CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213691Orig1s000

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: **May 12, 2020**

From: **Hamid Shafiei, Ph.D.**
Application Technical Lead, Branch IV
Division of New Drug Products 2
Office of New Drug Products

To: **To Executive Summary, IQA for Assessment # 1 of NDA 213691**

Subject: **Final Recommendation of "Approval"**

In original IQA review dated April 5, 2020, this NDA was not recommended for approval in the form it was presented due to unresolved labeling/labels issues identified by the Drug Product Reviewer, Dr. Ali Mohamadi as per 21 CFR 314.125(b)(6). The applicant submitted revised labeling and labels on May 12, 2020. The revised labeling and labels have been reviewed by Dr. Mohamadi on May 12, 2020 and found adequate to support the approval of this application from the labeling and labels perspective (see the Attachment).

Therefore, from the OPQ perspective, this NDA is recommended for **approval**.

Application Technical Lead:
Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

Memorandum

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

Date: 5/12/2020

From: Ali Mohamadi, Ph.D.
Drug Product Reviewer
Branch V Division of New Drug Products III
Office of New Drug Products

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

To: Labeling Review #1 of NDA 213691

Subject: Finalized Label/labeling of CMC Sections

At the time when Labeling Review of this application was completed (03/31/2020), this NDA was not recommended for approval due to unresolved CMC label/labeling issues. On 05/12/2020, the Applicant has submitted revised labels and labeling which satisfactorily addressed all CMC label/labeling issues (see the **Attachment**).

Recommendation:

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

Ali Mohamadi, Ph.D.
Drug Product Reviewer
Branch V, Division III, ONDP

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

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

Ali Mohamadi

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Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 5/12/2020 02:24:52PM
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Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 5/12/2020 04:45:40PM
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/s/

HAMID R SHAFIEI
05/12/2020 04:55:40 PM

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RECOMMENDATION

☒ Deemed not ready for Approval
☐ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213691
Assessment # 1

Drug Product Name	Trade Name (clobetasol propionate)
Dosage Form	Lotion
Strength	0.05%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Lupin, LTD
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission	07/19/2019	All
Response to Quality Information Request	10/08/2019	Drug Product
Response to Quality Information Request	10/17/2019	OPMA
Response to Quality Information Request	11/05/2019	Drug Product
Response to Quality Information Request	11/14/2019	Drug Product
Response to Clinical Information Request	11/26/2019	Clinical
Response to Quality Information Request	12/16/2019	Drug Product
Response to Quality Information Request	12/16/2019	OPMA
Response to Quality Information Request	01/08/2020	Drug Product and OPMA
Response to Quality Information Request	01/31/2020	Drug Product
Proprietary Name Review Request	02/13/2020	All

Reference ID: 4587030

Proprietary Name Review Request Amendment	03/04/2020	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Lawrence Perez, Ph.D.	Donna Christner, Ph.D.
Drug Product	Ali Mohamadi, Ph.D.	Moo-Jhong Rhee, Ph.D.
Manufacturing	James Norman, Ph.D.	Yubing Tang, Ph.D.
Microbiology	Paul Dexter, Ph.D.	Dacie Bridge, Ph.D.
Biopharmaceutics	Bryan Ericksen, Ph.D.	Vidula Kolhatkar, Ph.D.
Regulatory Business Process Manager	Bamidele (Florence) Aisida, Pharm. D., BCPS	
Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	Ali Mohamadi, Ph.D.	Moo-Jhong Rhee, Ph.D.

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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	07-Jan-2019	Weixiang Dai, Ph.D.
	III			----------	----------	Adequate information provided in the NDA
	III			----------	----------	Adequate information provided in the NDA

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

Document	Application Number	Description
NDA	21535	Listed Drug
ANDA	209147	Referenced for the drug product composition and manufacturing

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			

U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

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, clobetasol propionate and the drug product, Trade Name (clobetasol propionate) Lotion, 0.05% for topical administration.

- Labels/labeling issues have **not** 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 of the environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is deemed not ready for **APPROVAL** in its present form per 21 CFR 314.125(b)(6), until the deficiency noted in the **List of Deficiencies** is satisfactorily resolved..

