CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211527Orig1s000

PRODUCT QUALITY REVIEW(S)

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 211572
Assessment # 1

Drug Product Name	AKLIEF (trifarotene)
Dosage Form	Cream
Strength	0.005%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Galderma Research and Development, LLC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA Submission	10/04/2018	All
User Fee	10/29/2018	Administrative-All
Response to Quality Information Request	11/16/2018	OPQ-ONDP-DP
Quality Information – USAN Name for API	11/19/2018	OPQ-ONDP-DS-All
Updated Drug Substance General Information	11/20/2018	OPQ-ONDP-DS
Response to Clinical Inforamtion Request	12/11/2018	Clinical
Proprietary Name Request	12/19/2018	All
Response to Clinical Inforamtion Request	12/26/2018	Clinical
Response to Clinical Inforamtion Request	01/09/2019	Clinical
Clinical Safety Update	02/04/2019	Clinical
Response to Clinical Inforamtion Request	03/18/2019	Clinical
Response to Quality Information Request	03/25/2019	OPQ-ONDP-Biopharm
Response to Quality Information Request	04/01/2019	OPQ-ONDP-DS

Response to Clinical Inforamtion Request	04/16/2019	Clinical Pharmacology
Response to Quality Information Request	04/25/2019	OPQ-ONDP-DP
Clinical Pharmacology Information	05/03/2019	Clinical Pharmacology
Response to Quality Information Request	05/10/2019	OPQ-ONDP-Biopharm
Response to Quality Information Request	05/20/2019	OPQ-ONDP-DP
Response to Quality Information Request	05/23/2019	OPQ-ONDP-DP
Response to Quality Information Request	06/14/2019	OPQ-ONDP-DP
PI Labeling and Container Closure/Carton Labels	06/19/2019	All
PI Labeling and Container Closure/Carton Labels	08/12/2019	All
PI Labeling and Container Closure/Carton Labels	08/30/2019	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Ramsharan Mittal, Ph.D.	Donna Christner, Ph.D.
Drug Product	Hamid Shafiei, Ph.D.	Moo-Jhong Rhee, Ph.D.
Manufacturing	Vidya Pai, Ph.D.	Maotang Zhou, Ph.D.
Microbiology	Eric Adeeku, Ph.D.	Jesse Wells, 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)	Kui Zeng, Ph.D.	Connie Ruzicka, Ph.D.
Environmental	Hamid Shafiei, Ph.D.	Moo-Jhong Rhee, Ph.D.

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	March 25, 2019	Ramsharan Mittal, Ph.D.
	III			---	---	Adequate information is provided in the NDA
	III			_____	_____	Adequate information is provided in the NDA

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

Document	Application Number	Description
IND	111091	Clinical Investigation in the United States

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			

FDA U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

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

Galderma Research and Development, LLC has submitted this 505(b)(1) new drug application for AKLIEF (trifarotene) Cream, 0.005%. ALKIEF Cream is intended for topical treatment of acne vulgaris of the face and/or trunk in patients 9 years of age and older. Each gram of AKLIEF cream contains 50µg of trifarotene.

The active ingredient, trifarotene is a terphenyl acid derivative and has been classified as a rotenoid. Rotenoids, due to their ability to reduce inflammation and to normalize the desquamation of follicular epithelium, leading to the elimination of the comedones and the inhibition of new microcomedone formation, are prescribed for the treatment of acne vulgaris. Since trifarotene has not been previously approved in the United States as an active ingredient in any drug product, it has been classified and a new molecular entity (NME).

AKLIEF (trifarotene) Cream, 0.005% will be packaged and marketed as 30g, 45g, and 75g cream i (b) (4) /high density polyethylene (HDPE) white (b) (4) bottles closed with (b) (6) white pump dispensers and (b) (6) white overcaps (b) (6) (b) (6)

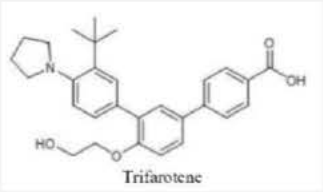
Proposed Indication(s) including Intended Patient Population	Treatment of acne vulgaris of the face and/or trunk in patients 9 years of age and older
Duration of Treatment	Not well-defined (the duration will be determined by the physician as needed to treat affected skin area)
Maximum Daily Dose	1.8g of cream containing 50mcg/g of trifarotene once a day (0.4g – 0.6g per actuation with up to 3 actuations to cover both face and trunk)
Alternative Methods of Administration	No alternative method of administration

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, trifarotene, a terphenyl acid derivative, is a retinoic acid receptor (RAR) agonist and is classified as a rotenoid. Trifarotene intended as a drug for the treatment of acne vulgaris. Since trifarotene has not been previously approved as an active ingredient in any drug product in the United States, it is classified as a new molecular entity (NME).

