CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211882Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 211882
Assessment # 1

Drug Product Name	ARAZLO™ (tazarotene)
Dosage Form	Lotion
Strength	0.045%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Bausch Health Americas, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA submission	02/22/2019	All Disciplines
Response to Quality Information Request	05/07/2019	OPQ/OPMA
Response to Quality Information Request	06/12/2019	OPQ/OPMA/DMA
Response to Quality Information Request	08/o2/2019	OPQ/ONDP-Drug Substance and Drug Product
Container and Carton Labels	09/23/2019	All Disciplines

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Ramsharan Mittal, PhD	Donna Christner, PhD
Drug Product	Ryan Holland, PhD	Moo-Jhong Rhee, PhD
Manufacturing	James Norman, PhD	Jean Tang, PhD
Microbiology	Dustin Thomas, PhD	Elizabeth Bearr, PhD
Biopharmaceutics	Kamrun Nahar, PhD	Vidula Kolhatkar, PhD
Regulatory Business Process Manager	Bamidele (Florence) Aisida, Pharm. D., BCPS	
Application Technical Lead	Hamid R. Shafiei, PhD	
Laboratory (OTR)	N/A	N/A
Environmental	Ryan Holland, PhD	Moo-Jhong Rhee, PhD

APPEARS THIS WAY ON ORIGINAL

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	04-Sep-2018	Reviewed by X. Hu, Ph.D.
	III			———	———	Adequate information is provided in the NDA

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

Document	Application Number	Description
NDA	209354	Referenced for the formulation

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			

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

- The applicant of this 505(b)(2) new drug application has provided **sufficient CMC information** to assure the identity, purity, strength, and quality of the drug substance, tazarotene and the drug product, ARAZLO™ (tazarotene) Lotion, 0.045% for topical administration.
- Labels/labeling issues have been **satisfactorily** addressed.
- The Office of Process and Facility has made an overall "**Acceptable**" recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment has been granted.

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

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The applicant, Bausch Health US, LLC. has submitted this 505(b)(2) application for ARAZLO (tazarotene) Lotion, 0.045% indicated for the treatment of acne vulgaris in patients 9 years of age and older. The lotion is intended for topical application as a thin layer to the affected skin area once daily.

The active ingredient, tazarotene is a retinoid prodrug that activate three members of retinoic acid receptors, RARα, RARβ, and RARγ. Although tazarotene's mechanism of action in the treatment of acne vulgaris is unknown, its anti-hyperproliferative, normalizing-of-differentiation, and anti-inflammatory properties may be linked to the observed efficacy.

Tazarotene was first approved in 1997, and since its original approval, multiple brand name and generic cream, gel, and foam drug products containing this active ingredient have been approved and are being marketed in the United States. Recently, a lotion drug product containing a combination of tazarotene and halobetasol as active ingredients, formulated with the same inactive ingredients, was approved on April 25, 2019 under NDA 20935 for the topical treatment of plaque psoriasis.

ARAZLO (tazarotene) Lotion, 0.045% is a white to off-white lotion and will be packaged and supplied as 3g for physician samples and as 45g for commercial use in white aluminum tube (b) (4) (b) (4) caps.

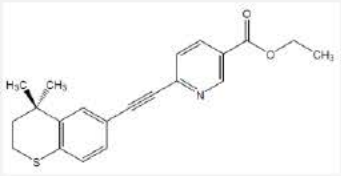
Proposed Indication(s) including Intended Patient Population	Treatment of acne vulgaris in patients 9 years of age and older
Duration of Treatment	As prescribed by physician
Maximum Daily Dose	A thin layer applied to the affected skin area once daily
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Choose an item.

The active ingredient, tazarotene is a retinoid prodrug that activates three members of retinoic acid receptors, RARα, RARβ, and RARγ. Due to its anti-proliferation, normalizing-of-differentiation, and anti-inflammatory properties, tazarotene has been found to be effective in the treatment of acne vulgaris.

Tazarotene is a pale yellow to brownish powder with a melting point with a range of 103ºC to 104ºC. It is soluble in toluene, acetone, ethyl acetate, tetrahydrofuran, and dichloromethane and is insoluble in water. It is non-hygroscopic with a pKa of 1.5 and log P of 5.6 with only one identified crystal form, (b) (4). Tazarotene has the chemical name of 6-[3,4-dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl]-3-pyridinecarboxylic acid ethyl ester, molecular formula of $C_{21}H_{21}NO_2S$, molecular weight of 351.46 g/mol, and the molecular structure below:



Tazarotene is produced through a (b) (4) (b) (4)

(b) (4)

Tazarotene is tested for release and accepted according to a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its retest date o (b) (4) months. The rested date o (b) (4) months is well supported by the stability data provided. The information regarding the manufacture of tazarotene supplied by (b) (4) is provided in DMF (b) (4). This DMF was most recently reviewed (Review # 4) on September 4, 2018 and was found to remain adequate by Dr. X Hu.