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Mylan Pharmaceuticals, Inc. has submitted this (505)(b)(2) new drug application for Trade Name (clobetasol propionate) Lotion, 0.05% for topical administration intended for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses only in patients 18 years of age or older. Treatment is limited to two consecutive weeks. For the treatment moderate to severe plaque psoriasis, treatment may be continued for an additional 2 weeks for localized lesions (less than 10% body surface area) that have not adequately improved after the initial 2-week treatment. However, the extension of the treatment beyond the recommended two weeks should be weighed against the risk of hypothalamic-pituitary-adrenal (HPA) axis suppression before prescribing. The total dosage of this drug product is limited to 50g/week.

The applicant has used Clobex® (clobetasol propionate) Lotion, 0.05% approved for the same indication under NDA 21535 in 2003 as the listed drug. A generic version of clobetasol propionate lotion at the same strength of 0.05% manufactured by Lupin, Ltd. has also been approved under ANDA 209147 since September 22, 2017.

The active ingredient, clobetasol propionate is a synthetic fluorinated corticosteroid and belongs to a class of synthetic steroids intended for topical use as anti-inflammatory and antipruritic agents.

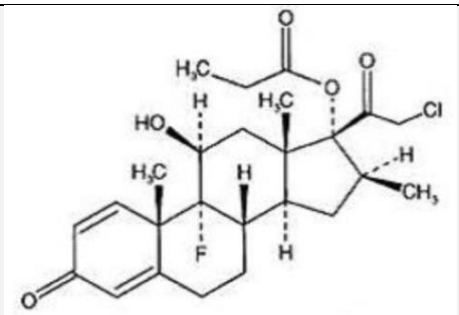
The drug product submitted in this application is the same exact formulation and is manufactured by same manufacturer, Lupin, Ltd. as in the approved generic application, ANDA 209147. The only difference is that this drug product will be packaged as 68g lotion in a container closure with a metered-dose that delivers 0.3g of the lotion with each pump actuation.

Proposed Indication(s) including Intended Patient Population	The relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses only in patients 18 years of age or older.
Duration of Treatment	2 weeks. May be extended to 4 weeks in case of moderate to severe psoriasis.
Maximum Daily Dose	Maximum of (b) (4) actuations per application ((b) (4) g) or (b) (4) actuation per 24 hours ((b) (4) g) with not more than 50g per week.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, clobetasol propionate is a synthetic fluorinated corticosteroid and is a compendial drug substance. It belongs to a class of synthetic steroids intended for topical use as anti-inflammatory and antipruritic agents. It is a white to almost white crystalline powder. It is insoluble in water (0.014 mg/g), sparingly soluble in methanol and ethanol, and soluble in acetone, chloroform and dioxane. It is slightly hygroscopic and has a melting range of 190°C to 200°C, pKa of 12.88, and specific rotation of +100° to +104° (10 mg/ml solution in dioxane at 20°C). Clobetasol propionate has the chemical name of 21-chloro-9-fluoro-11β, 17-dihydroxy-16β -methylpregna-1,4-diene-3,20-dione 17-propionate, the empirical formula of $C_{25}H_{32}ClFO_5$, the molecular weight of 466.97 and the chemical structure below:



The drug substance for this new drug application is manufactured by (b) (4). The information regarding the manufacture of clobetasol propionate supplied by (b) (4) (b) (4) is provided in DMF (b) (4) held by (b) (4)

Clobetasol propionate manufactured by (b) (4) is tested and released according to a specification that that assures the identity, strength, purity, and quality of the drug substance at release and throughout its retest date of (b) (4) months. The proposed specification also complies with the current USP monograph and ICH Q3A. The stability data supporting the retest date of (b) (4) months is provided in DMF (b) (4) This DMF has been recently reviewed by the OGD drug substance reviewer, Dr. Weixiang Dai on January 7, 2019 and found to be adequate.

In summary, based on Dr. Dai assessment of the DMF (b) (4) and the information provided in the drug substance module of this application, the Drug Substance Reviewer, Dr. Lawrence Perez has recommended that the drug substance information provided is adequate to support the approval of this NDA. Dr. Perez's review is provided in the Drug Substance Chapter of the IQA.

