CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213433Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 213433
Assessment # 1

Drug Product Name	WINLEVI (clascoterone)
Dosage Form	Cream
Strength	1%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Cassiopea, SpA
US agent, if applicable	Ground Zero Pharmaceuticals

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission	08/19/2019	All
User Fee Cover Sheet	08/22/2019	All
Response to Information Request - Clinical	08/29/2019	Clinical
Response to Information Request - Nonclinical	09/06/2019	Pharm/Tox
Response to Information Request - Clinical	09/27/2019	Clinical
Response to Information Request - Clinical	10/03/2019	Clinical
Response to Information Request - Clinical	10/11/2019	Clinical
Response to Information Request - Clinical	10/24/2019	Clinical
Response to Information Request - Clinical	10/25/2019	Clinical
Proprietary Name Request	10/28/2019	All
Response to Information Request - Clinical	11/22/2019	Clinical
Response to Information Request - Quality	12/02/2019	ONDP and OPMA

Response to Information Request - Clinical	12/17/2019	Clinical
Response to Information Request - Quality	12/27/2019	ONDP
Response to Information Request - Quality	01/10/2020	ONDP
Response to Information Request - Quality	01/10/2020	ONDP - Biopharm
Response to Information Request - Clinical	01/16/2020	Clinical
Response to Information Request - Quality	01/31/2020	ONDP
Response to Information Request - Clinical	02/10/2020	Clinical
Response to Information Request - Quality	02/21/2020	ONDP and OPMA
Response to Information Request - Clinical	03/13/2020	Clinical
Response to Information Request - Quality	03/27/2020	ONDP and OPMA
Response to Information Request - Clinical	04/13/2020	Clinical
Response to Information Request - Clinical	04/29/202	Clinical
Response to Information Request - Quality	05/05/2020	OPMA - Microbiology
Multiple Categories - Labeling	05/13/2020	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Jeffrey Medwid, Ph.D.	Donna Christner, Ph.D.
Drug Product	Zhengfang Ge, Ph.D.	Moo-Jhong Rhee, Ph.D.
Manufacturing	Amit Kokate, Ph.D.	Yubing Tang, Ph.D.
Microbiology	Jason God, Ph.D.	Denise Miller, Ph.D.
Biopharmaceutics	Swapna Pamu, Ph.D.	Vidula Kolhatkar, Ph.D.
Regulatory Business Process Manager	Melinda Bauerlien, MS	
Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	Raanan Bloom, Ph.D.	Michael Furness, Ph.D.

U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

- The applicant of this 505(b)(2) new drug application has provided **sufficient CMC information** to assure the identity, purity, strength, and quality of the drug substance (clascoterone) and the drug product, WINLEVI® (clascoterone) Cream, 1%.

- Labels/labeling issues have been **satisfactorily** addressed.

- The Office of Process and Facility has made an overall "**Acceptable**" recommendation regarding the facilities involved in this NDA.

- The claim for categorical exclusion from the preparation of environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is recommended for **APPROVAL** with expiration dating period of **36 months**.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The applicant, Cassiopea SpA has submitted this 505(b)(1) new drug application for WINLEVI® (clascoterone) Cream, 1% for topical administration. WINLEVI® is indicated for the treatment of acne vulgaris in patients 12 years of age or older.

The active ingredient clascoterone is an androgen receptor inhibitor formulated as a white to almost white cream for topical dermatological use. Clascoterone is a white to almost white powder which is practically insoluble in water.

Each gram of cream of WINLEVI container 10 mg of clascoterone as the active ingredient and cetyl alcohol, mono and diglycerides, mineral oil, propylene glycol, vitamin E, edetate disodium, polysorbate 80, citric acid monohydrate, and purified water as the inactive ingredients.

WINLEVI cream is packaged and supplied as 60g in an epoxy-lined aluminum blind-end tube with a polypropylene cap. This product should be stored at 2ºC – 8ºC (38ºF – 46ºF) during shelf-life storage. Patients are instructed to store this drug product at room temperature 20ºC – 25ºC (68ºF – 78ºF) while in use. WINLEVI should be used within one month

after opening. The unused product should be discarded 180 days after the date of dispensing.

WINLEVI cream is intended for topical administration to cleaned and dried affected skin area as uniform thin layer twice daily, in the morning and in the evening.

Proposed Indication(s) including Intended Patient Population	Treatment of acne vulgaris in patients 12 years of age or older
Duration of Treatment	As prescribed
Maximum Daily Dose	As prescribed
Alternative Methods of Administration	N/A

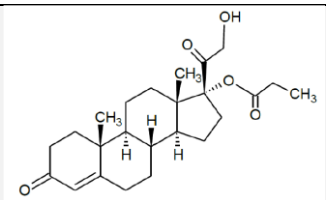
B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, clascoterone is an androgen receptor inhibitor with a good skin permeation. It binds weakly to the human androgen receptor, thus blocking the receptor and preventing downstream androgenetic gene activation. Clascoterone has been classified as a new molecular entity (NME) and is intended as the active ingredient of topical cream indicated for the treatment of acne vulgaris in patients 12 years of age or older.