Trifarotene is produced as a white to off-white to slightly yellow crystalline powder. It is slightly soluble in acetone, ethanol, and toluene, very slight soluble in isopropanol, and practically insoluble in water (b) (4) (b) (4) Trifarotene is non-hygroscopic and has pKa1 of 5.69 and pKa2 of 4.55. The chemical name for trifarotene is 4-{3-[3-tert-butyl-4-(pyrrolidin-1-yl) phenyl]-4-(2-hydroxyethoxy) phenyl} benzoic acid. It has the chemical formula of $C_{29}H_{33}NO_4$, the molecular weight of 459.59, and the chemical structure below:



Trifarotene

Trifarotene for early developmental studies were manufactured by Galderma. In 2011, the manufacturing process for this drug substance was transferred (b) (4)

Trifarotene is packaged (b) (4) (b) (4)

(b) (4) The API has been shown to be stable for 60 months under the long-term stability conditions of 25°C/60%RH and therefore, has been assigned the retest date o (b) (4) months.

Trifarotene manufactured by (b) (4) is produced according to cGMP and is tested and released according to the specification that includes testing and acceptance criteria for all physical and chemical attributes essential for the assurance of the identity, strength, purity, and quality of drug substance. Analytical methods used for release and stability testing of the drug substance have been appropriately validated for their intended purpose.

Detailed information regarding the manufacture, characterization of API and impurities, release and stability testing, analytical methods, specification, packaging, and retest date for trifarotene has been provided in DMF (b) (4) This DMF has been reviewed by the drug substance reviewer, Dr. Ramsharan Mittal. Dr. Mittal has found the information provided in DMF (b) (4) adequate to support this new drug application, and he has recommended the approval of this application from the drug substance perspective.

Drug Product: Adequate

AKLIEF (trifarotene) Cream, 0.005% is intended for topical administration to the face and/or trunk for the treatment of acne vulgaris in patients 9 years of age or older.

The active ingredient, trifarotene has been classified as a new molecular entity and is a rotenoid. The inactive components used in the composition of AKLIEF cream are all compendial materials with the exception of copolymer of acrylamide and sodium acryloyldimethyltaurate dispersed in 40% isohexadecane. However, this excipient has been previously approved as a component of the currently marketed drug product, Epiduo® Ge (b) (4)

AKLIEF is produced as (b) (6) (b) (4) The manufacturing process for this drug product consists o (b) (4) (b) (6) The cream formulation is filled a (b) (6) 30g, 45g, and 75g drug product into (b) (4) /high-density polyethylene (HDPE) (b) (4) bottles with whit (b) (4) pumps and white (b) (4) overcaps (b) (4) (b) (4)

(b) (4) The use of the proposed container

closure systems is supported by results from extractables/leachables and stability studies.

AKLIEF Cream is tested and released according to a specification that includes testing and acceptance criteria for all physical and chemical arributes essential for the assurance of the identity, strength, purity, and quality of the drug. The applicant has also provided sufficient stability data that clearly supports granting the proposed expiration dating period of 36 months.

The information provided in the Drug Product Module of this application has been reviewed by the Drug Product Reviewer, Dr. Hamid Shafiei who is also the Application Technical Lead (ATL). Dr. Shafiei has found the information provided in the drug product section of this new drug application adequate. Dr. Shafiei has also found the applicant's request for categorical exclusion from the preparation of the environmental assessment valid. Dr. Shafiei has recommended the approval of this application from the drug product perspective.

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. Hamid Shafiei. Dr. Shafiei has found the final PI as well as immediate container and carton labels have satisfactorily resolved all outstanding issues noted in his Labeling Review #1, and therefore, he has recommended the approval of this application from the labeling/labels perspective (see the addendum, dated September 3, to the Labeling Review #1).

Manufacturing: Adequate

AKLIEF (trifarotene) Cream, 0.005% is a light cream formulation produced through (b) (4) The manufacturing process for AKLIEF consists o (b) (4) (b) (4)

The final cream formulation is filled as (b) (6) 30g, 45g, and 75g drug product into (b) (4) /high-density polyethylene (HDPE) (b) (4) bottles with white (b) (4) pumps and white (b) (4) overcaps (b) (4) (b) (4)

The drug substance is manufactured by [redacted] (b) (4) has significant experience in the manufacture of the active ingredients including NMEs and is currently compliant with the cGMP requiremen [redacted] (b) (4) has significant experience with the manufacture of topical dosage forms and is currently compliant with the cGMP requirements. Therefore, PAIs were not conducted. The additional testing facilities listed in this new drug application have also been deemed acceptable for their intended testing roles.

