

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209355Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: September 20, 2018
From: Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: CMC Review #1 of NDA 209355

Subject: Final Approval Recommendation for NDA 209355

At the time when the CMC review #1 was written, resolution of issues on Labels and Labeling was pending.

Label/Labeling

On August 29, 2018, the NDA applicant submitted an amendment providing the finalized mock up container and carton labels. Additionally, the applicant also agreed to all the CMC changes made to the Prescribing Information (PI). All the label/labeling issues are now satisfactorily resolved. The review of the CMC sections of the final Prescribing Information, and mock up container and carton labels has been conducted by Dr. Hong Cai and is attached below (**Attachment - 1**).

Recommendation:

The revised Prescribing Information, and mock-up container and carton labels are now satisfactory from the CMC perspective. Therefore, from the OPQ's perspective, this NDA is recommended for **APPROVAL** with an expiration dating period of 36 months for the drug product when stored at room temperature.

Application Technical Lead's Assessment and Signature

The NDA is recommended for approval from the OPQ's perspective.

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
9/20/2018



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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: September 4, 2018

From: Hong Cai, Ph.D.
Drug Product Reviewer
Office of New Drug Products
Branch V/DNDP II

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Office of New Drug Products
Branch V/DNDP II

To: CMC Labeling Review #1 of NDA209355
for BRYHALI™ (halobetasol propionate) lotion, 0.01%

Subject: Final Recommendation - APPROVAL

At the time when Labeling Review of NDA209355 was completed on July 23, 2018, this NDA was not recommended for approval in its present form per 21 CFR 314.125(b)(8). Specifically, it was noted that labeling (Prescribing Information, container/carton) negotiations had not been completed, and in its present form, the labeling did not comply with the requirements under 21 CFR 201. The NDA for this drug product was otherwise complete and adequate from the drug product perspective.

On August 29, 2018, the applicant Dow Pharmaceutical Sciences acknowledged the requested changes and provided the most updated Prescribing Information according to FDA proposed edits. **Attachment-1** is the CMC related sections of Prescribing Information and **Attachment-2** contains the mockup of the container/carton labels. It is noted that the requested statement to clarify that the presentation "Ortho Dermatologic" in the carton and container labels is the trade mark and it is applied as requested, but only to the carton labeling, not to the container (tube) labels. The applicant indicated this is "due to lack of real estate on the tubes". The applicant has justified [REDACTED] (b) (4)

[REDACTED]
[REDACTED]
[REDACTED] Therefore, the label/labeling is deemed acceptable from the CMC labeling perspective.

Recommendation:

The outstanding CMC label/labeling issues have been satisfactorily resolved, and therefore, this application is now recommended for **approval** from the labeling perspective.

Hong Cai, Ph.D.
Drug Product Reviewer
Branch V, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch V, Division II, ONDP

Attachment-1: (submitted on August 29, 2018, SN0017)

FULL PRESCRIBING INFORMATION:

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BRYHALI safely and effectively. See full prescribing information for BRYHALI.

BRYHALI™ (halobetasol propionate) lotion, for topical use
Initial U.S. Approval: 1990

----- **DOSAGE FORMS AND STRENGTHS** -----
Lotion, 0.01% (3)

3 DOSAGE FORMS AND STRENGTHS

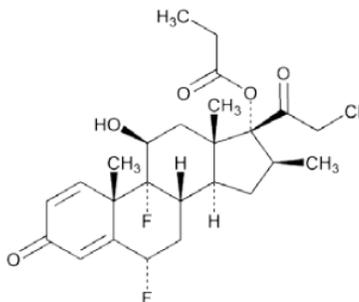
Lotion, 0.01%

Each gram of BRYHALI Lotion contains 0.1 mg (0.01%) halobetasol propionate (b) (4)

11 DESCRIPTION

BRYHALI (halobetasol propionate) lotion contains a corticosteroid, halobetasol propionate, as the active ingredient in a white to off-white lotion formulation intended for topical use.

Halobetasol propionate is a synthetic corticosteroid. The chemical name for halobetasol propionate is 21-chloro-6 α , 9-difluoro-11 β , 17-dihydroxy-16 β -methylpregna-1, 4-diene-3, 20-dione, 17-propionate. Halobetasol propionate is a white to off-white crystalline powder with a molecular weight of 484.96 and a molecular formula of C₂₅H₃₁ClF₂O₅. It is practically insoluble in water and freely soluble in dichloromethane and in acetone. The structural formula for halobetasol propionate is represented below:



Each gram of BRYHALI Lotion contains 0.1 mg (0.01%) halobetasol propionate in a white to off-white lotion base consisting of carbomer copolymer type B, carbomer homopolymer type A, diethyl sebacate, edetate disodium dihydrate, light mineral oil, methylparaben, propylparaben, purified water, sodium hydroxide, sorbitan monooleate and sorbitol solution, 70%.

16 HOW SUPPLIED/STORAGE AND HANDLING

BRYHALI (halobetasol propionate) lotion, 0.01% is a white to off-white lotion supplied in a white aluminum tube as follows:

- 45 g (NDC 0187-0002-45)
- 60 g (NDC 0187-0002-60)
- 100 g (NDC 0187-0002-01)

Storage and Handling Conditions

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from freezing.

Manufactured for:

Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

By:

Valeant Pharmaceuticals International, Inc.
Laval, Quebec H7L 4A8, Canada

U.S. Patent Numbers: 6,517,847 and 8,809,307

Bryhali (b) (4) and Ortho Dermatologics (b) (4) are (b) (4) trademarks of Valeant Pharmaceuticals International, Inc. or its affiliates.

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Rhee

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Cai

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Integrated Quality Assessment (IQA) for NDA 209355

Office of Pharmaceutical Quality (OPQ)

Executive Summary for NDA 209355

Recommendation:

From the OPQ perspective, this 505(b)(2) NDA is *not* deemed ready for approval as of this review in its present form per 21CFR 314.125(b)(6).