In summary, relying on Dr. Hu's recent review of DMF (b) (4) and the review of the additional information provided in the Drug Substance Module of this application, the Drug Substance Review, Dr. Joseph Leginus has concluded that the information provided in this application regarding the drug substance, tazarotene, is adequate to support approval of this application from the drug substance perspective. Dr. Leginus's review is provided in the Drug Substance Chapter of the Integrated Quality Assessment (IQA).

Drug Product: Choose an item.

ARAZLO™ (tazarotene) Lotion, 0.045% has been developed for the treatment of acne vulgaris in patients 9 years of age or older.

ARAZLO™ lotion formulation is the same formulation used for the approved combination drug product, DUOBRII™ (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% with the exception this drug product does not contain halobetasol. Since the quantitative amount of halobetasol used in DUOBRII formulation is almost negligible (0.1mg/g), the quantitative compositions of excipients in the two lotions are considered identical.

Each gram of ARAZLO™ lotion contains 0.45mg of tazarotene as the active ingredient and diethyl sebacate, light mineral oil, sorbitan monooleate, sorbitol solution (70%), methylparaben, propylparaben, edetate disodium dihydrate, carbomer copolymer type B (b) (4) carbomer homopolymer type A (b) (4), sodium hydroxide, and purified water as inactive ingredients. Excipients used in the composition of this lotion are all compendial materials.

ARAZLO™ lotion is manufactured by Bausch Health Companies Inc., Quebec, Canada in accordance to the current good manufacturing practices and is tested and release against a drug product specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 36

months. The proposed expiration dating period of 36 months is supported by the stability data submitted in the application and is granted.

In summary, the drug product module of this application has been reviewed by the Drug Product Reviewer, Dr. Ryan Holland. Dr. Holland has found the drug product information submitted in the application sufficient to support the approval of this application from the drug product perspective. Dr. Holland's review is provided in the Drug Product Chapter of the IQA.

Labeling: Choose an item.

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. Ryan Holland. Dr. Holland has found the final PI as well as immediate container and carton labels adequate to support approval of this application. Dr. Ryan's labeling/labels review is provided in the Labeling Chapter of the IQA.

Manufacturing: Choose an item.

ARAZLOTM lotion is manufactured a (b) (4)

(b) (4)

The manufacturing process including critical steps, critical parameters, in-process testing and controls, and executed batch records have been reviewed by the Offices Pharmaceutical Manufacturing Assessment (OPMA) Reviewer Dr. James Norman. Dr. Norman has found the manufacturing process information provided in the application adequate to support the approval of this application.

Dr. Norman has also evaluated the information regarding the facilities involved in this application. Dr. Norman has found all facilities involved in the manufacture of drug substance and drug product adequate to support the approval of this application.

Dr. Norman review of the manufacturing process and evaluation of the facilities are provided in the Manufacturing Chapter of the IQA.

Biopharmaceutics: Choose an item.

This application was originally submitted without in-vitro release testing (IVRT) method and acceptance criteria. An IR was submitted to the applicant to develop and validate an in-vitro release testing method and propose and acceptance criteria. In response to the IR, the applicant did

not develop and validate an IVRT method and instead provided a justification referencing SUPAC SS that this drug product does not require development an of an IVRT method. The applicant stated that tazarotene (b) (4) (b) (4) The applicant justification has been reviewed by the Biopharm Reviewer, Dr. Kamrun Nahar. Dr. Nahar has found the applicant justification based on the SUPAC SS acceptable and that the biopharmaceutics information provided in the application adequate to support the approval of this NDA. Dr. Nahar's review is provided in the Biopharmaceutics Chapter of the IQA.

Microbiology (if applicable): Choose an item.

ARAZLO™ (tazarotene) Lotion, 0.045% is a non-sterile drug product and is tested for microbial limits according to USP <61> and USP <62>. Antimicrobial effective testing is also conducted for this drug product according to USP <51>.

Based the new requirement a method for detection of *Bulkholderia cepacia complex* in the drug product was developed and the drug product was examined for three strains of *Bulkholderia, B. capacian, B cenocepacia, and B. multivorans*. Based on this data, adequate risk mitigation for potential microbial growth was conducted.