Drug Product: Adequate

Trade Name (clobetasol propionate) Lotion, 0.05% for topical administration has been developed for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses only in patients 18 years of age or older.

Trade Name lotion is a white to off white, opaque to translucent, homogeneous, and lump-free lotion free of phase separation. It is a preservative-free, non-sterile, aqueous based lotion formulation and its composition is the same as the composition of the approved lotion under ANDA 209147 (approved September 2017). The drug product is also manufactured by the same drug product manufacturer in ANDA 209147. However, this drug product is packaged as 68g to ensure the delivery of

(b) (4) g of lotion in a container closure equipped with a metered-dose pump to deliver 0.3g (0.15mg of clobetasol propionate) with each actuation.

Each gram of Trade Name Lotion contains 0.5mg of clobetasol propionate as the active ingredient and hypromellose [(b) (4)], carbomer 1342, propylene glycol, mineral oil (b) (4), PEG-6 isostearate, sodium hydroxide, and purified water as inactive ingredients. Excipients used in the composition of this drug product are compendial materials and/or excipients used in the approved ANDA 209147 at the same exact amounts. The quantity of each excipient used in the composition of the drug product is also below permitted level in IIG database for topical drug products.

Trade Name lotion is manufactured by Lupin, Ltd., the manufacturer of the drug product of the approved ANDA 209147 for Mylan Pharmaceuticals, Inc. in accordance to current good manufacturing practices (cGMP) and tested and release against a specification that assures the identity, strength, purity, and quality of the drug product as well as the container closure pump delivery at release and throughout its proposed expiration dating period of 24 months. The proposed expiration dating period of 24 months is supported by the stability data submitted in the application and is granted.

In summary, the drug product reviewer, Dr. Ali Mohamadi has found the drug product information submitted in the application sufficient to support the approval of this application from the drug product perspective. Dr. Mohamadi'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. Ali Mohamadi. Dr. Mohamadi has noted a deficiency (see the **List of Deficiencies**) and made a recommendation that this application is not deemed ready for approval in its presnt form per 21 CFR 314.125(b)(6) until the deficiency is satisfactorily resolved. Dr. Mohamadi's labeling/labels review is provided in the Labeling Chapter of the IQA.

Manufacturing: Adequate

(b) (4)

(b) (4)

The manufacturing process for this application has been reviewed by the OPMA Reviewer, Dr. James Norman. Dr. Norman has found the manufacturing process and in-process controls adequate to support the approval of this application. Dr. Norman has also found the facilities involved in the manufacture and testing of Trade Name lotion acceptable. Dr. Norman's review is provided in the Manufacturing Chapter of the IQA.

Biopharmaceutics: Adequate

The proposed formulation for Trade Name lotion is the same lotion formulation approved under ANDA 209147. No biowaiver request was submitted in this application and therefore, no bridging studies is needed.

The applicant has developed an in-vivo release testing (IVRT) method and has provided the IVRT method development report. The biopharmaceutics section of this NDA has been reviewed by the Biopharm Reviewer, Dr. Bryan Ericksen. Dr. Ericksen has found the biopharmaceutics information provided in this application adequate to support the approval of this application. Dr. Ericksen's review is provided in the Biopharmaceutics Chapter of the IQA.

Microbiology (if applicable): Adequate

Trade Name lotion is a preservative -free, non-sterile, aqueous- based lotion packaged in a bottle with a metered-dose pump and is intended as a multidose unit.

The drug product is tested for microbial limits according to USP <61> and USP <62>. Although the drug product is a preservative-free, it is intended as a multidose product and testing for antimicrobial effectiveness is required. The applicant developed validated method for antimicrobial effectiveness testing according to USP <51> category 2 aqueous product and has submitted the method, method validation, and relevant data in the application. The applicant also provided a risk-based assessment and a validated protocol and relevant data demonstrating that the proposed aqueous drug product is free of *Burkholderia Cepacia complex* (USP <60>).