**NDA 209355
Review # 1**

Drug Name/Dosage Form	Bryhali (halobetasol propionate) Lotion
Strength	0.01%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Dow Pharmaceutical Sciences, Inc. Sean Humphrey Suite C, 1330 Redwood Way Petaluma, CA 94954
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	12-05-2017	All
Amendment	01-16-2018	Drug product manufacturing process
Amendment	02-09-2018	Drug product and quality microbiology
Amendment	02-22-2018	Drug substance
Amendment	05-16-2018	Drug product and drug product manufacturing process
Amendment	05-24-2018	Drug product manufacturing process
Amendment	06-20-2018	Drug product
Amendment	07-02-2018	Drug product

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ramsharan Mittal	Branch II/Division of New Drug API
Drug Product	Hong Cai	Branch V/Division of New Drug Products II
Process	Zhao Wang	Branch V/Division of Process Assessment III
Microbiology	Jason Morgan	Branch I/Division of Microbiology Assessment
Facility	Zhao Wang	Branch III/Division of Inspection Assessment
Biopharmaceutics	Vidula Kolhatkar	Branch III/Division of Biopharmaceutics
Regulatory Business Process Manager	Bamidele (Florence) Aisida	Branch I/Division of Regulatory and Business Management I/Office of Program and Regulatory Operations
Application Technical Lead	Yichun Sun	Branch V/Division of New Drug Products II

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	1	March 22, 2018	Adequate
	Type III		4	N/A	N/A	

Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
End-of-Phase 2 Meeting Minutes	IND 126779	Discussions of the development plan for halobetasol propionate lotion.
Pre-NDA Meeting Minutes	IND 126779	Discussions of the content and format of the proposed NDA submission.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	----	N/A	----	----
Pharmacology/Toxicology	----	N/A	----	----
CDRH	----	N/A	----	----
Clinical	----	N/A	----	----
Other	----	N/A	----	----

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product.

The facility review team from the Office of Process and Facility (OPF) has issued an “Acceptable” recommendation for the facilities involved in this application.

However, the issues on labels/labeling are *not* completely resolved as of this review.

Therefore, from the OPQ perspective, this NDA is *not* ready for approval in its present form per 21 CFR 314.125(b)(6) until the aforementioned issues are satisfactorily resolved (See the **List of Deficiencies** on p. 14).

II. Summary of Quality Assessments

A. Product Overview

The NDA of Bryhali (halobetasol propionate) Lotion, 0.01% for topical use is submitted as a 505(b)(2) application by Dow Pharmaceutical Sciences, Inc. (a subsidiary of Valeant Pharmaceutical International). The listed drug used for the basis of this 505(b)(2) application is NDA 019967 [Ultravate (halobetasol propionate) Cream, 0.05%].

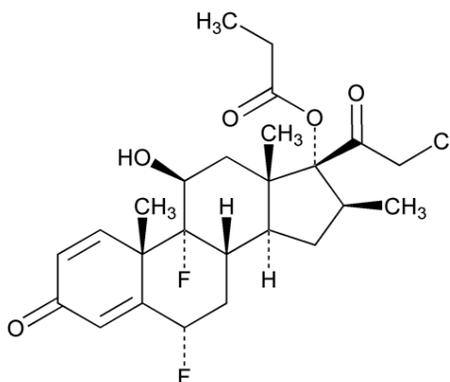
The indication and recommended dose of the drug product are summarized in the following Table.

Proposed Indication(s) including Intended Patient Population	Bryhali lotion is indicated for the topical treatment of plaque psoriasis.
Duration of Treatment	Treatment beyond 8 weeks is not recommended.
Maximum Daily Dose	The total dosage should not exceed approximately 50 g per week.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

Bryhali lotion is a product containing 0.01% (w/w) halobetasol propionate. Halobetasol propionate, is a synthetic corticosteroid. The chemical name for halobetasol propionate is 21-chloro-6 α , 9-difluoro-11 β , 17-dihydroxy-16 β -methylpregna-1, 4-diene-3,20-dione 17-propionate. The chemical structure of halobetasol propionate is:



It has a molecular formula of $C_{25}H_{31}ClF_2O_5$ and a molecular weight of 484.96 g/mol. Halobetasol propionate is a white to off-white crystalline powder. It is practically insoluble in water, freely soluble in dichloromethane and in acetone. The drug substance is manufactured by (b) (4). Detailed CMC information of halobetasol propionate drug substance for this NDA is referred to DMF # (b) (4).

DMF # (b) (4) was reviewed by Dr. Ramsharan Mittal on March 22, 2018 and found adequate in supporting the approval of this NDA. The review on the CMC information of the drug substance in the NDA has also been conducted by Dr. Ramsharan Mittal. The NDA is recommended for **approval** from drug substance perspective (See **CHAPTER I: Review of Drug Substance**).

Drug Product

The drug product, Bryhali, is a topical lotion which contains 0.01% (w/w) halobetasol propionate. The inactive ingredients used in the drug product include: carbomer copolymer type B, carbomer homopolymer type A, diethyl sebacate, edetate disodium dihydrate, light mineral oil, methylparaben, propylparaben, purified water, sodium hydroxide, sorbitan monooleate and sorbitol solution, 70%. All the inactive ingredients are of compendial grade. The drug product is packaged as a nominal 3, 45, 60 or 100 g fill size in (b) (4) aluminum tube with (b) (4) and a (b) (4) cap. The container closure system is deemed acceptable for its intended use in terms of its safety, protection of the drug product, and compatibility with the drug formulation based on information provided.

The final specification for the halobetasol propionate lotion is deemed adequate to ensure the identity, strength, purity, and quality of the drug product during its expiration dating period. The long-term stability data up to 30 months for the three registration batches of the drug product produced at (b) (4) scale are provided in the NDA submission. The stability data submitted are sufficient to support the proposed expiration dating period of 36 months when stored at room temperature. The results of in-use studies support that the product can be continuously used over the course of 8 weeks with no undesirable trends to physical, chemical or microbial characteristics. The estimated EIC (expected introduction concentration) for the drug substance is well below 1 ppb. The claim of categorical exclusion is acceptable per 21 CFR 25.31 (b).

The NDA is recommended for **approval** from the drug product perspective. The recommended expiration dating period of the drug product is 36 months. The review on the CMC information of the drug product has been conducted by Dr. Hong Cai (See **CHAPTER II: Review of Drug Product**).

Labeling and Labels

The sections of the Prescribing Information related to CMC, and container (tube) and carton labels of the drug product of the NDA have been reviewed by Dr. Hong Cai. Labeling and label issues have *not* been resolved satisfactorily as of this review (See **CHAPTER III: Review of Labeling and Labels**).