Clascoterone is a white or almost white powder. It is practically insoluble in water, slightly soluble in ether, and very soluble in methanol and ethanol. It presents different polymorphic forms and the polymorphic form identified as Form (b) (4) shows a melting range of (b) (4) °C. It also has the specific optical rotation of (b) (4) (b) (4)

Clascoterone (USAN) also identified throughout the application as Cortexolone-17α-propionate (INN) has the chemical name, [(8R,9S,10R,13S,14S,17R)-17-(2-hydroxyacetyl)-10,13-dimethyl-3-oxo-2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenanthren-17-yl] propanoate, a molecular formula of $C_{24}H_{34}O_5$, a molecular weight of 402.5 g/mol, and the chemical structure below:



Clascoterone is manufactured in accordance to current Good Manufacturing Practices (cGMP) requirements by (b) (4) and is packaged in (b) (4). It is tested and release against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest date of (b) (4) months when stored in a (b) (4) Information regarding the manufacture of clascoterone supplied by (b) (4) is provided in DMF (b) (4). This DMF was reviewed by the Drug Substance Reviewer, Dr. Jeffrey Medwid on December 18, 2019 and was found to be adequate.

In summary, based on the review of the manufacturing information provided in DMF (b) (4) and the review of the additional information provided in the Drug Substance Module of this application, Dr. Medwid has concluded that the drug substance information provided is adequate to support approval of this application from the drug substance perspective. Dr. Medwid's review is provided in the Drug Substance Chapter of the Integrated Quality Assessment (IQA).

Drug Product: Adequate

WINLEVI® (clascoterone) Cream, 1% for topical administration has been developed for the treatment of acne vulgaris in patients 12 years of age or older. It is intended for twice a day topical application as uniform thin layer to cleaned dried affected skin area.

WINLEVI has been formulated as a white to almost white (b) (4) cream. Each gram of the cream contains 10mg (1%) clascoterone as the active ingredient and cetyl alcohol, mono and diglycerides, mineral oil, propylene glycol, vitamin E, edetate disodium, polysorbate 80, citric acid monohydrate, and purified water as inactive ingredients. Inactive ingredients used in the composition of the drug product are all compendial materials. Clascoterone was found to be (b) (4) Therefore, the pH of final cream formulation was adjusted to (b) (4) for the Phase 3 studies. (b) (4) storage condition of 5ºC± 3ºC was used and recommended as the shelf-life storage condition for the commercial drug product.

WINLEVI cream is manufactured in accordance to cGMP requirements by Cassiopea SpA and is packaged as 60g in epoxy-lined blind-end aluminum tubes with polypropylene caps. The drug product is tested against a specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its proposed shelf-life of 36 months. The applicant has provided sufficient stability data that supports the expiration dating period of 36 months for the drug product stored at 2ºC – 8ºC (38ºF – 46ºF). The applicant has also provided sufficient stability data that supports the storage of the drug product at room temperature, 20ºC – 25ºC (68ºF – 78ºF) while in use.

The drug product module of this application has been reviewed by the Drug Product Reviewer, Dr. Zhengfang Ge. Dr. Ge has concluded that the information provided in the drug product module is adequate to support the approval of this application from the drug product perspective. Dr. Ge's review is provided in the Drug Product Chapter of the IQA.

Labeling: Adequate

The CMC sections of the Prescribing Information (PI) as well as the immediate container and carton labels have been reviewed by the Drug Product Reviewer, Dr. Zhengfang Ge. Dr. Ge has found that the final PI as well as immediate container and carton labels submitted to the application have satisfactorily resolved all deficiencies noted in her Labeling Review #1, and therefore, she has recommended approval of this application from the CMC labeling/labels perspective.

Dr. Ge's Labeling Review # 1 dated April 9, 2020 followed by her addendum to the Labeling Review # 1 dated July 13, 2020 noting her final recommendation of approval of PI labeling as well as container and carton labels from the CMC perspective are provided in the Labeling Chapter of the IQA.

Environmental Assessment: Adequate

The applicant has requested a categorical exclusion from preparation of environmental assessment according to 21 CFR 25.31(b) based on the estimated introductory concentration of the active moiety into aquatic environment of (b) (4) µg/L which is less than 1ppb. The applicant has also provided the statement that to their knowledge, no extra ordinary circumstances exits per 21 CFR 25.31(d) and has provided supportive information for this statement.

Since the active ingredient of this new drug application is a new molecular entity and is an androgen receptor inhibitor, the acceptability of the request for the categorical exclusion has been reviewed by the

Environmental Assessment Reviewer, Dr. Raanan Bloom. Dr. Bloom has found the applicant's request for the categorical exclusion from preparation of environmental assessment adequate. Therefore, the categorical exclusion for this application is granted. Dr. Bloom's review is provided in the Environmental Assessment Chapter of the IQA (right after the Labeling Chapter).

Manufacturing: Adequate

Manufacturing Process:

The manufacturing process for WINLEVI cream entails the preparations of (b) (4) product specification.

The manufacturing process for WINLEVI cream has been reviewed by the OPMA Reviewer, Dr. Amit Kokate. Dr. Kokate has concluded that the proposed commercial manufacturing process is adequate.