The microbiology section of this application has been reviewed by the Microbiology Reviewer, Dr. Paul Dexter. Dr. Dexter has found the

microbiology information provided in the application adequate to support the approval of this application from the microbiology perspective. Dr. Dexter's review is provided in the 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**
The amount of drug delivered with each actuation	Metered-dose pump delivery	M For a dermal product	Pump delivery is tested as an attribute in the drug product specification	L Acceptable	None

D. List of Deficiencies:

- In the section 11, DESCRIPTION section of the full Prescribing Information, the required established name is not present, therefore, it must be stated as follows with the approved trade name:

  Tradename (clobetasol propionate) lotion

Application Technical Lead:

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

Reference ID: 4587030

Hamid Shafiei

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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:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

[redacted] (b) (4) **(clobetasol propionate) lotion, 0.05%, for topical use**
Initial U.S. Approval: 1985

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	[redacted] (b) (4)	**Inadequate** Note: Proprietary name is found unacceptable by the Office of Prescription Drug Promotion (OPDP).
Established name(s)	clobetasol propionate lotion, 0.05%, for topical use	**Adequate** Note: "Lotion" also used in the referenced drug.
Route(s) of administration	topical use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	lotion, 0.05% w/w	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	N/A

Reference ID: 4587030

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

- Not for oral, ophthalmic, or intravaginal use. (2)
- [redacted] lotion should be applied [redacted] the affected skin areas twice daily [redacted] and rubbed in gently. (2)
- [redacted] lotion contains a [redacted] topical corticosteroid; therefore, treatment should be limited to 2 weeks. For moderate to severe plaque psoriasis, [redacted] additional 2 weeks for localized lesions (<10% body surface area) that have not sufficiently improved. (2)
- Total dosage should not exceed 50 g per week (i.e., [redacted]). (2)

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)	See above	Note: Based on the label claim, pump can deliver NLT (b) (4) actuations equivalent to (b) (4) g of lotion. It should be changed to NLT 138 actuations equivalent to NLT 41.4 g lotion based on drug product specification (in Module 3.2.P.5.1 (sequence 0004(4)).

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Lotion, 0.05% w/w (3)

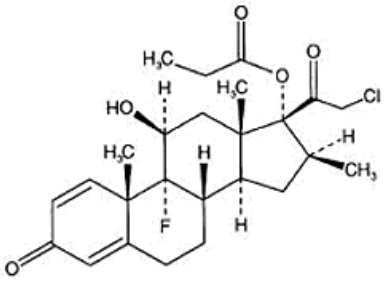
Reference ID: 4587030

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Lotion	**Adequate**
Strength(s) in metric system	0.05%	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	White to off white, opaque to translucent homogenous and lump free lotion without any phase separation packed in white bottle with a metered dose pump having an integral pump locking feature	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	N/A

1.2.3 Section 11 (DESCRIPTION)

(b) (4) lotion contains clobetasol propionate, a synthetic fluorinated corticosteroid, for topical use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents. Clobetasol propionate is 21-chloro-9-fluoro-11β, 17-dihydroxy-16β -methylpregna-1,4-diene-3,20-dione 17-propionate, with the empirical formula $C_{25}H_{32}ClFO_5$, and a molecular weight of 466.97 (CAS Registry Number 25122-46-7).
The following is the chemical structure:

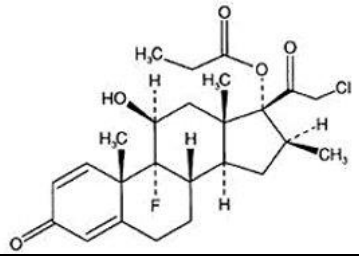
Reference ID: 4587030



Clobetasol propionate

Clobetasol propionate, USP is a white to almost white crystalline powder that is practically insoluble in water. (b) (4) lotion is a white to off white, opaque to translucent, homogenous and lump free lotion composed of carbomer 1342, hypromellose, mineral oil, PEG-6 isostearate, propylene glycol, purified water and sodium hydroxide. Each pump actuation delivers 0.15 mg of clobetasol propionate in 0.30 g of lotion.

