. (b) (4), the primary failure mode for dissolution is the failure of (b) (4) .

The Applicant manufactured four aberrant batches with a combination of decreased ((b) (4)% vs. reference (b) (4)%) or increased ((b) (4)% vs. reference (b) (4)%) (b) (4) levels and decreased ((b) (4) vs. reference (b) (4)) or increased ((b) (4) vs. reference (b) (4).

Based on the difference in dissolution data (**Table 4**) at the early time points (5 minutes and 15 minutes) and the calculated f2 values (**Table 5**), the Applicant concluded that the proposed dissolution method is able to detect changes in (b) (4) levels and (b) (4) of the capsule.

Table 4 Dissolution profile data of reference batch and aberrant batches with varying (b) (4) levels and varying (b) (4)

Lot (descriptor)	Statistic	Sampling time (minutes)				
		5	15	30	45	60
Lot 1301444 (b) (4)	Mean	93	101	101	102	102
	SD	3.9	1.2	0.6	0.5	0.9
	RSD, %	4	1	1	1	1
Lot 1301445 (b) (4)	Mean	71	99	102	101	101
	SD	35.4	3.3	1.8	1.1	0.6
	RSD, %	50	3	2	1	1
Lot 1301446 (b) (4)	Mean	67	91	100	102	103
	SD	20.2	9.3	3.7	1.9	0.8
	RSD, %	30	10	4	2	1
Lot 1301447 (b) (4)	Mean	51	92	102	103	104
	SD	14.1	6.1	2.3	0.6	0.5
	RSD, %	28	7	2	1	1
Lot 1153030[1] (nominal) (b) (4)	Mean	1	86	98	NT	NT
	SD	1.0	9.4	3.4	NT	NT
	RSD, %	103	11	4	NT	NT

Test conditions: 900 mL of 0.5% Triton X-100 in 0.01N HCl, Apparatus 2, 75 rpm, n=6.

1. Bulk Lot #; Primary stability packaged lot is 1177632.

Table 5 Summary of f2 values

Reference	Test	f2
Lot 1153030 (nominal) (b) (4)	Lot 1301444 (b) (4)	13.4
	Lot 1301445	19.3
	Lot 1301446	20.9
	Lot 1301447	26.7
Lot 1301444 (b) (4)	Lot 1301445	44.6
Lot 1301447 (b) (4)	Lot 1301446	51.4
Lot 1301444 (b) (4)	Lot 1301447	30.3
Lot 1301445 (b) (4)	Lot 1301446	63.4

(b) (4)

Reviewer's comment: As discussed in the earlier sections the dissolution method is not considered as discriminating.

Justification for Dissolution Acceptance Criterion

The Applicant submitted dissolution profile data for all clinical and registration batches (3 batches for 200 mg, 2 batches for 150 mg, and 3 batches for 100 mg) at multiple stability time points (month 0 up to month 24).[2] Based on the dissolution data, the Applicant proposed Q =(b) (4)% in 30 minutes for quality control of the proposed drug product. The proposed acceptance criterion is acceptable.

[2] \\CDSESUB1\evsprod\nda213953\0000\m3\32-body-data\32p-drug-prod\sov2012-f1\32p5-contr-drug-prod\32p54-batch-analys\dissol-excel-attach.pdf

Vidula Kolhatkar

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Jia Yin

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HONG CAI
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