Manufacturing Facilities:

Based on the compliance profile, acceptable profile code, and experience in proposed manufacturing responsibilities, the drug substance manufacturing and testing sites have been recommended as acceptable. The drug product manufacturing site was originally recommended for preapproval inspection (PAI). Due to current travel restrictions associated with COVID-19 pandemic, in lieu of PAI, the acceptability of drug product manufacturing facility was determined based on the review of the facility and manufacturing documents and records that were submitted to the application per Agency's request, in accordance to 704(a)(4).

Facilities involved in this application were also reviewed by the OPMA Reviewer Dr. Amit Kokate. Dr. Kokate has recommended that the overall facilities involved in this application as adequate.

Dr. Kokate review of the manufacturing process and facilities is provided in the Manufacturing Chapter of the IQA.

Biopharmaceutics: Adequate

The biopharmaceutic review of this application was mainly focused on the adequacy of the proposed in-vitro release testing (IVRT) method, method

validation, proposed IVRT acceptance criterion, and the review of comparative IVRT data from batches tested.

The proposed IVRT method, method validation, acceptance criteria, and IVRT results were reviewed and evaluated by the Biopharmaceutics Reviewer, Dr. Swapna Pamu. Dr. Pamu has found the proposed IVRT method and acceptance criteria adequate and supported by the data provided. In summary, Dr. Pamu has found the biopharmaceutics information provided adequate to support the approval of this application from the biopharmaceutics perspective. Dr. Pamu's review is provided in Biopharmaceutics Chapter of the IQA.

Microbiology (if applicable): Adequate

WINLEVI (clascoterone) Cream, is an (b) (4), self-preserved, multi-dose nonsterile drug product for topical use.

Since the drug product is a self-preserved cream, one batch of finished drug product was tested for antimicrobial effectiveness (AET) and have shown to meet the requirements in USP <51>. As a nonsterile cutaneous drug product, WILEVI have shown to comply with the requirements in USP <1111> and the final drug product specification includes testing and acceptance criteria in accordance to USP <60>, USP <61>, and USP <62>.

The microbiology section of this application has been reviewed by the Microbiology Reviewer, Dr. Jason God. Dr. God has found the microbiology information and the updated drug product specification adequate to support the approval of this application from the microbiology perspective. Dr. God's review is provided in Microbiology Chapter of the IQA.

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**
Assay, Degradation Products, and Uniformity of Dosage Unit	(b) (4)	M to H	(b) (4)	L (Acceptable)	None

			(b) (4)		

D. List of Deficiencies for Complete Response

None

Application Technical:

Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 8/10/2020 03:21:42PM
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U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)		Adequate	10/06/2019	Reviewed by Jeffrey Medwid, Ph.D.
	III			----------	----------	Sufficient information is provided in the NDA

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

Document	Application Number	Description
N/A	N/A	N/A

2. CONSULTS

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

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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:

The Prescribing Information is deemed not ADEQUATE as proposed until it is revised satisfactorily to meet the regulatory requirements (See the **List of Deficiencies** at the end of this review).

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use WINLEVI cream safely and effectively. See full prescribing information for WINLEVI cream.

WINLEVI® (clascoterone) cream, for topical use
Initial U.S. Approval: YYYY

INDICATIONS AND USAGE
WINLEVI® (clascoterone) cream is an androgen receptor inhibitor indicated for the topical treatment of acne vulgaris in patients 9 years of age and older. (1)

DOSAGE AND ADMINISTRATION
- Apply a thin layer (approximately 1 gram) to affected area twice daily (morning and evening). Avoid contact with eyes and mucous membranes. (2)
- Not for ophthalmic, oral or vaginal use. (2)

DOSAGE FORMS AND STRENGTHS
Cream 1%. (3)

CONTRAINDICATIONS
None. (4)

WARNINGS AND PRECAUTIONS
- (b) (4)
- [redacted]

ADVERSE REACTIONS
The most frequent local skin reactions were erythema/reddening, scaling/dryness, and pruritus. These reactions occurred in a similar percentage of patients treated with vehicle. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cassiopea at 1-800-###-#### or FDA at 1-800-FDA-1088 or http://www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	**WINLEVI**	
Established name(s)	(clascoterone) cream	Adequate
Route(s) of administration	topical	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Cream, 1 %	Adequate

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
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.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

2 DOSAGE AND ADMINISTRATION

Cleanse the affected area gently. After the skin is dry, apply a thin uniform layer of WINLEVI cream [redacted] (b) (4) twice per day, in the morning and the evening, to the affected area. Avoid accidental transfer of WINLEVI cream into eyes, mouth or other mucous membranes. If contact with mucous membranes occurs, rinse thoroughly with water.

WINLEVI cream is for topical use only. WINLEVI cream is not for ophthalmic, oral or vaginal use.

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)	[redacted] (b) (4) twice per day	**Adequate**

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

3 DOSAGE FORMS AND STRENGTHS

Cream 1%. Each gram of WINLEVI cream contains 10 mg of clascoterone.

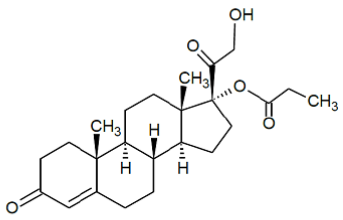
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	cream	**Adequate**
Strength(s) in metric system	1%, each gram of cream contains 10 mg clascoterone	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Not provided	**Not Adequate** - Add "white to almost white cream"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
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.	N/A	

1.2.3 Section 11 (DESCRIPTION)

11 DESCRIPTION

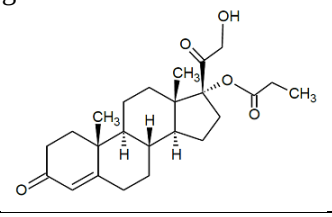
WINLEVI cream contains clascoterone, an androgen receptor inhibitor, in a cream base for topical dermatologic use. WINLEVI cream is a white to almost white cream.