Drug Product Manufacturing Process

The bulk drug product is prepared

(b) (4)
(b) (4)

The batch formula, manufacturing process parameters, and in-process controls and tests are deemed adequate to ensure the robustness of the drug product manufacturing process. The NDA is recommended for **approval** from the perspective of drug product manufacturing process. The review on the drug product manufacturing process has been conducted by Dr. Zhao Wang (See **CHAPTER IV: Review of Drug Product Manufacturing Process**).

Biopharmaceutics

The applicant is seeking approval for halobetasol propionate lotion, 0.01%. The applicant has not submitted any in vitro release test (IVRT) related information

for the proposed product. There was a manufacturing site change from Dow Pharmaceutical Sciences facility in Petaluma, CA to Valeant Pharmaceuticals International, Inc. facility at Laval (Canada) prior to Phase 3 clinical trials. However, Phase 3 studies were conducted with batches manufactured at the proposed commercial site. Therefore, additional data are not needed to support the manufacturing site change. Additionally, the lack of an IVRT method and in vitro release acceptance criteria will not affect the approvability of this NDA.

The Division of Biopharmaceutics defers the approvability decision on this NDA to the other review disciplines. The review on Biopharmaceutics of the drug product of the NDA has been conducted by Dr. Vidula Kolhatkar (See **CHAPTER IV: Review of Biopharmaceutics**).

Quality Microbiology

The drug product is a non-sterile lotion containing 0.01% halobetasol propionate.

(b) (4)

. Microbial limit tests per USP <61> and <62> for Total Aerobic Microbial Count and Total Combined Yeast/Mold Count, and specified organisms (*P. aeruginosa* and *S. aureus*) are included in the drug product specification. Test for *Bulkholderia Cepacia Complex* (Bcc) (b) (4)

are also included in the drug product specification. The test methods have been properly validated.

The results of stability studies indicated that proposed 36-month expiration dating period is acceptable (b) (4)

The drug product's microbiological quality throughout its expiration dating period can be assured by the stability testing program. The NDA is recommended for **Approval** from the perspective of quality microbiology. The review on microbiology controls of the drug product of the NDA has been conducted by Dr. Jason Morgan (See **CHAPTER V: Review of Quality Microbiology**).

Facilities**Facilities Related to Drug Substance Manufacture and Testing:**

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Final Recommendation
 (b) (4)			Approve based on profile
			Approve based on profile

Facilities Related to Drug Product Manufacture and Testing:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Final Recommendation
(b) (4)			Approve based on profile
			Approve based on profile
			Approve based on profile
			Approve based on profile
			Approve based on profile
			Approve based on profile
			Approve based on profile
			No Further Evaluation (NFE)

All the facilities are deemed acceptable in their identified functions and responsibilities to support the **approval** of NDA 209355. The facility review of the NDA has been conducted by Dr. Zhao Wang (See **CHAPTER VII: Review of Facilities**).

C. Special Product Quality Labeling Recommendations

Protect from freezing.

D. Final Risk Assessment (Attachment I)

E. List of Deficiencies (Attachment II)

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessments - NDA

a) Drug Product

Final Risk Assessment for NDA 209355 [Bryhali (halobetasol propionate) Lotion, 0.01%, for topical use]

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay halobetasol propionate and its degradation products	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	3	4	3	36	An HPLC method is used to quantitate the content (halobetasol propionate assay) and its degradation products in the drug product at release and during stability studies. The assay results ranged from (b) (4) % were observed in stability samples of all testing conditions including stressed tests under cold-warm and freeze-thaw cycles. However, no reportable peaks were observed for individual unspecified impurities (degradants) in stability samples stored in all testing conditions.
Assay – methylparaben	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	3	3	2	18	An HPLC method is used to quantitate the level of methylparaben in the drug product at release and during stability studies. The level of methylparaben ranged from (b) (4) % of the target level was observed in stability samples of all testing conditions.
Assay – propylparaben	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	3	3	2	18	An HPLC method is used to quantitate the level of propylparaben in the drug product at release and during stability studies. The level of propylparaben ranged from (b) (4) % of the target level was observed in stability samples of all testing conditions.

<p>Uniformity in containers – halobetasol propionate</p>	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	2	4	3	24	<p>The test is conducted per USP <3> at release and during stability studies. All stability samples met the requirements for stage 1 testing: (b) (4) (b) (4)% of label claim with a maximum difference within each tube of not more than (NMT) (b) (4)%.</p>
<p>Emulsion Droplet Size</p>	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	2	4	3	24	<p>Single Particle Optical Sensing. D10 = NMT (b) (4) μm D50 = NMT (b) (4) μm D90 = NMT (b) (4) μm The droplet size distribution of the lotion showed no significant trending during stability studies in all testing conditions.</p>
<p>Microbial Testing</p>	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	3	2	3	18	<p>Microbiological examination tests per USP <61> and USP <62> are in the drug product specification. An in-house method is used to test <i>Bulkholderia Cepacia Complex</i> (Bcc) in the drug product. However, the tests were not performed during stability studies (b) (4) (b) (4) was conducted and the test results indicated that the levels (b) (4) in the drug product were adequate (b) (4) (b) (4)</p>
<p>pH</p>	<ul style="list-style-type: none"> • Formulation • Raw materials 	2	2	3	12	<p>The pH of the drug product is monitored at release and during stability studies. No significant change in pH value was observed for</p>

	<ul style="list-style-type: none"> • Process parameters • Scale/equipment • Site 					the stability samples stored under all testing conditions. The pH values range from (b) (4) for samples packaged in all fill sizes and stored at the various test conditions.
Viscosity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	2	3	3	18	Viscosity of the drug product is monitored at release and during stability studies. The viscosity of the stability samples ranged from (b) (4) to (b) (4) cP and met the specification after stored for 24 months at 25°C/60%RH, for 6 months at 40°C/75%RH.
Minimum Fill	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	2	2	3	12	The test is performed per USP <755> and is only conducted at release.
Package Integrity	<ul style="list-style-type: none"> • Formulation • Container components • Process parameters 	3	2	2	12	Visual check. This test is only performed during stability studies. No deterioration was observed on the stability samples (except two stability samples showed (b) (4) inconsistencies on the internal surface of the tube) of all testing conditions. The (b) (4) inconsistencies were attributable to unknown external damage to the tube and were not related to the drug product stability.