Section 11 (DESCRIPTION)Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	(b) (4), Clobetasol propionate, USP	**Inadequate** Note: Tradename is found unacceptable by OPDP. Tradename and established name should be revised to: Tradename (clobetasol propionate) lotion,
Dosage form(s) and route(s) of administration	Lotion	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	carbomer 1342, hypromellose, mineral oil, PEG-6 isostearate, propylene glycol, purified water and sodium hydroxide.	**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	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A Note: Ethanol is not present. Propylene Glycol is present
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Corticosteroid	**Adequate**

Chemical name, structural formula, molecular weight	Clobetasol propionate, $C_{25}H_{32}ClFO_5$, MW: 466.97 	**Adequate**
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A	N/A
For oral prescription drug products, include gluten statement if applicable	N/A	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	N/A

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4) lotion, 0.05% is a white to off white, opaque to translucent, homogenous and lump free lotion without any phase separation provided in a white bottle with a metered-dose pump having an integral pump locking feature. Each pump actuation delivers 0.15 mg of clobetasol propionate, USP in 0.30 g of lotion. The metered-dose pump is capable of dispensing (b) (4) actuations to deliver (b) (4) g of lotion. It is available as follows:

NDC 49502-537-35

one 68 g metered-dose pump

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled

Room Temperature]. Protect from freezing.

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Lotion	**Adequate**
Strength(s) in metric system	0.05%	**Adequate**
Available units (e.g., bottles of 100 tablets)	one 68 g metered-dose pump	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	lotion, 0.05% is a white to off white, opaque to translucent, homogenous and lump free lotion without any phase separation provided in a white bottle with a metered-dose pump having an integral pump locking feature. NDC 49502-537-35	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	N/A
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.)	Protect from freezing	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	N/A

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Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].	**Adequate**
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	N/A
Include information about child-resistant packaging	N/A	N/A

1.2.5 Other Sections of Labeling

Based on the label claim, each pump can deliver NLT (b) (4) actuations equivalent NLT (b) (4) g lotion. This should be changed to NLT 138 actuations equivalent to NLT 41.4 g lotion based on drug product specification in Module 3.2.P.5.1 (sequence 0004(4)). Current labeling still shows the wrong statement (number 3, annotated labeling): "*Metered-dose pump capable of dispensing* (b) (4) *actuations to deliver* (b) (4) *g of lotion*." The correct statement should be: "*Metered-dose pump capable of dispensing NLT 138 actuations to deliver* (b) (4) (b) (4) *NLT 41.4 g of lotion*.".

1.2.6 Manufacturing Information After Section 17 (for drug products)

Manufactured for:
Mylan Specialty L.P.
Morgantown, WV 26505 U.S.A.
Manufactured by:
Lupin Limited
Pithampur (M.P.) – 454 775, India

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 for: Mylan Specialty L.P. Morgantown, WV 26505 Manufactured by: Lupin Limited Pithampur (M.P.) – 454 775, India	**Adequate**