Chemically, clascoterone is cortexolone-17α propionate. The compound has the empirical formula $C_{24}H_{34}O_5$ and molecular weight of 402.5 g/mol. The structural formula is shown below.



Each gram of WINLEVI cream 1% contains 10 mg of clascoterone in a cream base of cetyl alcohol, citric acid monohydrate, edetate disodium, mineral oil, mono- and di-glycerides, polysorbate 80, propylene glycol, purified water, and vitamin E.

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	WINLEVI cream	**Not Adequate** - Change "WINLEVI cream" to "Winlevi (clascoterone) cream" …
Dosage form(s) and route(s) of administration	cream for topical dermatologicl use	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Each gram of WINLEVI cream 1% contains 10 mg of clascoterone in a cream base of cetyl alcohol, citric acid monohydrate, edetate disodium, mineral oil, mono- and di-glycerides, polysorbate 80, propylene glycol, purified water, and vitamin E	**Adequate**
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.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	androgen receptor inhibitor	**Adequate**

Chemical name, structural formula, molecular weight	Chemically, clascoterone is cortexolone-17α propionate. The compound has the empirical formula $C_{24}H_{34}O_5$ and molecular weight of 402.5 g/mol 	**Adequate**
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Not provided	**Not Adequate** - Add "clascoterone is a white to almost white powder, practically insoluble in water"

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

16 HOW SUPPLIED/STORAGE AND HANDLING

WINLEVI cream 1% is supplied in an epoxy-lined aluminum blind-end tube with a polypropylene cap closure:

NDC xxxx-xxxx-xx 60-gram tube

Prior to Dispensing: Store the product in a refrigerator between 36°F and 46°F (2°C and 8°C). Do not freeze.

Dispensing Instructions for the Pharmacist: Direct the patient to store the product while in use at room temperature up to 77°F (25°C). Do not freeze. The product should be used within 1 month after opening.

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Cream	**Adequate**
Strength(s) in metric system	1%	**Adequate**
Available units (e.g., bottles of 100 tablets)	60-gram tube	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	cream	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
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.	N/A	**Adequate**
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.)	Do not freeze. The product should be used in 1 month	**Adequate**
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."	N/A	
Storage conditions. Where applicable, use USP storage range	**Prior to Dispensing:** Store the product in a refrigerator	**Adequate**

rather than storage at a single temperature.	between 36°F and 46°F (2°C and 8°C). Do not freeze. **Dispensing Instructions for the Pharmacist:** Direct the patient to store the product while in use at room temperature up to 77°F (25°C). Do not freeze. The product should be used within 1 month after opening.	
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 statements such as "latex-free."	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

N/A

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	Manufactured & Packaged by: Cosmo S.p.A. Via Cristoforo. Colombo, 1 20020, Lainate Milan, Italy For: Cassiopea Inc. San Diego, California xxxxx	Adequate

2.0 PATIENT LABELING

The following CMC information is provided in the Patient Labeling and is adequate

Important Information: WINLEVI cream is for use on the skin only (topical). Do not use WINLEVI cream in or on your mouth, eyes, or vagina.

How should I store WINLEVI cream?

Store WINLEVI cream at room temperature, (b) (4)

Keep WINLEVI cream and all medicines out of the reach of children.

What are the ingredients in WINLEVI cream?

Active ingredient: clascoterone
Inactive ingredients: cetyl alcohol, citric acid monohydrate, edetate disodium, mineral oil, mono- and di-glycerides, polysorbate 80, propylene glycol, purified water, and vitamin E

Evaluation:

The How Should I store* WINLEVI cream Section *should be revised to the following:

Store the product while in use at room temperature up to 77°F (25°C). Discard the unused product 1 month after opening.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Winlevi clascoterone cream 1%	**Not Adequate** Established name clascoterone should be with separate strength from the established name. -change to Winlevi (clascoterone) cream 1%
Dosage strength	1%	**Adequate**
Route of administration	For topical use only Not for ophthalmic, oral or vaginal use	**Adequate**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	60-gram	**Adequate**
"Rx only" displayed on the principal display	Provided	**Adequate**
NDC number	Provided	**Adequate**
Lot number and expiration date	Provided	**Not Adequate** Add lot number and expiration date on carton label
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	On Labels for Container and Carton: Store WINLEVI cream 1% while in use at room temperature up to 77°F (25°C). Do not freeze. The product should be used within 1 month after opening. On Shipping Cases (b) (4) Labels: Store the product in a refrigerator between 36°F and 46°F (2°C and 8°C). Do not freeze.	**Not Adequate** The storage condition on the label of the shipping cases is **adequate**. However, the storage condition on the container and carton labels should be changed to the following: Store the product while in use at room temperature up to 77°F (25°C). Discard the unused product 180 days after the date of dispensing. The product should be used within 1 month after opening.