FMECA: Failure Mode, Effects and Criticality Analysis

RPN: Risk Priority Number

$$RPN = \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} O \times \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} S \times \begin{bmatrix} 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{bmatrix} D$$

Low Risk- RPN ≤ 25

Moderate Risk - 25 < RPN ≤ 60

High Risk - RPN > 60

ATTACHMENT II: List of Deficiencies

Label and labeling deficiencies:

A. Regarding Prescribing Information (PI)

1. Remove the strength 0.01% from the product title in the Highlights section.
2. In the “Description” section (#11):
 - Include the presentation of the propriety name with the established name as “Tradename (halobetasol propionate) lotion” at least once.
 - Provide the physical properties of the active ingredient halobetasol propionate, such as pKa or pH.

B. Regarding Labels

Both Tube and Carton labels:

The manufacturer/distributor names listed on the labels should be consistent with that in the PI. However, “Ortho Dermatologics” appears on the tube and carton labels but not listed in the PI. If this company is a distributor, it must be qualified per 21 CFR 201.1(h)(5) and stated consistently in PI and labels.

OVERALL ASSESSMENT AND SIGNATURES:**Application Technical Lead's Assessment and Signature**

From the OPQ perspective, the NDA is not deemed ready for approval as of this review in its present form per 21CFR 314.125(b)(6).

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
8/10/2018



Yichun
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CHAPTER III: Review of Labeling and Labels

LABELING

I. Prescribing Information

1. Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use (b) (4) safely and effectively. See full prescribing information for

(b) (4) (halobetasol propionate) lotion, 0.01% for topical use
Initial U.S. Approval: 1990

----- **INDICATIONS AND USAGE** -----

(b) (4) Lotion is a corticosteroid indicated for the topical treatment of plaque psoriasis. (1)

----- **DOSAGE AND ADMINISTRATION** -----

- Apply a thin layer of (b) (4) Lotion to the affected areas once daily. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)
- Avoid use on the face, groin, or axillae. (2)

----- **DOSAGE FORMS AND STRENGTHS** -----

Lotion, 0.01% (3)

Each gram of (b) (4) Lotion contains 0.1 mg (0.01%) halobetasol propionate. (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))		
Proprietary name and established name	(b) (4) (halobetasol propionate) lotion (b) (4)	Satisfactory Note: The (b) (4) should be removed.
Dosage form, route of administration	lotion, for topical use	Satisfactory
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))		
Summary of the dosage form and strength	Lotion, 0.01% (3)	Satisfactory

	Each gram of (b) (4) Lotion contains 0.1 mg (0.01%) halobetasol propionate. (3)	
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2. Section 2 Dosage and Administration

2 DOSAGE AND ADMINISTRATION

Apply a thin layer of (b) (4) Lotion to cover (b) (4) affected areas once daily (b) (4) rub in gently. (b) (4)

(b) (4) Lotion is not for oral, ophthalmic, or intravaginal use.

Treatment beyond 8 weeks is not recommended, and the total dosage should not exceed approximately 50 g per week. Do not use with occlusive dressings unless directed by a physician.

(b) (4) Lotion should not be used on the face, groin, or in the axillae.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (12))		
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	See the information pasted above	NA There is no additional preparation once the drug product is squeezed out of the tube prior to administration to the affected area.

3. Section 3 Dosage Forms and Strengths

3 DOSAGE FORMS AND STRENGTHS

Lotion, 0.01%

Each gram of (b) (4) Lotion contains 0.1 mg (0.01%) halobetasol propionate in a white to off-white lotion.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	Lotion	Satisfactory
Strengths: in metric system	0.01%	Satisfactory
Active moiety expression of strength with equivalence statement (if applicable)	Each gram of (b) (4) Lotion contains 0.1 mg (0.01%) halobetasol propionate in a white to off-white lotion.	Not Applicable The active ingredient is halobetasol propionate which is not a salt form.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Each gram of (b) (4) Lotion contains 0.1 mg (0.01%) halobetasol propionate in a white to off-white lotion.	Satisfactory

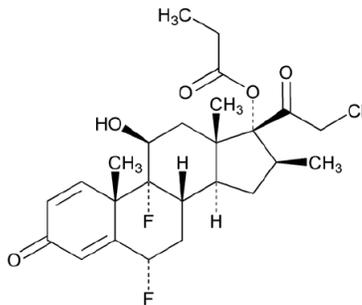
4. Section 11 Description

11 DESCRIPTION

(b) (4) Lotion contains a corticosteroid, halobetasol propionate, as the active ingredient in a white to off-white lotion formulation intended for topical use.

Halobetasol propionate is a synthetic corticosteroid. The chemical name for halobetasol propionate is (b) (4)

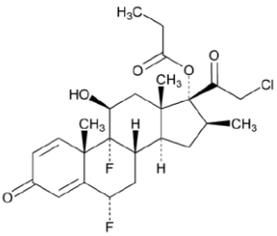
(b) (4) The structural formula for halobetasol propionate is represented below:



(b) (4)

Each gram of (b) (4) Lotion contains 0.1 mg (0.01%) halobetasol propionate in a white to off-white lotion base consisting of carbomer copolymer type B, carbomer homopolymer type A, diethyl sebacate, edetate disodium dihydrate, light mineral oil, methylparaben, propylparaben, purified water, sodium hydroxide, sorbitan monooleate and sorbitol solution, 70%.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))		
Proprietary name and established name	(b) (4) Lotion	Not Satisfactory The established name should appear at least once in section #11. Revise to: (b) (4) (halobetasol propionate) Lotion
Dosage form and route of administration	(b) (4) Lotion contains a corticosteroid, halobetasol propionate, as the active ingredient in a white to off-white lotion formulation intended for topical use.	Satisfactory
Active moiety expression of strength with equivalence statement (if applicable)	Not Applicable	Not Applicable
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Each gram of (b) (4) Lotion contains 0.1 mg (0.01%) halobetasol propionate in a white to off-white lotion base consisting of carbomer copolymer type B, carbomer homopolymer type A, diethyl sebacate, edetate disodium dihydrate, light mineral oil, methylparaben, propylparaben, purified water, sodium hydroxide, sorbitan monooleate and sorbitol solution, 70%.	Satisfactory
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	(b) (4) Lotion contains a corticosteroid, halobetasol propionate	Satisfactory

<p>Chemical name, structural formula, molecular weight</p>	<p>The chemical name for halobetasol propionate is (b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p>  <p>(b) (4)</p>	<p>Satisfactory</p>
<p>If radioactive, statement of important nuclear characteristics.</p>	<p>NA</p>	<p>NA</p>
<p>Other important chemical or physical properties (such as pKa or pH)</p>	<p>Not provided.</p>	<p>Not Satisfactory Provide the physical properties of the active ingredient halobetasol propionate, such as pKa or pH.</p>

5. Section 16 How Supplied/Storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4) (halobetasol propionate) Lotion, 0.01% is a white to off-white lotion supplied in a white aluminum tube as follows:

- 45 g (NDC 0187-0002-45)
- 60 g (NDC 0187-0002-60)
- 100 g (NDC 0187-0002-01)

Storage and Handling Conditions

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from freezing.