2.0 PATIENT LABELING

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

***Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."*:** None

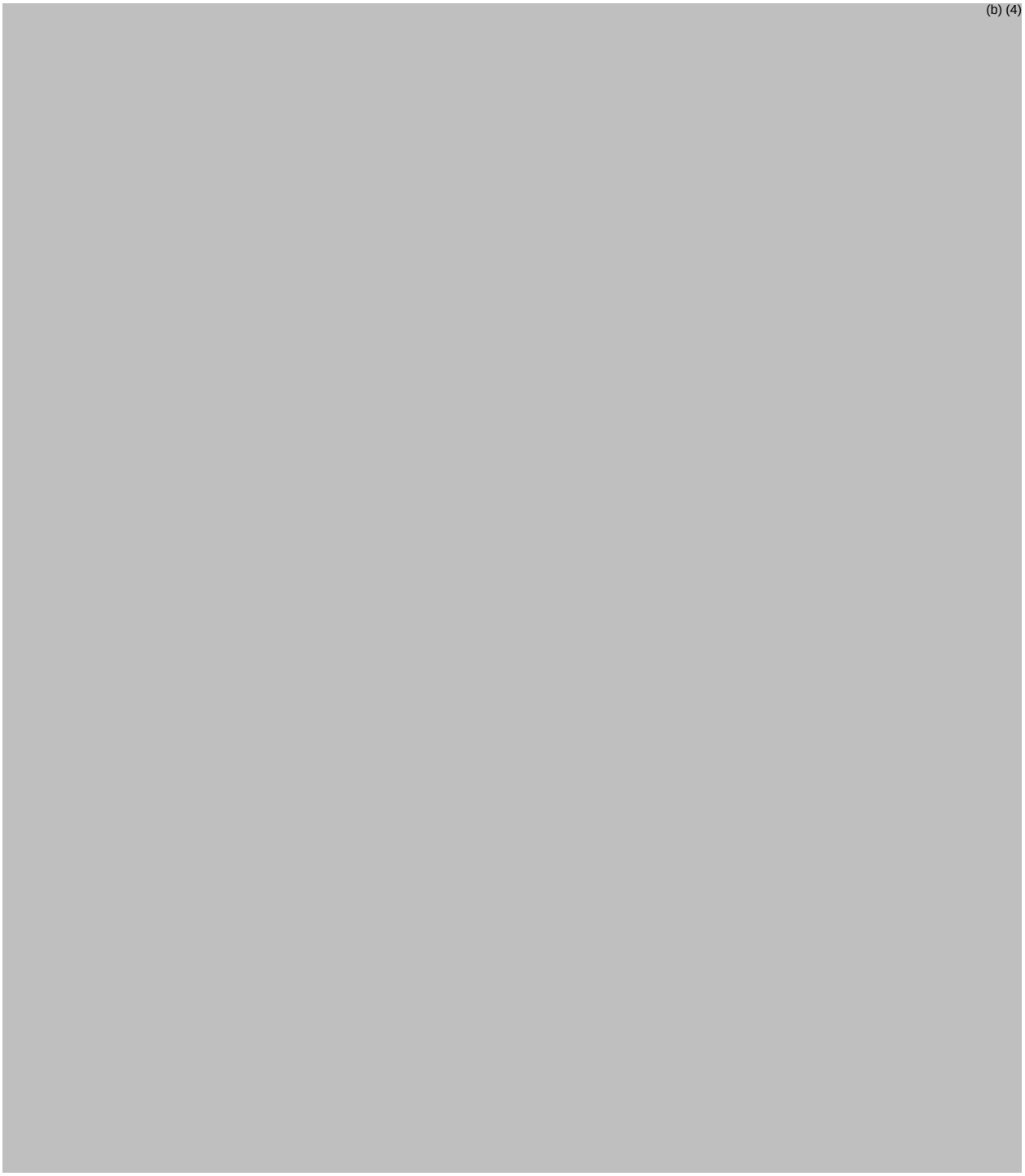
3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

Reference ID: 4587030


(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	(b) (4)	**Adequate** Note: Proprietary name was found unacceptable by OPDP, but the established name is **satisfactory.**
Dosage strength		**Adequate**
Route of administration		**Adequate**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	68 g	N/A
"Rx only" displayed on the principal display	Rx only	**Adequate**
NDC number	49502-537-35	**Adequate**
Lot number and expiration date	Space is allocated for the expiry date and lot number	**Adequate**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from freezing.	**Adequate**
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code		**Adequate**

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Mylan Specialty L.P. Morgantown, WV 26505 Manufactured by: Lupin Limited Pithampur (M.P.) – 454 775, India	**Adequate**
Medication Guide (if applicable)	Apply twice daily, once in the morning and once at night (not to exceed (b) (4) actuations/application or (b) (4) actuations/day). Use only enough to cover the affected areas. Do not apply (b) (4) to the face, underarms, or groin, and avoid contact with eyes and lips.	**Adequate**
No text on Ferrule and Cap overseal	No text	**Adequate**
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	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: *{ Inadequate}*

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies:

A. Regarding Prescribing Information

- In the **Description** section, the tradename and established name must be correctly expressed at least one in the running text as following:

Reference ID: 4587030

Tradename (clobetasol propionate) lotion

B. Regarding Carton and Container Labels
None

Overall Assessment and Recommendation:

From the ONDP perspective, this application is not deemed ready for approval in its present form per 21 CFR 314.125(b)(6) until the established name in the PI/Description section is correctly expressed as indicated in the **List of Deficiencies.**

Primary Labeling Assessor Name and Date:

Ali Mohamadi, Ph.D.
Primary Assessor
DNDP II/ONDP/OPQ
March 31, 2020

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

I agree with Dr. Mohamadi's assessment on the labeling and labels, and therefore, I concur with his recommendation that this application is not ready for approval in its present form until the established name in the PI?Description is correctly expressed as noted in the **List of Deficiencies.**

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
DNDP II/ONDP/OPQ
March 31, 2020

Reference ID: 4587030

Ali Mohamadi

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Moo Jhong Rhee

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BIOPHARMACEUTICS

Product Background:

The current submission is for the approval of Clobetasol Propionate lotion, 0.05%, indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses for up to 2 weeks and moderate to server plaque psoriasis for up to 4 weeks.