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	**Adequate**
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.		**Adequate**
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Provided	**Adequate**

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Provided	**Adequate**
Medication Guide (if applicable)	Provided	**Adequate**
No text on Ferrule and Cap overseal	N/A	
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.	N/A	
And others, if space is available	Usual dose, and Keep out of reach of children, are provided in carton label.	**Adequate**

Assessment of Carton and Container Labeling: *Inadequate*

- The established name should be in parenthesis. The title of the drug product on the labels should be displayed as follows:

Winlevi (clascoterone) cream
1%

- The storage condition on the carton/container labels should be changed to the following:

  Storage: Must be refrigerated, store at 2°C to 8°C (36°F to 46°F) until dispensed to the patient. Once dispensed, patient is to store WINLEVI Cream 1% at room temperature up to 77°F (25°C) for 1 month. Do not freeze. Discard the unused portion 1 month after first opening.

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies

A. For Prescribing Information:

Section 3 Dosage Forms and Strengths

- Add "white to almost white cream" to

Section 11 Description

- Change the 1st sentence to Winlevi (clascoterone)…
- Add "white to almost white cream" for the active ingredient

Section 16: How Supplied

Change the storage condition to the following

- **Prior to Dispensing:** Store the product in a refrigerator between 36°F and 46°F (2°C and 8°C). Do not freeze.

- **Dispensing Instructions for the Pharmacist:** Direct the patient to store the product while in use at room temperature up to 77°F (25°C). The product should be used within 1 month after opening.

B. For Patient Instruction:

Revise "The How Should I store WINLEVI cream" to the following:

Store the product while in use at room temperature up to 77°F (25°C). The product should be used within 1 month after opening.

C. For Container/Carton Labels:

- The established name should be in parenthesis. The title of the drug product on the labels should be displayed as follows with a separate line for strength:

  Winlevi (clascoterone) cream
  1%

- The storage condition on the carton/container labels should be changed to the following:

  Storage: Must be refrigerated, store at 2°C to 8°C (36°F to 46°F) until dispensed to the patient. Once dispensed, patient is to store WINLEVI Cream 1% at room temperature up to 77°F (25°C) for 1 month. Do not freeze. Discard the unused portion 1 month after first opening.

Overall Assessment and Recommendation:

The NDA is not ready for approval in its present form per CFR 314.125(b)(6) until the outstanding labeling issues listed in the **List of Deficiencies** are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Zhengfang Ge, Ph. D.
Reviewer, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT

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

I agree with Dr. Ge's assessment on the labeling as well as labels, and therefore, I concur with her recommendation that this application is **not ready for approval** in its present from the CMC labeling perspective until the deficiencies delineated in the **List of Deficiencies** are satisfactorily resolved.

Moo-Jhong Rhee, Ph. D.
Branch Chief, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

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Moo Jhong Rhee

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

Date: **July 10, 2020**

From: **Zhengfang Ge, Ph.D.**
ONDP/Division II/Branch IV

Through: **Wendy Wilson, Ph.D.**
Director, ONDP/Division II

To: **Labeling Review of NDA 213433: Winlevi (clascoterone) cream**

Subject: **Final Recommendation for Labeling/Labels**

The labeling review #1 has noted the following issues:

For Prescribing Information:

Section 3 Dosage Forms and Strengths

- Add "white to almost white cream"

Section 11 Description

- Change the 1st sentence to Winlevi (clascoterone)…
- Add "white to almost white cream" for the active ingredient

Section 16: How Supplied

Change the storage condition to the following

- Prior to Dispensing: Store the product in a refrigerator between 36°F and 46°F (2°C and 8°C). Do not freeze.

- Dispensing Instructions for the Pharmacist: Direct the patient to store the product while in use at room temperature up to 77°F (25°C). The product should be used within 1 month after opening.

For Patient Instruction:

- Revise "The How Should I store WINLEVI cream" to the following:

- Store the product while in use at room temperature up to 77°F (25°C). The product should be used within 1 month after opening.

For Container/Carton Labels:

- The established name should be in parenthesis. The title of the drug product on the labels should be displayed as follows with a separate line for strength:

Winlevi (clascoterone) cream
1%

- The storage condition on the carton/container labels should be changed to the following:

Storage: Must be refrigerated, store at 36°F to 46°F (2°C to 8°C) until dispensed to the patient. Once dispensed, patient is to store WINLEVI Cream 1% at room temperature up to 77°F (25°C) for 1 month. Do not freeze. Discard the unused portion 1 month after first opening.

The above CMC requests along with the DMEPA's requests have been implemented in the revised labeling. The storage condition has been revised to the following language which is supported by the stability data.

> **Prior to Dispensing:** Store the product in a refrigerator between 36°F and 46°F (2°C and 8°C). Do not freeze.
>
> **Dispensing Instructions for the Pharmacist:** Direct the patient to store the product while in use at room temperature, between 68°F and 77°F (20°C to 25°C). Do not freeze. Discard the unused product 180 days after the date of dispensing or 1 month after first opening, whichever is sooner.

The revised container/carton labels are satisfactory and provided in the **Attachment**.

Recommendation:

This NDA is **now** recommended for **Approval** from the labeling perspective.