The information regarding the test methods, acceptance criteria, and risk mitigations for bioburden growth has been reviewed by the Microbiology Reviewer, D, Dustin Thomas. Dr. Thomas has found the bioburden information provided in the application adequate to support approval of this NDA. Dr. Thomas'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**
Content uniformity (b) (4)	Solubility of API	M	(b) (4)	Acceptable	None

			(b) (4)		

D. List of Deficiencies:

None

Application Technical Lead:

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

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

ARAZLO™ (tazarotene) Lotion, 0.045% for topical use

Initial U.S. Approval: 1997

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	ARAZLO	Adequate
Established name(s)	Tazarotene Lotion	Adequate
Route(s) of administration	Topical	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Lotion, 0.045% Each gram of ARAZLO Lotion contains 0.45 mg (0.045%) tazarotene in a white to off-white topical lotion.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	n/a	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

- Apply a thin layer of ARAZLO Lotion to the affected areas once daily. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

Item	Information Provided in the NDA	Assessor's Comments
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)	Apply a thin layer of ARAZLO lotion to the affected areas once daily. Avoid the eyes, mouth, paranasal creases, and mucous membranes. ARAZLO lotion is for topical use only. Not for oral, ophthalmic, or intravaginal use.	Adequate: Dosage and administration instructions are present and clearly stated.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Lotion, 0.045% (3)

Each gram of ARAZLO Lotion contains 0.45 mg (0.045%) tazarotene. (3)

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	Lotion	Adequate
Strength(s) in metric system	Each gram of ARAZLO lotion contains 0.45 mg (0.045%) tazarotene API	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	n/a	API is not a salt
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	ARAZLO is a white to off-white topical lotion	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	Drug product is not a tablet

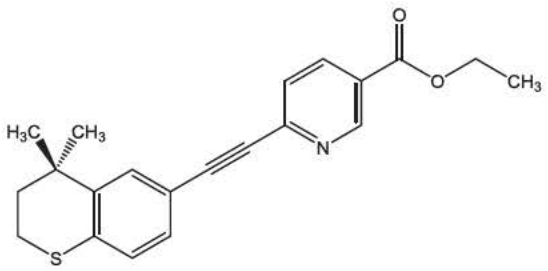
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	n/a	Drug product is not an injectable dosage form

1.2.3 Section 11 (DESCRIPTION)

ARAZLO (tazarotene) is a white to off-white lotion containing 0.045% tazarotene by weight for topical administration.

Tazarotene is a member of the acetylenic class of retinoids. The chemical name for tazarotene is 6-[(3,4-Dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl]-3-pyridinecarboxylic acid ethyl ester. The structural formula for tazarotene is represented below:

Tazarotene:



Molecular Formula: $C_{21}H_{21}NO_2S$ Molecular Weight: 351.46

Each gram of ARAZLO Lotion contains 0.45 mg (0.045%) tazarotene 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 the NDA	Assessor's Comments
Proprietary and established name(s)	ARAZLO; Tazarotene lotion	Adequate
Dosage form(s) and route(s) of administration	Lotion containing 0.045% tazarotene by weight for topical administration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	n/a	API is not a salt

List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	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%.	Adequate: All excipients are compendial and listed by the proper USP names.
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	Drug product is not an injectable dosage form
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	Drug product does not contain alcohol
Statement of being sterile (if applicable)	n/a	Drug product is not intended to be a sterile product
Pharmacological/ therapeutic class	Acetylenic class of retinoids	Adequate
Chemical name, structural formula, molecular weight	6-[(3,4-Dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl]-3-pyridinecarboxylic acid ethyl ester Molecular Formula: C21H21NO2S Molecular Weight: 351.46	Adequate; Chemical name, and molecular weight/ formula are correct
If radioactive, statement of important nuclear characteristics.	n/a	Drug product is not radioactive
Other important chemical or physical properties (such as pKa or pH)	n/a	The API does not have exchangeable protons
For oral prescription drug products, include gluten statement if applicable	n/a	Drug product is not an oral dosage form
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”	n/a	All information is accurate and necessary to describe the product. No marketing terms are included

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

ARAZLO (tazarotene) Lotion, 0.045% is a white to off-white lotion supplied in a white aluminum tube as follows:

- 45 g (NDC 0187-2098-45)

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.