NDA-213691-ORIG-1

Drug Product Name / Strength: Clobetasol Propionate lotion / 0.05%

Route of Administration: Topical

Applicant Name: Mylan Pharmaceuticals, Inc.

Review Summary: Adequate

No biowaiver was requested, and no bridging of formulations is necessary. An in vitro release testing (IVRT) method was presented, and the Applicant submitted an IVRT method development report in response to an information request.

NDA 213691 for Clobetasol Propionate lotion, 0.05%, is Adequate from the Biopharmaceutics perspective.

List Submissions being reviewed (table):

07/19/19	NDA 213691/Sequence 0001/Original Submission
11/26/2019	NDA 213691/Sequence 0006/Response to Information Request

Concise Description Outstanding Issues Remaining:

None

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

Reviewer's Assessment: Adequate

The summary biopharm document in Module 2.7 gives ED50 data and mentions a bioequivalence study, but contains no IVRT data. However, in the Pharmaceutical Development

Report on pp. 188-192, an IVRT method was detailed and IVRT results were presented. A Franz cell was used with parameters as follows:

Franz cell parameters:

Instrument name: Hanson's Franz diffusion cell

Membrane : Polyether sulfone (PES), 0.45µ, 25mm diameter (Manufacturer – (b) (4)

RPM : 400

Cell Volume : 7.0mL

Rinse Volume : 1.2mL

Collect Volume : 1.2mL

Temperature : 32±0.5°C

Time Points : 0.5, 1, 2, 3, 4 and 6 Hrs.

Receptor medium: Water:Ethanol (800:200)

Cumulative drug release and slope results are shown in the following two tables:

Table 2.54: Cumulative Drug Release profile of Test and Listed product

Square root of Time (Hours)	Cumulative Drug Release (µ/sq.cm)			
	Test Product (Batch No.: K690016)		Listed Product (Batch No.: HFES)	
	Set-1	Set-2	Set-1	Set-2
0.7	(b) (4)			
1.0				
1.4				
1.7				
2.0				
2.4				

Table 2.55: Drug Release parameters of Test and Listed product

Parameter	Test Product Batch No.: K690016		Listed Product Batch No.: HFES	
Slope of Set 1	T1	12.561	R1	11.676
	T2	11.812	R2	12.734
	T3	12.593	R3	12.453
Slope of Set 2	T4	13.149	R4	12.837
	T5	12.191	R5	12.957
	T6	12.51	R6	11.949

According to the SUPAC-SS guidance, the 8th and 29th sorted test/reference ratios met the respective acceptance criteria:

Table 2.56: % Sorted Ascending T/R ratio

S. No.	% Sorted Ascending T/R ratio	Limit
8th	96.60%	Should be NLT 75%
29th	105.10%	Should be NMT 133.33%

These IVRT results passed for the test product with respect to the reference product. Note that, in general, the comparison between two products is unnecessary from the biopharmaceutics perspective. No acceptance criteria were proposed, and there is no IVRT specification in Module 3.2.P.5.1.

In response to an information request, on November 26, 2019 the Applicant provided a method development report. See \\cdsesub1\evsprod\nda213691\0006\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\ivrt-meth-dev\ivrt-meth-dev-report-body.pdf

(b) (4)

(b) (4)

(b) (4) The IVRT method was precise and able to discriminate between 0.025%, 0.05%, and 0.075% Clobetasol Propionate formulations. This IVRT method and the development report are adequate.

An IVRT validation report was presented in Module 3.2.P.5.3. It focused on the HPLC method and included linearity, precision, sensitivity, determination of sink condition, a membrane binding study (the same as membrane inertness), receptor solution stability, limit of quantitation (sensitivity) determination, and robustness. It did not include a calculation of mass balance. However, this feature is not necessary for a complete validation report. For this reason, the validation report is adequate.