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Zhengfang Ge

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Wendy Wilson- Lee

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CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

NDA-213433-ORIG

R REGIONAL INFORMATION

Environmental Analysis

Assessment: *Adequate*

The submitted categorical exclusion is appropriate for the estimated amount of clascoterone to be used for the requested indication. A supported statement of 'no extraordinary circumstances' has been submitted. The claim of categorical exclusion is adequate.

Applicant's Position:

The applicant submitted a claim for categorical exclusion (EDR Section 1.12.14) under 21 Code of Federal Regulations (CFR) Section 25.31 on the basis that the estimated introductory concentration (EIC) of the active moiety (clascoterone) into the aquatic environment is less than 1 part per billion (ppb) or µg/L. The applicant states that, to their knowledge, no extraordinary circumstances exist under 21 CFR Section 25.15(d) that would warrant preparation of an EA. In a revised claim, the applicant provides a recalculated EIC and supporting information for the 'no extraordinary circumstances' statement.

FDA Assessment:

The initial claim for exclusion submitted with the original application estimated the EIC based on drug product and not, as required, on the estimated Kg of drug substance sold in the U.S. An IR was sent on 11/01/2019, advising the applicant to recalculate the EIC based on 'Kg drug substance sold' and to address the androgen receptor activity of the drug as related to aquatic toxicity. A link to the FDA Guidance for drugs with estrogenic, androgenic, or thyroid activity in the environment was provided.

The applicant submitted a revised claim for exclusion using Kg drug substance sold/yr estimates from 2020 to 2025 to provide a 5th year EIC of (b) (4) µg/L. This is a conservative estimate. The calculation assumes that all drug substance sold in the U.S./year is used, flows directly into publicly owned treatment works and discharged as effluent with no loss due to the product's topical administration, metabolism, (bio) degradation, or dilution. This EIC calculation meets the exclusion available at 21 CFR 25.31(b).

In support of the 'no extraordinary circumstances' statement, the applicant uses a "read across" analysis comparing clascoterone to other antiandrogen compounds, including progesterone, flutamide, finasteride, and cyproterone acetate. Of the compounds, comparison to flutamide appears most appropriate since flutamide has been tested in a variety of fish models (see

references in EDR Section 1.12.14). At water concentrations of 412 µg/L, flutamide elicited only minor phenotypic alterations in flathead minnow. At higher concentrations (651 – 1000 µg/L), significant effects were observed in mekada and at 1700 µg/L in zebrafish. At concentrations between 10 and 50 µg/L, there were only small changes in the spiggin secretion in stickleback fish, an androgen-dependent function. Comparison of clascoterone EICs to flutamide water concentrations that elicit responses in exposed fish, provide a sufficient margin of safety for the effects of clascoterone in the aquatic environment.

We note that by year 2022, the amount of clascoterone estimated to be sold increases significantly, with a concurrent increase in EIC. For future claims of categorical exclusion, the EA team may request the applicant to review the literature and, if warranted, conduct chronic fish toxicity studies, including androgen receptor inhibition, at these higher EICs values.

Primary Environmental Assessor Name and Date:

Raanan Bloom, Ph.D.; 4/7/2020

Secondary Assessor Name and Date:

Scott Furness, Ph.D.;

Raanan Bloom

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Michael Furness

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BIOPHARMACEUTICS

Product Background:
NDA: 213433
Drug Product Name / Strength: Clascoterone Cream 1%
Route of Administration: Topical
Applicant Name: Cassiopea SpA
Indication: Treatment of Acne vulgaris in patients 9 years of age and older.

Review Summary: Adequate

The proposed product, Clascoterone Cream 1% is indicated for the treatment of Acne vulgaris in patients 9 years of age and older, and is intended for topical use only. Application was submitted through 505(b)(1) pathway on 08/19/2019.

Biopharmaceutics assessment focuses on the evaluation of IVRT method development, validation, comparative IVRT data and in vitro release acceptance criteria.

Upon review of in vitro release data, the proposed IVRT method is adequate. Based on the submitted IVRT data, proposed IVRT acceptance criteria is acceptable. The approved in vitro release method and acceptance criteria are stated below:

Apparatus	Membrane	Receptor fluid	RPM	Temp	Sampling volume	Sampling Times	Acceptance criterion
PermeGear vertical glass diffusion jacketed cells with orifice diameter 11.28mm, receptor chamber capacity of 8 mL and internal diameter of 30 mm and diffusion area of 1.00 cm^2	Whatman plain nylon 0.2micron membrane filter, 25 mm diameter	6% Brij C20 in 0.9% NaCl	500+/-50	32°C +/- 1°C	200 µL	1, 2, 3, 5 and 7 hours	(b) (4) µg/cm^2/$hr^{1/2}$

From the Biopharmaceutics perspective NDA-213433 for Clascoterone Cream 1% is adequate.

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Application 213433 - Sequence 0001 - 0001 (1) 08/19/2019 ORIG-1 /New/NDA	08/19/2019
Application 213433 - Sequence 0016 - 0016 (16) 01/10/2020 ORIG-1 /Quality/Response To Information Request	01/10/2020
Application 213433 - Sequence 0015 - 0015 (15) 01/10/2020 ORIG-1 /Quality/Response To Information Request	01/10/2020
Application 213433 - Sequence 0014 - 0014 (14) 12/27/2019 ORIG-1 /Quality/Response To Information Request	12/27/2019
Application 213433 - Sequence 0012 - 0012 (12) 12/02/2019 ORIG-1 /Quality/Response To Information Request	12/02/2019

Highlight Key Outstanding Issues from Last Cycle: None.