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	Lotion	Adequate
Strength(s) in metric system	0.045%	Adequate
Available units (e.g., bottles of 100 tablets)	45 g tube	Adequate: Only the 45 g tube is listed in this section.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white to off-white lotion NDC: 0187-2098-45 for 45 g tubes	Adequate: NDC number is available for the 45 g tubes.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	Drug product is not a tablet
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	Drug product is not an injectable dosage form
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: Special handling concerns are clearly stated.
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	Drug product is not stored with desiccant
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	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].	Adequate: Standard numerical storage conditions are clearly stated.

Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	n/a	
Include information about child-resistant packaging	n/a	The Patient Information sheet states, "Keep ARAZLO and all medicines out of the reach of children.

1.2.5 Other Sections of Labeling

Not applicable

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	**Manufactured for:** Bausch Health US, LLC Bridgewater, NJ 08807 USA **By:** Bausch Health Companies Inc, Laval, Quebec H7L 4A8, Canada	Adequate: Manufacturers information is up to date.

2.0 PATIENT LABELING

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

A patient information insert is also provided as part of the labeling package. The established name is correct and consistent between the prescribing information insert and the patient information insert. In addition, the following information is accurately included in the patient information insert:

- Strength and route of administration
- Dosage and administration instructions/precautions
- Manufacturers information
- Storage and handling instructions/precautions

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT.":

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

3 g

(b) (4)

45 g

(b) (4)

[redacted]

Item	Information Provided in the NDA	Assessor's Comments
Proprietary name; established name, and dosage form	ARAZLO; tazarotene lotion	Adequate: font size and prominence are satisfactory
Dosage strength	0.045%	Adequate
Route of administration	Topical	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	n/a	API is not a salt
Net contents (e.g. tablet count)	Net Wt. 3 g per tube, or Net Wt. 45 g per tube	Adequate
"Rx only" displayed on the principal display	Yes	Adequate

NDC number	0187-2098-10 for 3 g tubes and 0187-2098-45 for 45 g tubes	Adequate
Lot number and expiration date	Yes	Adequate: lot number and expiration date will be embossed on the crimped end of the tubes.
Storage conditions. If applicable, include a space on the container labeling for the user to write the new BUD.	45 g tube : 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	Adequate: Although full storage condition is not stated on the 3 g tubes due to the limited space, it is acceptable. .
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	n/a	Drug product is not an injectable dosage form
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	n/a	No other package terms included
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	Drug product does not contain alcohol
Bar code	Yes	Adequate
Name of manufacturer/distributor	Manufactured for: Bausch Health US, LLC Bridgewater, NJ 08807 USA By: Bausch Health Companies Inc. Laval, Quebec H7L 4A8, Canada	Adequate
No text on Ferrule and Cap overseal	n/a	No text on cap
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	n/a	The drug substance and product are not compendial

difference shall be plainly stated on its label.		

3.2 Carton Labeling

3 g

(b) (4)

45 g

(b) (4)

[redacted]

Item	Information Provided in the NDA	Assessor's Comments
Proprietary name, established name, and dosage form (font size and prominence	ARAZLO, tazarotene lotion	Adequate: font size and prominence are satisfactory
Dosage strength	0.045%	Adequate
Route of administration	Topical	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	n/a	API is not a salt
Net contents (e.g. tablet count)	10 tubes Net Wt. 3 g per tube, or Net Wt. 45 g per tube	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	0187-2098-10 for 3 g tubes and 0187-2098-45 for 45 g tubes	Adequate
Lot number and expiration date	Yes	Adequate

Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	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	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	n/a	Drug product is not an injectable dosage form
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	n/a	No other package terms included
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	Drug product does not contain alcohol
Bar code	Yes	Adequate
Name of manufacturer/distributor	Manufactured for: Bausch Health US, LLC Bridgewater, NJ 08807 USA By: Bausch Health Companies Inc. Laval, Quebec H7L 4A8, Canada	Adequate: The manufacturing facility should be added to the container label for the 3 g tubes.
No text on Ferrule and Cap overseal	n/a	No text on cap
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	The drug substance and product are not compendial

Assessment of Carton and Container Labeling: Adequate

4.0 List of Deficiencies: None

Overall Assessment and Recommendation:

The Prescribing Information and container/carton labels in NDA 211882 are deemed adequate, and therefore, this NDA is recommended for **Approval** from the CMC Label and Labeling Perspective.