It should be noted that although this is a NDA for Clobetasol Propionate lotion / 0.05% packaged in a new container closure system (metered-dose pump) allowing patients to effectively monitor dosing, this product was previously approved under ANDA 209147, in which the lotion was packaged in a bottle with a (b) (4) top cap.

Bridging of Formulations

Reviewer's Assessment: Adequate

Section 2.3.6 of the Pharmaceutical Development Report in Module 3.2.P.2 states that the registration batches and large scale batch were all manufactured at the same facility. In addition, the batch formula in Module 3.2.P.3 shows that the same formulation was used for the registration batches and the "intended batches". Therefore, no bridging of formulations is necessary.

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name:

Bryan Ericksen, Ph.D.

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

Vidula Kolhatkar, Ph.D.

Vidula Kolhatkar

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Bryan Ericksen

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	213691
Assessment Cycle Number	01
Drug Product Name/ Strength	(b) (4) (Clobetasol Propionate) Lotion, 0.05% Metered-Dose Pump
Route of Administration	Topical Lotion
Applicant Name	Mylan Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	
Manufacturing Site	Lupin Limited (b) (4) Dist.- Dhar, Pithampur, Madhya Pradesh, India, 454775
Method of Sterilization	Non-sterile drug product

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
0001 (1)	**7/19/2019**
0002 (2)	**10/8/2019**
0009 (9)	**1/8/2020**

List Submissions being assessed (table):

Highlight Key Issues from Last Cycle and Their Resolution:

Remarks: The NDA references Clobetasol Propionate Lotion, 0.05% (ANDA 209147; approved on 9/22/2017) which refers to the RLD Clobex® (NDA #N021535; approved on 4/11/2016). The subject NDA product remains the same as the ANDA product except that the drug product is packaged in a bottle with a metered dose pump.

Contains a comparability protocol for implementation of an imprinted metered-dose pump actuator and container labels printed with a new ink.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): Not applicable

Supporting Documents: Not applicable

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product**
  (P.1: Description and Composition of the drug product)

  [redacted] (Clobetasol Propionate) Lotion, 0.05% (0.15 mg/actuation) is a white to off white, opaque to translucent, homogeneous and lump-free lotion free of phase separation. The drug product is a preservative-free, non-sterile, aqueous based lotion that is packaged in a white bottle with a metered-dose pump that has an integral pump locking feature. Each actuation delivers 0.3 g of lotion; the fill weight is [redacted] g/bottle. The drug product is multi-dose.

  Note to the Reviewer: The drug product is presumed to be multi-dose based on the labeling instructions and that the drug is packaged with a metered-dose pump.

- **Drug Product Composition**
  (P.1: Description and Composition of the Drug Product)

Component	Function	Quantity (% w/w)	Quantity (mg/g)
Clobetasol Propionate [redacted], USP	API	0.05	0.500
Hypromellose [redacted] USP	[redacted]		
Carbomer 1342, NF			
Propylene Glyco [redacted] USP			
[redacted]			
Mineral Oil [redacted] USP			
PEG-6 Isostearate, IH (in-house)			
Sodium hydroxide, NF			
Purified water, USP [redacted]			
[redacted]			

- **Description of Container Closure System**
  (P.1: Description and Composition of the Drug Product; P.7: Container Closure System).

Component	Description	Manufacturer
Bottle	100 mL, 24 mm neck, Opaque, round, white, HDPE bottle; [redacted]	[redacted]
Metered Dose Pump	280 µl opaque white lotion screw pump with translucent cap, dip tube, and lock/unlock symbols and arrow in black ink	
Overcap	Opaque white [redacted] cap; [redacted]	

Note to the reviewer: The CCS used for the commercial batches is the same as the first three registration batches, except for the addition of the imprint on the metered-dose pump and the overcap on the bottles. The fourth batch was prepared with the imprinting. Furthermore, the applicant states that the proposed drug product is considered a drug-device combination product due to the presence of the metered-dose pump.

Assessment: *Adequate*

P.2 PHARMACEUTICAL DEVELOPMENT
P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

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