Manufactured for:

(b) (4) a division of Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

By:

Valeant Pharmaceuticals International, Inc.
Laval, Quebec H7L 4A8, Canada

U.S. Patent Numbers: 6,517,847 and 8,809,307

(b) (4) is a trademark of Valeant Pharmaceuticals International, Inc. or its affiliates.

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Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c) (17))		
Strength of dosage form	(b) (4) (halobetasol propionate) Lotion, 0.01%	Satisfactory
Available units (e.g., bottles of 100 tablets)	<ul style="list-style-type: none"> • 45 g • 60 g • 100 g 	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4) (halobetasol propionate) Lotion, 0.01% is a white to off-white lotion supplied in a white aluminum tube as follows: <ul style="list-style-type: none"> • 45 g (NDC 0187-0002-45) • 60 g (NDC 0187-0002-60) • 100 g (NDC 0187-0002-01) 	Satisfactory
Special handling (e.g., protect from light)	Protect from freezing.	Satisfactory
Storage conditions	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from freezing.	Satisfactory

Item	Information provided in the container label	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)))	(b) (4) (halobetasol propionate) Lotion	Satisfactory
Dosage strength	0.01%	Satisfactory.
Net contents	Net Wt. 45g Net Wt. 60g Net Wt. 100g (b) (4)	Satisfactory
"Rx only" displayed prominently on the main panel	Rx only	Satisfactory
NDC number (21 CFR 207.35(b)(3)(i))	Configuration: 45g: NDC 0187-0002-45 60g: NDC 0187-0002-60 100g: NDC 0187-0002-01 (b) (4)	Satisfactory
Lot number and expiration date (21 CFR 201.17)	See crimp for lot number and expiration date.	Satisfactory
Storage conditions	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from freezing.	Satisfactory
Bar code (21CFR 201.25)	Provided. See the image above	Satisfactory
Name of manufacturer/distributor	An example copied from 100 g configuration: Mfg. for: Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC Bridgewater, NJ 08807 USA By: Valeant Pharmaceuticals International, Inc. Laval, Quebec H7L 4A8, Canada © Valeant Pharmaceuticals North America LLC 9615300	Not Satisfactory The manufacturer/distributor names listed should be consistent with that in PI. It is noted that "Ortho Dermatologics" appears on the tube and carton labels but not listed in the statement for the manufacturer/distributor names. Clarify this discrepancy.
And others, if space is available	Not Applicable	Not Applicable

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

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	(b) (4) (halobetasol propionate) Lotion	Satisfactory
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	0.01%	Satisfactory
Net quantity of dosage form	Net Wt. 45g Net Wt. 60g Net Wt. 100g (b) (4)	Satisfactory
"Rx only" displayed prominently on the main panel	Rx only	Satisfactory
Lot number and expiration date	Space holder is indicated.	Satisfactory
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from freezing.	Satisfactory
"See package insert for dosage information"	Usual Dosage: Apply a thin layer to affected areas once daily. See package insert for complete prescribing information.	Satisfactory
Bar code (21CFR 201.25)	Provided. See the sample images above.	Satisfactory
NDC number (21 CFR 207.35(b)(3)(i))	Configuration: 45g: NDC 0187-0002-45 60g: NDC 0187-0002-60 100g: NDC 0187-0002-01 (b) (4)	Satisfactory

<p>Manufacturer/distributor's name</p>	<p>An example copied from the 100 g configuration: Manufactured for: Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC Bridgewater, NJ 08807 USA By: Valeant Pharmaceuticals International, Inc. Laval, Quebec H7L 4A8, Canada Product of Canada 9615400 U.S. Patent Numbers: 6,517,847 and 8,809,307 (b) (4) is a trademark of Valeant Pharmaceuticals International, Inc. or its affiliates. © Valeant Pharmaceuticals North America LLC</p>	<p>Not Satisfactory The manufacturer/distributor names listed should be consistent with that in PI. It is noted that “Ortho Dermatologics” appears on the tube and carton labels but not listed in the statement for the manufacturer/distributor names. Clarify this discrepancy.</p>
<p>Quantitative ingredient information (injectables)</p>	<p>Each gram contains: 0.1 mg (0.01%) halobetasol propionate in a white to off-white lotion base consisting of carbomer copolymer type B, carbomer homopolymer type A, diethyl sebacate, edetate disodium dihydrate, light mineral oil, methylparaben, propylparaben, purified water, sodium hydroxide, sorbitan monooleate and sorbitol solution, 70%.</p>	<p>Satisfactory</p>
<p>Statement of being sterile (if applicable)</p>	<p>Not applicable. It is topical administrated lotion.</p>	<p>Not Applicable.</p>

Reviewer’s Assessment of Labels: *Inadequate.*

This review is based on the applicant submission of draft Prescribing Information (PI), Carton and Container labels on December 05, 2017 (SN0001).

See the reviewer comments in the column of the above tables for the Product Title and Dosage Forms and Strengths of the Highlight Section, Dosage Forms and Strengths (#3), Description (#11) and #16 (How Supplied/Storage and Handling) of the full prescribing information of PI and the Carton and Container Labels.

It is also noted that the trade name (b) (4) is not approved at the time of this review. The comment use (b) (4) as the placeholder for future approved tradename.

Overall Recommendation:

From the ONDP perspective, this application is *not* deemed ready for approval per 314.125(b)(6) until the deficiencies listed at the end in the “**List of Deficiencies**” are satisfactorily resolved.

List of Deficiencies:**A. Regarding PI**

1. Remove the strength 0.01% from the product title in the Highlights section.
2. In the “**Description**” section (#11):
 - a. Include the presentation of the propriety name with the established name as “*Tradename (halobetasol propionate) lotion*” at least once.
 - b. Provide the physical properties of the active ingredient halobetasol propionate, such as pKa or pH.
3. In the “**How supplied/storage and Handling**” section (#16): None.