Primary Labeling Assessor Name and Date:

Ryan Holland, Ph.D.
Reviewer, DNDP II/ONDP/OPQ

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

I agree with Dr. Holland's assessment on the labeling and labels, and concur with his recommendation of **Approval** from the CMC labeling perspective.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V, DNDP II/ONDP/OPQ

Ryan Holland

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Moo Jhong Rhee

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QUALITY REVIEW

BIOPHARMACEUTICS

Product Background:

NDA: NDA-211882-ORIG-1

Drug Product Name / Strength: Tazarotene 0.045%, topical lotion

Route of Administration: Topical lotion

Applicant Name: Bausch Health US, LLC

Indication: Acne vulgaris

Review recommendation: Adequate

Review Summary:

The proposed drug product, Tazarotene 0.045%, topical lotion is used for treatment of acne vulgaris. The applicant did not develop an in vitro release method for the proposed Tazarotene lotion. Therefore, an information request (IR) was sent with recommendation for the applicant to develop an in vitro release (IVR) method and propose an acceptance criteria. In response to the IR, the applicant denied developing an IVR method and referenced the SUPAC SS guidance to justify not developing an in vitro release method. Tazarotene lotion is an emulsio (b) (4) (b) (4) (b) (4)

acceptable and the NDA 211882 is **adequate** for approval.

Background Summary:

Dow pharmaceutical Sciences, a division of Bausch Health Companies, Inc. has developed a topical product containing 0.045% Tazaroten (b) (4) intended for the treatment of Acne Vulgaris. The drug is intended to apply on the skin once-a-day to cover affected areas. The drug is soluble in Toluene, acetone, ethyl acetate and tetrahydrofuran when heated to 50°-60°C and does not exhibit polymorphism (b) (4) (b) (4)

All phase 3 lots of IDP 123 lotion studied under IND 126277 were manufactured at Laval using the same process proposed for commercial use. All drug products and placebo batches were manufactured by Bausch Health Companies Inc. (formerly Valeant Pharmaceutical International Inc.) at Laval. All 6 clinical studies evaluated the to-be-marketed formulation IDP-123 Lotion. Supportive development and stability batches have been manufactured at the Dow Pharmaceuticals Sciences facility in Petaluma, California

before Phase 3 batches were manufactured. No significant changes were made between the ICH registration stability and proposed commercial scale manufacture, both are (b) (4) Kg scale. Placebo was? also be manufactured at this scale. A slight variation in process was made (b) (4) (b) (4) This change was made before Phase 3 and this change did not affect the stability and robustness of the final lotion. According to the applicant this modification in process (b) (4). Prior to phase 3 clinical supplies, batch sizes of (b) (4) kg were made.

Composition of proposed drug product:

Table 1: Composition of the Tazarotene 0.045%, topical lotion

Component	Reference to Quality Standard	Function	Concentration (% w/w)
Tazarotene	In-house	Active	0.045
Diethyl sebacate	NF	(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 homopolymer type A (b) (4)	NF		
Sodium hydroxide	NF		
Purified water	USP		

USP = United States Pharmacopeia
NF = National Formulary
qs = quantity sufficient

Initially, the Applicant did not submit an in vitro drug release (IVR) method. Therefore, the applicant was recommended to provide the FDA in vitro release study method and data. In response the applicant denied developing and provide IVR method and report.

List Submissions being reviewed:
NDA 211882: 0001 (1) 02/22/2019 ORIG-1/ Multiple Categories/ Subcategories
NDA 211882: 0002 (2) 05/07/2019 ORIG-1/ Quality Response to Information Request

Highlight of Key Outstanding Issues from Last Cycle: None

Concise Description of Outstanding Issues: None

In vitro release method and acceptance criteria:

The applicant did not submit an in vitro release (IVR) method and data for the proposed Tazarotene lotion. Therefore, the applicant was recommended to develop an IVR method. In response to the information request (IR) the applicant denied to develop an IVR method and referenced the-SUPAC SS guidance: Nonsterile Semisolid Dosage Forms Scale-Up and post approval Changes: Chemistry, Manufacturing, and Controls: In Vitro Release Testing and in Vivo Bioequivalence Documentation to justify for not developing an in vitro release method. As per the SUPAC-SS guidance, an in vitro release rate is a useful test to assess product sameness between pre-change and post-change products. Tazarotene lotion is an emulsio (b) (4) (b) (4) (b) (4) Hence, from **ate** for approval. Refer to the Appendix 2 for detail of the IR, response and reviewer's assessment.

Reviewer's signature

Primary Biopharmaceutics Reviewer Name:

Kamrun Nahar, Ph.D.

Secondary Biopharmaceutics Reviewer Name:

Vidula Kolhatkar, Ph.D.