The manufacturing process and facilities provided in this application have been reviewed by the Process and Facilities reviewer, Dr. Vidya Pai. Dr. Pai has concluded that the manufacturing process and manufacturing facilities proposed in this new drug application are adequate.

Biopharmaceutics: Adequate

The applicant has developed and validated an IVRT method for AKLIEF Cream using an in-vitro release Workstation automated system of cells diffusion. The applicant has proposed drug release acceptance criterion of [redacted] (b) (4) $\mu g/cm^2/h^{1/2}$. The applicant has committed to test the first three commercial batches of the drug product for in-vitro release during both release and stability. The applicant has also committed to routinely test all batches for in-vitro release during the drug product release testing.

The proposed in-vitro release test method, acceptance criterion, and testing commitments have been reviewed by the Biopharm reviewer, Dr. Bryan Ericksen. Dr. Ericksen has concluded that applicant proposed in-vitro release test method, acceptance criterion, and testing commitments are adequate to support approval of this application.

Microbiology (if applicable): Adequate

The information regarding drug product microbial quality including proposed test methods and acceptance criteria for bioburden (microbial limit tested according to USP <61> and USP <62>) as well as [redacted] (b) (4) provided in this application have been reviewed by the Microbiology reviewer, Dr. Eric Adeeku. Dr. Adeeku has found the information provided regarding microbial quality of the drug product is adequate to support approval of this application.

C. Risk Assessment

From Initial Risk Identification	Assessment

Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay and Related substances	(b) (4)	H	Controlled (b) (4)	Acceptable (L)	Any changes to (b) (6) process should be supported by results (b) (4) (b) (4)
Bulk Homogeneity	(b) (4)	H	Controlled (b) (4)	Acceptable (L)	Risk of impacts on the homogeneity of the bulk product (b) (4)
Purity	Impurities leaching from the proposed container closure systems during shelf-life storage.	M	Determined as insignificant through testing of the container closures for extractables/ leachables	Acceptable (L)	Any changes to container closure systems may require additional extractables/leachables testing.

D. List of Deficiencies for Complete Response: None

Application Technical Lead:

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

Hamid Shafiei

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LABELING

R. Regional Information

1.14 Labeling

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

AKLIEF® (trifarotene) Cream 50 mcg/g
For topical use
Initial U.S. Approval: 2019

2) DOSAGE FORMS AND STRENGTHS

Each gram of AKLIEF Cream contains 50 mcg (micrograms) of trifarotene in a white cream. (3)□

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	AKLIEF® (trifarotene)	Provided. **Satisfactory**
Dosage form, route of administration	Cream (b) (4) For topical use	Provided but needs revision. (b) (4) should be removed. "Cream" should be changed "cream". **Unsatisfactory**
Controlled drug substance symbol (if applicable)	Not applicable	Not applicable
Dosage Forms and Strengths (201.57(a)(8))	(b) (4)	Provided but should be revised to "Cream: 0.005% trifarotene" **Unsatisfactory**
Whether the drug product is scored	Not applicable	Not applicable

Revised the Title to "AKLIEF® (trifarotene) cream for topical use". Revised the Dosage Form and Strength to "Cream: 0.005% trifarotene".

2. "FULL PRESCRIBING INFORMATION

1) #3: DOSAGE FORM AND STRENGTHS

Cream.
Each gram of AKLIEF Cream contains 50 mcg (micrograms) of trifarotene in a white cream

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	Cream	Provided. **Satisfactory**
Strengths: in metric system	Each gram of AKLIEF Cream contains 50 mcg (micrograms) of trifarotene in a white cream	Provided but should be revised to "Cream: 0.005%. Each gram of AKLIEF contains 50 mcg of trifarotene in a white cream". **Unsatisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable	Not applicable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	a white cream	Provided **Satisfactory**

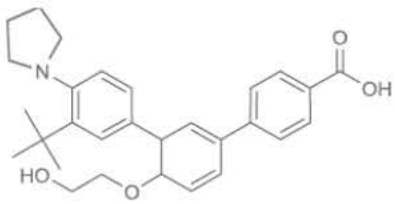
The following revision is recommended:

Cream: 0.005%. Each gram of AKLIEF contains 50 mcg of trifarotene in a white cream".