B. Regarding Labels**a) Both Tube and Cartons:**

The manufacturer/distributor names listed should be consistent with that in PI. It is noted that “Ortho Dermatologics” appears on the tube and carton labels but not listed in the statement for the manufacturer/distributor names. Clarify this discrepancy.

Overall Assessment and Recommendation:

From the ONDP perspective, this application is *not* deemed ready for approval in its present form per 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Hong Cai, Ph.D.

Drug product Reviewer

Branch V/DNDP II/ONDP/OPQ

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

I agree with Dr. Cai's assessment on the labeling and labels, and concur with her recommendation that this application is not ready for approval in its present form until the deficiencies noted in the **List of the Deficiencies** are satisfactorily resolved.

Moo-Jhong Rhee, Ph.D.

Chief

Branch V/DNDP II/ONDP/OPQ



Hong
Cai

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Moo Jhong
Rhee

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CHAPTER V: Review of Biopharmaceutics

BIOPHARMACEUTICS

Product Background:**NDA: 209355****Drug Product Name / Strength: Halobetasol propionate Lotion, 0.01%****Route of Administration: Topical****Formulation: Lotion****Applicant Name: Dow Pharmaceutical Sciences, Inc.****Indication(s): Treatment of plaque psoriasis**

Review Summary: The applicant is seeking approval for NDA 209355 for Halobetasol propionate Lotion, 0.01%.

There was no biopharmaceutics information to review in this application.

The applicant did not submit any information related to in vitro release test. The lack of an IVRT method and in vitro release acceptance criteria will not affect the approvability of this NDA.

Recommendation: The Division of Biopharmaceutics defers the approvability decision on this NDA to the other review disciplines.

Concise Description of Outstanding Issues Remaining: None

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment:

The applicant has not submitted any in vitro release test related information for the proposed product. The lack of an IVRT method and in vitro release acceptance criteria will not affect the approvability of this NDA.

Bridging of Formulations**Reviewer's Assessment:**

There was a manufacturing site change from Dow Pharmaceutical Sciences facility in Petaluma, CA to Valeant Pharmaceuticals International, Inc. facility at Laval (Canada) prior to Phase 3 clinical trials. Phase 3 studies were conducted with batches manufactured at the proposed commercial site. Therefore, additional data are not needed to support the manufacturing site change.

List of Deficiencies:

None

The Division of Biopharmaceutics defers the approvability decision on this NDA to the other review disciplines.

Primary Biopharmaceutics Reviewer Name and Date:

Vidula Kolhatkar, Ph.D. August 01, 2018

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

Okpo Eradiri, Ph.D. August 02, 2018.



Vidula
Kolhatkar

Digitally signed by Vidula Kolhatkar
Date: 8/02/2018 09:45:10AM
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Okponanabofa
Eradiiri

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CHAPTER VI: Review of Quality Microbiology

MICROBIOLOGY**Product Background:**

NDA: 209355

Drug Product Name / Strength: Halobetasol Propionate, 0.01%

Proprietary Name: (b) (4) Lotion

Route of Administration: Topical Lotion

Applicant Name: Dow Pharmaceutical Sciences, Inc.
c/o Valeant Pharmaceuticals North America, LLC
400 Somerset Corporate Blvd
Bridgewater, NJ 08807
Telephone: 707-796-7222
Fax: 908-927-1856

Manufacturing Site: Valeant Pharmaceuticals International, Inc.
2150 St. Elzear Boulevard West
Laval, Quebec H7L 4A8, Canada
FEI: 3002807186

Method of Sterilization: Not applicable; the drug product is non-sterile.

Review Recommendation: Recommended for approval from the standpoint of product quality microbiology.

Review Summary: The drug product is supplied as a nominal 3, 45, 60, or 100 g fill size in (b) (4) aluminum tube with (b) (4) and (b) (4) cap.

List Submissions Being Reviewed: 12/05/2017

Highlight Key Outstanding Issues from Last Cycle: None

Remarks: N/A

Concise Description Outstanding Issues Remaining: See the review summary.

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

As the product is non-sterile, the drug substance will not be reviewed.

P.1 Description of the Composition of the Drug Product

- Description of drug product** – Halobetasol Propionate, 0.01% is a topical corticosteroid lotion packaged as a nominal 3, 45, 60, or 100 g fill size in (b) (4) (b) (4) aluminum tube with (b) (4) and (b) (4) cap.
- Drug product composition** – The drug product is composed of halobetasol propionate, diethyl sebacate, light mineral oil, sorbitan monooleate, sorbitol solution (70%), methylparaben, propylparaben, edetate disodium dehydrate, carbomer copolymer type B (b) (4) carbomer copolymer type A (b) (4) sodium hydroxide, and purified water. Additional information regarding the product composition, as derived from Section 3.2.P.1, in the Description and Composition of the Drug Product, is as follows:

Component	Pharmacopoeial Reference	Function	% w/w
Halobetasol Propionate	USP	Active	0.01
Diethyl Sebacate	NF	(b) (4)	(b) (4)
Light Mineral Oil	NF		
Sorbitan Monooleate	NF		
Sorbitol Solution, 70%	USP		
Methylparaben	NF		
Propylparaben	NF		
Edetate Disodium Dihydrate	USP		
Carbomer Copolymer Type B (b) (4)	NF		
Carbomer Copolymer Type A (b) (4)	NF		
Sodium Hydroxide	NF		
Purified Water	USP		

- Description of container closure system** – The drug product is supplied as (b) (4) (b) (4) aluminum tube with (b) (4) and (b) (4) cap, and both are purchased from (b) (4). The tube has (b) (4) and is sealed on one side with a sealant crimp.

Reviewer's Assessment: *Acceptable*

- The description of the drug product composition and container/closure system is adequate.

P.2 Pharmaceutical Development
P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

Reviewer’s Assessment: Not Applicable

Antimicrobial Effectiveness Testing
 (Section 3.2.P.2.5.1, Microbiological Attributes)

The drug product is supplied as a multiple-dose non-sterile topical lotion in an aluminum tube with (b) (4) screw cap. (b) (4)

(b) (4)
 (b) (4)
 Drug product (b) (4)

(b) (4) were prepared and individually challenged with *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Aspergillus brasiliensis*, and *Candida albicans*. Drug products were inoculated with a minimum of 1.0x10⁵ to 1.0x10⁶ CFU/g of each strain. For the bacterial challenge, as compared to the initial count, a greater than 2 log reduction for each strain was observed at day 14, and no increase from the day 14 count was observed at day 28; for the yeast and mold challenge, no increase from the initial count was observed at days 14 or 28.