Concise Description Outstanding Issues Remaining: N/A

BCS Designation:
Reviewer's Assessment: Not reported.

Solubility: Cortexolone-17α-propionate is practically insoluble in water, slightly soluble in ether and very soluble in alcohols like methanol and ethanol.

Permeability: Not reported.

Table 1: Formulation composition

Table 1. Cortexolone 17α-propionate 1% cream formula.

COMPONENT	AMOUNT (g/100g)
Cortexolone 17α-propionate	1.00
Cetyl alcohol	(b) (4)
Mono- and di-glycerides	
Mineral oil	
Propylene glycol	
Vitamin E	
Edetate disodium	
Polysorbate 80	
Purified water	

(b) (4)

In vitro release method
Information Request 1 dated 11/1/2019:

Applicant was asked to develop and validate the IVRT method and propose *in vitro* release acceptance criteria (range) for the proposed drug product to be used systemically at release and during stability as a quality control parameter.

Applicant's response[1, 2]
In response to the above deficiency the Applicant developed an In Vitro Release Test (IVRT) with Franz-cell to indirectly evaluate the physiochemical characteristics of the cream and the product performance of industrial batches and also to verify the effects that the minor changes applied to the manufacturing process over time could have had on the product performance.

(b) (4)

[1] Application 213433 - Sequence 0012 - Quality information amendment
[2] Application 213433 - Sequence 0014 - Quality information amendment

Reviewer's comments:

(b) (4)

Therefore, in reviewer's opinion selection of medium, membrane and sampling time points are justified and acceptable in IVRT method. Please see appendix for additional details.

The final IVRT Method parameters are provided below

Cell description:	PermeGear vertical glass diffusion jacketed cells with orifice diameter 11.28 mm, receptor chamber capacity of 8 mL and internal diameter of 30 mm and diffusion area of 1.00 cm^2
Membrane:	Whatman 7402-002 Plain Nylon 0.2 µm Membrane Filter, 25 mm diameter;
Receptor fluid:	Dissolve 9.0 g of Sodium chloride in 1000 ml of water, add 60 g of Macrogol Cetostearyl Ether (Brij C20® or equivalent). Stir to dissolve and then sonicate to degas;
Stirring speed:	500 rpm ± 50 rpm;
Temperature:	32°C ± 1°C;
Sample amount:	200 mg;
Sampling volume:	200 µL;
Sampling timepoints:	1,2,3,5,7 hours ± 2 min;
Sampling mode:	sampled volume replaced.

IVRT method validation:
The applicant submitted an IVRT method validation report # 19-1-06 for its Cortexolone 17a-propionate Cream 1% in Sequence 14, Module 3.2.P.5.3.

The IVRT method was validated for its specificity, selectivity, linearity, range, accuracy (% recovery), precision (system precision, method precision, intermediate precision), robustness and solution stability. The reviewer checked the method validation report and noted that all the method validation parameters met their acceptance criteria.
The validation work foresaw the execution of a Franz cell test on six cells for each of the following products:

Process validation batches at standard potency:
- *Cortexolone 17α-propionate 1% cream* batch LL076
- *Cortexolone 17α-propionate 1% cream* batch LL139
- *Cortexolone 17α-propionate 1% cream* batch LL209

Batch at altered (lower and higher) potency:
- *Cortexolone 17α-propionate 0.5% cream* batch 7471/1
- *Cortexolone 17α-propionate 1.5% cream* batch 7472/1

In specificity experiment, release rate from altered batches (0.5% and 1.5%) were compared to validation batch (1%). Pairwise comparisons fell outside the limits of 75.00% and 133.33%.

Table 12: *Selectivity results*

Potency		1.0 %		
	Batch	LL076	LL139	LL209
0.5 %	7471/1	V_8 = **59.67** V_{29} = 76.00	V_8 = **59.52** V_{29} = 74.61	V_8 = **57.87** V_{29} = 72.13
1.5 %	7472/1	V_8 = 118.00 V_{29} = **146.93**	V_8 = 122.35 V_{29} = **152.13**	V_8 = 123.38 V_{29} = **145.33**

Based on the release rate, IVRT method is considered to be sensitive to detect the differences in release rate.

All the results obtained during the validation work of the method for the evaluation of Cortexolone 17α-propionate 1% cream release by Franz cell test comply with the acceptance criteria.

The IVRT method was demonstrated to be specific, linear, accurate, precise and robust.

Applicant submitted the analytical method validation report #11-1-12 in Module 3.2.P.5.3 for the assay of cortexolone[3] which will be evaluated by drug product reviewer.

[3] Application 213433 - Sequence 0014 - Validation of Analytical Procedures

Reviewer's assessment:

To characterize the linearity, precision and reproducibility of the IVRT method, three IVRT runs were conducted, each with a set of 6 cells, on three different days with the validation batches. The linearity of the release rate (slope) was calculated across the range of sampling times for within and across runs and R^2 is NLT 0.98.