Appendix 1

Attachment 1 - Information Request c

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	Non-sterile lotion for treatment of acne vulgaris
NDA Number	211882
Assessment Cycle Number	0001
Drug Product Name/ Strength	Arazlo (tazarotene), 0.045%
Route of Administration	Topical Lotion
Applicant Name	Bausch Health US, LLC
Therapeutic Classification/ OND Division	
Manufacturing Site	Bausch Health Companies, Inc 2150 St. Elzear Boulevard West Laval, Quebec, Canada H7L 4A8
Method of Sterilization	N/A – Drug product is non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
NDA 211882	**02/22/2019**
0003	**06/12/2019**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The submission is in the eCTD format.

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

Supporting Documents: N/A

S DRUG SUBSTANCE – N/A Drug substance is non-sterile

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- Description of drug product – non-sterile white to off-whit (b) (4) multi-dose (b) (4) lotion, pH (b) (4) for topical, cutaneous use. Packaged as 3 g or 45 g in an aluminum tube.

- Drug Product Composition

Component	Function	Concentration (%w/v)
Tazarotene, In-house	API	0.045
Diethyl sebacate, NF	(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:

Component	Description	Supplier
Tube	3 g or 45 g fill Aluminum tub (b) (4) (b) (4)	(b) (4)
Cap		

Assessment: *Adequate*

The description of the drug product is adequate.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

- Antimicrobial Effectiveness Testing

(3.2.P.2 Microbiological Attributes; 3.2.P.5.3 Validation of Analytical Procedures – Antimicrobial Effectiveness)

Antimicrobial effectiveness testing was performed according to USP <51> for (b) (4) products (b) (4) (b) (4)

(b) (4)

Acceptance criteria:

- Bacteria - NLT (b) (4) log reduction at (b) (4) days
- Bacteria (b) (4) betwee (b) (4) and (b) (4) days
- Molds and Yeast (b) (4) a (b) (4) and (b) (4) days

All organisms showe (b) (4) log reduction at th (b) (4) day time point and no increase between (b) (4) an (b) (4) days across all antimicrobial concentrations. No increase in mold/yeast growth was observed ove (b) (4) days at all antimicrobial concentrations. All acceptance criteria were met.

Assessment: *Adequate*

Antimicrobial effectiveness testing is adequate.

P.3 MANUFACTURE

P.3.1 MANUFACTURERS

Bausch Health Companies, Inc
2150 St. Elzear Boulevard West
Laval, Quebec, Canada H7L 4A8

This site is responsible for manufacture, packaging, release and stability testing of the drug product.

Alternate release and stability testing facility
Bausch Health Americas, Inc.
1330 Redwood Way Suite C
Petaluma, CA 9495

(b) (4)

Assessment: *Adequate*

The manufacturing location description is adequate.

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Assessment: *Adequate*

The testing schedule of post-approval stability batches is adequate.

P.8.3 STABILITY DATA

(3.2.P.8.1 Stability Summary and Conclusions; 3.2.P.8.3 Stability Data – 25C)

Stability results were provided for up to 36 months (Lots 8082919 and 8082920) and up to 18 months (Lot 8097938) at 25±2°C/60±5% RH (b) (4) (b) (4) (b) (4) Antimicrobial Effectiveness Testing of all points meet USP <51> acceptance criteria.

Assessment: *Adequate*

Microbial limits data was not initially provided. An IR requesting microbial limits testing on stability was sent 05/29/2019 and the applicant responded 06/12/2019 stating that microbial limits will be added to the stability testing.

R REGIONAL INFORMATION

Executed Batch Records: Bulk lots 8082919, 8082920, and 8097938

Assessment: *Adequate*

Comparability Protocols – N/A

Assessment: *N/A*

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

(1.14.1 Draft labeling)

Storage temperature: 20°C - 25°C

Assessment: *Adequate*

MICROBIOLOGY LIST OF DEFICIENCIES: N/A

Primary Microbiology Assessor: Dustin Thomas, PhD *06/14/2019*

Secondary Assessor: Elizabeth Bearr, PhD *06/14/2019*

Dustin Thomas

Digitally signed by Dustin Thomas
Date: 8/28/2019 10:33:34AM
GUID: 5a9d7e03000dc17a5f2fc069bb182920

Elizabeth Bearr

Digitally signed by Elizabeth Bearr
Date: 8/28/2019 10:58:24AM
GUID: 55370d1e00cfd67fc04d8bfbedbf3096

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/s/

HAMID R SHAFIEI
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