The results (b) (4) are summarized as follows:

Formulation Lot #		4351-89	DP1614 (b) (4)
Disposition		PASS	PASS
Test Organism	Time Interval	Log Reduction	Log Reduction
<i>P. aeruginosa</i>	14 Day	>4.6	>3.5
	28 Day	NI	NI
<i>E. coli</i>	14 Day	>3.3	>3.3
	28 Day	NI	NI
<i>S. aureus</i>	14 Day	>4.7	>3.0
	28 Day	NI	NI
<i>C. albicans</i>	14 Day	NI	NI
	28 Day	NI	NI
<i>A. brasiliensis</i>	14 Day	NI	NI
	28 Day	NI	NI

An information request was sent to the applicant, dated 01/23/2018, and a response was received 02/09/2018. The following information was requested:

1) (b) (4)

(b) (4). Please provide the following information:

- a. A summary of the CFU counts for each strain inoculum and corresponding test time point; and
- b. A brief description of the sample preparation method, to include diluents (type and volume), neutralizer, and incubation times/temperatures.

The applicant responses are summarized as follows:

1.a) The applicant provided an updated table in Section 3.2.P.2, Microbiological Attributes, with the corresponding CFU counts inoculated for each strain, along with CFU counts recovered at each time point. The updated table is summarized as follows (copied from Table 3.2.P.2.5-1):

Formulation Lot #		4351-89	DP1614
(b) (4)			
Disposition		PASS	PASS
Test Organism	Time Interval	Log Reduction (CFU/g)	Log Reduction (CFU/g)
<i>P. aeruginosa</i>	Inoculated (CFU/g)	4.1E+05	3.5E+05
	14 Day	>4.6 (<10)	>3.5 (<100)
	28 Day	NI (<10)	NI (<10)
<i>E. coli</i>	Inoculated (CFU/g)	2.0E+05	2.1E+05
	14 Day	>3.3 (<100)	>3.3 (<100)
	28 Day	NI (<10)	NI (<10)
<i>S. aureus</i>	Inoculated (CFU/g)	5.5E+05	1.1E+05
	14 Day	>4.7 (<10)	>3.0 (<100)
	28 Day	NI (<10)	NI (<10)
<i>C. albicans</i>	Inoculated (CFU/g)	9.0E+05	8.0E+05
	14 Day	NI (<100)	NI (<100)
	28 Day	NI (<10)	NI (<10)
<i>A. brasiliensis</i>	Inoculated (CFU/g)	2.3E+05	4.2E+05
	14 Day	NI(8.0E+03)	NI(2.2E+04)
	28 Day	NI(6.8E+03)	NI(5.5E+02)

(b) (4)

(b) (4)

Reviewer's Assessment: *Acceptable*

- The applicant has met the regulatory expectation [REDACTED] (b) (4)

P.3 Manufacture**P.3.1 Manufacturers****Drug Product:**

Valeant Pharmaceuticals International, Inc.
2150 St. Elzear Boulevard West
Laval, Quebec H7L 4A8, Canada

P. 3.3 Description of the Manufacturing Process and Process Controls**OVERALL MANUFACTURING OPERATION**

(Section 3.2.P.3.3, Description of Manufacturing Process and Process Controls)

(b) (4)

Reprocessing: The applicant states that they will not [REDACTED] (b) (4).

Reviewer's Assessment: *Acceptable***P.5 Control of Drug Product****P. 5.1 Specification**

The product release specification includes the following microbiological tests:

Test	Acceptance Criterion	Method
TAMC	NMT (b) (4) CFU/g	USP
TYMC	NMT (b) (4) CFU/g	USP
Objectionable Microorganisms	Absence of <i>S. aureus</i> , <i>P. aeruginosa</i> , and <i>B. cepacia</i>	USP/In-house method for Bcc

Reviewer's Assessment: Acceptable

- The applicant provided microbial limit test methods equivalent to USP<61/62>, and the microbial limits are within those described in USP<1111> for a non-sterile topical drug product.

Component Bioburden

The applicant provided acceptance criteria for bioburden monitoring of the drug product components, which are summarized as follows:

Component	TAMC	TYMC	Specified Microorganisms	Test Method
Halobetasol Propionate	-	-	-	-
Diethyl Sebecate	-	-	-	-
Light Mineral Oil	-	-	-	-
Sorbitan Monooleate	NMT (b) (4) CFU/ml	NMT (b) (4) CFU/ml	-	QCM-578
Sorbitol Solution, 70%	NMT (b) (4) CFU/ml	NMT (b) (4) CFU/ml	Absence of <i>E. coli</i> and <i>Salmonellae</i>	USP
Methylparaben	-	-	-	-
Propylparaben	-	-	-	-
Edetate Disodium Dihydrate	-	-	-	-
Carbomer Copolymer Type B (b) (4)	-	-	-	-
Carbomer Copolymer Type A (b) (4)	-	-	-	-
Sodium Hydroxide	-	-	-	-
Purified Water	NMT (b) (4) CFU/ml	-	Absence of <i>E. coli</i> , <i>Salmonella</i> , <i>S. aureus</i> , and <i>P. aeruginosa</i>	QCM-578

P.5.2 Analytical Procedures

Reviewer's Assessment: See section P.5.1 and P.5.3

P.5.3 Validation of Analytical Procedures

Microbial Limits and Specified Microorganisms

(Section 3.2.P.5.3, Validation of Analytical Procedures)

- Test Method: Equivalent to USP<61/62>, in-house method for BCC testing
- Acceptance Criteria: NMT (b) (4) CFU/g for TAMC, NMT (b) (4) CFU/g for TYMC, and absence of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Burkholderia cepacia*

Microbial Limits: The applicant provided data for microbial limit method suitability and recovery of specified organisms testing in Section 3.2.P.5.3, Validation – Microbial Testing – USP. The tests were performed according to USP<61/62> using the pour plate method, and other selective/differential media. For TAMC and TYMC, testing was performed to demonstrate no interference between the drug product and the test microorganisms, which included *Staphylococcus aureus* (ATCC 6538), *Pseudomonas aeruginosa* (ATCC 9027), *Bacillus subtilis* (ATCC 6633), *Candida albicans* (ATCC 10231), and *Aspergillus brasiliensis* (ATCC 16404). A 10 g sample of the drug product was suspended in 90 ml of modified Tryptic Soy Broth (TSB with neutralizer). Following inoculation NMT (b) (4) CFU of each test strain, recovery of each was within the acceptance criteria. No growth interference was noted.