For accuracy determination two batches were used and compared pairwise. The 90% confidence interval for each pairwise comparison results are within the limits of 75.00% and 133.33%. Precision and reproducibility experiments variability in release rates are within 15%

For sensitivity, specificity and selectivity experiments two intentionally altered (0.5% and 1.5% potency) batches were compared with validation batch. Pairwise comparisons fell outside the limits of 75.00% and 133.33%. Based on the release rate, IVRT method is sensitive to detect the differences in release rate.

Therefore, in reviewer's opinion IVRT method was demonstrated to be specific, linear, accurate, precise and robust (Please see appendix for more details).

Method validation data are adequate.

(b) (4)

[redacted]

[4] Application 213433 - Sequence 0015 - Quality information amendment

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(b) (4)

Reviewer also calculated and verified the above results and these are in agreement with the results provided by the applicant. The in vitro release test result indicate that the drug product release rate is similar over time.

In Vitro Drug Release Study to support the process change[6]

The in vitro release test was used to evaluate if the minor changes (b) (4) applied to the manufacturing process of engineering and validation batches, after the manufacturing of the pivotal phase III clinical batch 6800/1, might have had any impact on the physiochemical characteristics of the drug product and its performance. To do this, results of the in vitro release test performed on samples of clinical batch 6800/1, were compared with results obtained with the 3 validation batches (LL076, LL139 and LL209). The results indicate that the release rate in all batches are comparable.

Comparative IVRT data for Phase 3 batch (6800/1) and registration batches:

	Batch			
	6800/1	LL076	LL139	LL209
Cell	**Slope (release rate)**			
A	(b) (4)			
B				
C				
D				
E				
F				
mean	**75.49**	**65.28**	**63.79**	**64.99**
SD	**4.60**	**8.52**	**5.96**	**2.91**

Results were analyzed as described in USP <1724>, considering batch 6800/1 as the reference (R) and batches LL076, LL139 and LL209 as test batch (T); T/R slope ratios were evaluated to get the 90% confidence intervals to see if these fall within the 75% to 133.33% .

T/R slope*100 ratios	**LL076 to 6800/1**	**LL139 to 6800/1**	**LL209 to 6800/1**
8th T/R *100	76.9	75.9	81.5
29th T/R *100	98.1	91.3	92.6
First step: limits 75%-133.33%	**PASS**	**PASS**	**PASS**

[6] Application 213433 - Sequence 0012 - Drug Product (CB-03-01Cream 1%)

Reviewer's comment: Reviewer also calculated and verified the above results and these are in agreement with the results provided by the applicant.

In vitro release acceptance criteria:
Applicant proposed IVRT specification of (b) (4) $\mu g/cm^2/hr^{1/2}$ for release and shelf life. Based on the submitted data obtained from the Phase 3 batch and all the registration batches, applicant's proposed specification is acceptable.

List of Deficiencies: None

Primary Biopharmaceutics Reviewer Name and Date:
Swapna Pamu, MS

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Vidula Kolhatkar, Ph.D.

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APPROVED BY:

Primary Biopharmaceutics Reviewer:
Swapna Pamu, MS

Secondary Biopharmaceutics Reviewer
Vidula Kolhatkar, Ph.D.

Vidula Kolhatkar

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CHAPTER VII: MICROBIOLOGY

Product Information	Non-sterile, topical cream indicated for treatment of acne vulgaris
NDA Number	213433
Assessment Cycle Number	1
Drug Product Name/ Strength	Winlevi (clascoterone) / 1%
Route of Administration	Topical
Applicant Name	Cassiopea SpA
Therapeutic Classification/ OND Division	
Manufacturing Site	Cosmo SpA Via C. Colombo, 1 Lainate, Milan, Italy 20020
Method of Sterilization	N/A – drug product is non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary: This review covers the microbiological quality of the non-sterile drug product.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD seq 0001	**08/19/2019**
eCTD seq 0015	**01/10/2020**
eCTD seq 0020	**02/21/2020**
eCTD seq 0022	**03/27/2020**
eCTD seq 0025	**05/08/2020**

Highlight Key Issues from Last Cycle and Their Resolution: (None)

Remarks: Drug product is [redacted](b) (4), self-preserved, multi-use, topical cream.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed):
(None)

Supporting Documents: (None)

S DRUG SUBSTANCE

Drug substance is supplied non-sterile.

Assessment: ***Adequate***

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Non-sterile, white to almost white homogenous cream.

- **Drug product composition –**

Table 1: Composition of clascoterone 1%

Component	Reference to standard	Amount g/100 g (% w/w)	Function
Cortexolone 17 α - propionate (CB-03-01)	-	1.0	active ingredient
Cetyl alcohol	NF	(b) (4)	
Mono- and di-glycerides	NF		
Mineral oil	USP		
Propylene glycol	USP		
Vitamin E	USP		
Edetate disodium	USP		
Polysorbate 80	NF		
Citric acid Monohydrate*	USP		
Purified water	USP		

Table 1 was reproduced from Table 1 in "Description and Composition of the Drug Product (CB-03-01, Cream 1%)," located in Module 3.2.P.1

- **Description of container closure system –** Epoxy-lined, 60g aluminum tube with polypropylene closure. A 10g tube of the same composition is used for physician samples.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

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Denise Miller

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Jason God

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