Specified Microorganisms: The test for specified microorganisms, *S. aureus* and *P. aeruginosa*, was performed using Mannitol Salt Agar and Cetrinide Agar, respectively. Following inoculation with the appropriate microorganism and incubation, each plate was incubated for 18 hours at 30-35°C. All negative controls were negative for growth, and all positive controls and test samples were positive for growth, meeting the acceptance criteria.

Test for *Burkholderia cepacia* complex (BCC): The applicant provided method validation data for the *B. cepacia* test in Section 3.2.P.5.3, Validation – Microbial Testing - Bcc - USP. The method was validated to determine the absence of common BCC strains, to include: *B. cepacia*, *B. cenocepacia*, and *B. multivorans*. (b) (4)

[Redacted]

(b) (4)



The applicant responses are summarized as follows:

1) The applicant provided updated BCC method validation data using the drug product formulation in Section 3.2.P.5.3, Validation of Analytical Procedures – Microbial Testing

– Bcc. (b) (4)

After inoculation of the drug product with NMT (b) (4) CFU, growth of *B. cepacia* and *B. multivorans* occurred at less than 24 hours, and growth of *B. cenocepacia* occurred at less than 48 hours of incubation. No growth was observed on negative control plates. The data from the method validation using the drug product is summarized as follows (*copied from Section 3.2.P.5.3.5, Validation of Analytical Procedures – Microbial Testing – Bcc, pg. 2*):

Incubation with product for less than 24 hours						
Challenge Microorganism	Media	Media Incubation Time (Hours)	Product Growth	Positive Control Growth	Negative Control Growth	Pass/Fail
<i>Burkholderia cepacia</i> (ATCC 25416)	<i>Burkholderia cepacia</i> Selective Agar (BCSA)	<24	Positive	Positive	Negative	Pass
		<48	N/A	N/A	N/A	N/A
<i>Burkholderia cenocepacia</i> (ATCC BAA-245)		<24	Negative	Negative	Negative	N/A
		<48	Positive	Positive	Negative	Pass
<i>Burkholderia multivorans</i> (ATCC BAA-247)		<24	Positive	Positive	Negative	Pass
		<48	N/A	N/A	N/A	N/A

Reviewer’s Assessment: *Acceptable*

- The applicant provided acceptable method validation data to support their test for *Burkholderia cepacia* complex (BCC) in the subject drug product.

P.7 Container Closure

Summary table of the container closure system proposed

Reviewer’s Assessment: See section P.1.

P.8 Stability

P. 8.1 Stability Summary and Conclusion

The proposed expiry is 36 months at 20-25°C, with excursions permitted to 15-30°C.

Reviewer’s Assessment: *Acceptable*

- The applicant's proposed 36 month expiry is acceptable based on the provided microbial test data.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The product stability specification includes the following microbiological tests:

Test	Acceptance Criterion	Method
TAMC	NMT (b) (4) CFU/g	USP
TYMC	NMT CFU/g	USP
Objectionable Microorganisms	Absence of <i>S. aureus</i> , <i>P. aeruginosa</i> , and <i>B. cepacia</i>	USP/In-house method for Bcc

Post-approval stability conditions will be 25±2°C/60±5% RH. (b) (4)

[Redacted]

The testing schedule in the post-approval protocol is as follows:

Test Schedule for Initial Commercial Stability Batches									
36 months, 25±2°C/40±5% RH									
Interval (Month)	0	3	6	9	12	18	24	30	36
TAMC/TYMC	X	-	-	-	-	-	-	-	-
Objectionable Microorganisms	X	-	-	-	-	-	-	-	-

The applicant committed to initiate and conduct post-approval stability studies on the first three commercial production batches, with the results of the testing to be submitted as part of either routine annual reporting or as specified by the Agency, as they become available. If additional data beyond the expiry, on at least three production batches, support extension of the expiration period, the expiration may be extended and the data will be filed in an annual report. If any lot is found to be out-of-specification, the deviation will be discussed with the Agency, and if deemed necessary, the lot will be withdrawn from the market.

Reviewer's Assessment: *Acceptable*

- The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life.

P.8.3 Stability Data

The applicant provided (b) (4) data up to 24 months for the 3, 45, and 100 g fill sizes.

Reviewer's Assessment: *Acceptable*

- The applicant provided acceptable microbiology stability data.

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: *Not Applicable*

A.2.1 Materials of Biological Origin

Reviewer's Assessment: *Not Applicable*

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: *Not Applicable*

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: *Not Applicable*

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: *Not Applicable*

R Regional Information

Executed Batch Records

Executed compounded batch: Lot 8082922

Executed filling batches: Lots 8083840, 8083839, 8083845, and 8083841

Reviewer's Assessment: *Acceptable*

- The applicant has met the regulatory expectation regarding executed batch records.

Comparability Protocols**Reviewer's Assessment: *Not Applicable*****2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q)
MODULE 1****2.A. Package Insert**

Maximum dose: The maximum dose of the drug product is 50 g/week, and treatment beyond 8 weeks is not recommended.

Storage: 20-25°C, with excursions permitted to 15-30°C.

Description: The drug product is supplied as a white to off-white lotion in a white aluminum tube.

Reviewer's Assessment: *Acceptable****Post-Approval Commitments: See P.8.2*****Reviewer's Assessment: *Not Applicable******List of Deficiencies: N/A******Primary Microbiology Reviewer Name and Date:* Jason K. Morgan, Ph.D., 02/12/2018*****Secondary Reviewer Name and Date:* John W. Metcalfe, Ph.D., 02/13/2018**



Jason
Morgan

Digitally signed by Jason Morgan
Date: 2/14/2018 06:53:17AM
GUID: 573cb41f005b429215eef443f34949a3



John
Metcalf

Digitally signed by John Metcalfe
Date: 2/14/2018 08:36:43AM
GUID: 503451f000004f68b7145543c615dbba
Comments: I concur with the primary reviewer's assessment.

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/s/

MATTHEW E WHITE
11/08/2018