2) #11: DESCRIPTION

AKLIEF Cream (b) (4)

The chemical name of trifarotene is 3"-tert-Butyl-4'-(2-hydroxy-ethoxy)-4"-pyrrolidin-1-yl-[1,1',3',1"]terphenyl-4-carboxylic acid, (b) (4) (b) (4) and following structural formula:



(b) (4)

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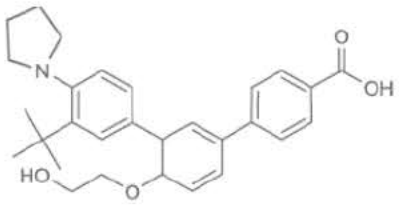
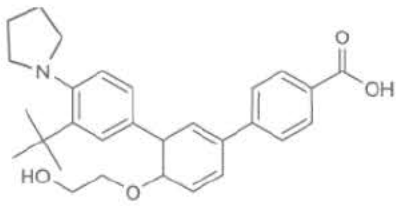
QUALITY ASSESSMENT

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	(b) (4)	Provided but should be revised to "AKLIEF Cream for topical use contains 0.005% (50mcg/g) trifarotene." **Unsatisfactory**
Dosage form and route of administration	(b) (4)	Provided **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable	Not applicable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	(b) (4)	Provided but some editorial changes will be suggested. **Satisfactory**
Statement of being sterile (if applicable)	Not applicable	Not applicable
Pharmacological/ therapeutic class	(b) (4)	Provided but some editorial changes will be suggested. **Satisfactory**
Chemical name, structural formula, molecular weight	The chemical name of trifarotene is 3"-tert-Butyl-4'-(2-hydroxy-ethoxy)-4"-pyrrolidin-1-yl-[1,1',3',1"]terphenyl-4-carboxylic acid (b) (4) and following structural formula: 	Provided but some editorial changes will be suggested. **Satisfactory**
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Not provided	Not Provided. **Unsatisfactory**

The following revision is recommended:

AKLIEF Cream for topical administration contains 0.005% (50mcg/g) trifarotene. Trifarotene is a terphenyl acid derivative (b) (4)

The chemical name of trifarotene is 3"-tert-Butyl-4'-(2-hydroxy-ethoxy)-4"-pyrrolidin-1-yl-[1,1',3',1"]terphenyl-4-carboxylic acid. Trifarotene has the molecular formula of $C_{29}H_{33}NO_4$, the molecular weight of 459.58, and the following structural formula:



Trifarotene is a white to off-white to slightly yellow powder with the melting of 245°C It is practically insoluble in water with pKa1 of 5.69 and pKa2 of 4.55.

AKLIEF (trifarotene) Cream, 0.005% contains the following inactive ingredients: (b) (4)

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

AKLIEF Cream is white in color, and is supplied as follows: (b) (4)

- 30 gram pump NDC 0299-5935-30
- 45 gram pump NDC 0299-5935-45
- 75 gram pump NDC 0299-5935-75

Storage and handling

- Store at 20 to 25˚C (68 to 77˚F) with excursions permitted to 15°to 30°C (59° to 86°F).

(b) (4)

- Keep out of reach of children.
- Keep away from heat.

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	Cream	Strength of the dosage form not provided. **Unsatisfactory**
Available units (e.g., bottles of 100 tablets)	(b) (4) 30 gram pump 45 gram pump 75 gram pump	Provided. **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4) • 30 gram pump NDC 0299-5935-30 • 45 gram pump NDC 0299-5935-45 • 75 gram pump NDC 0299-5935-75	Provided. **Satisfactory**
Special handling (e.g., protect from light)	(b) (4) Keep out of reach of children. Keep away from heat. (b) (4)	Provided **Satisfactory**
Storage conditions	-Store at 20 to 25˚C (68 to 77˚F) with excursions permitted to 15°to 30°C (59° to 86°F).	Provided. **Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Marketed by: Galderma Laboratories, L.P. Fort Worth, Texas 76177 Made in Canada	Provided at the end of the PI. **Satisfactory**

The following revision is recommended:

AKLIEF Cream, 0.005% is provided as a white cream supplied in the following packaging configurations with corresponding NDC numbers:

(b) (4)

- 30 gram pump NDC 0299-5935-30
- 45 gram pump NDC 0299-5935-45
- 75 gram pump NDC 0299-5935-75

Storage and handling

- Store at 20 to 25˚C (68 to 77˚F) with excursions permitted to 15°to 30°C (59° to 86°F).

(b) (4)

- Keep out of reach of children.
- Keep away from heat.

(b) (4)

II. Labels

1. IMMEDIATE CONTAINER

(b) (4)

30-g pump/bottle label

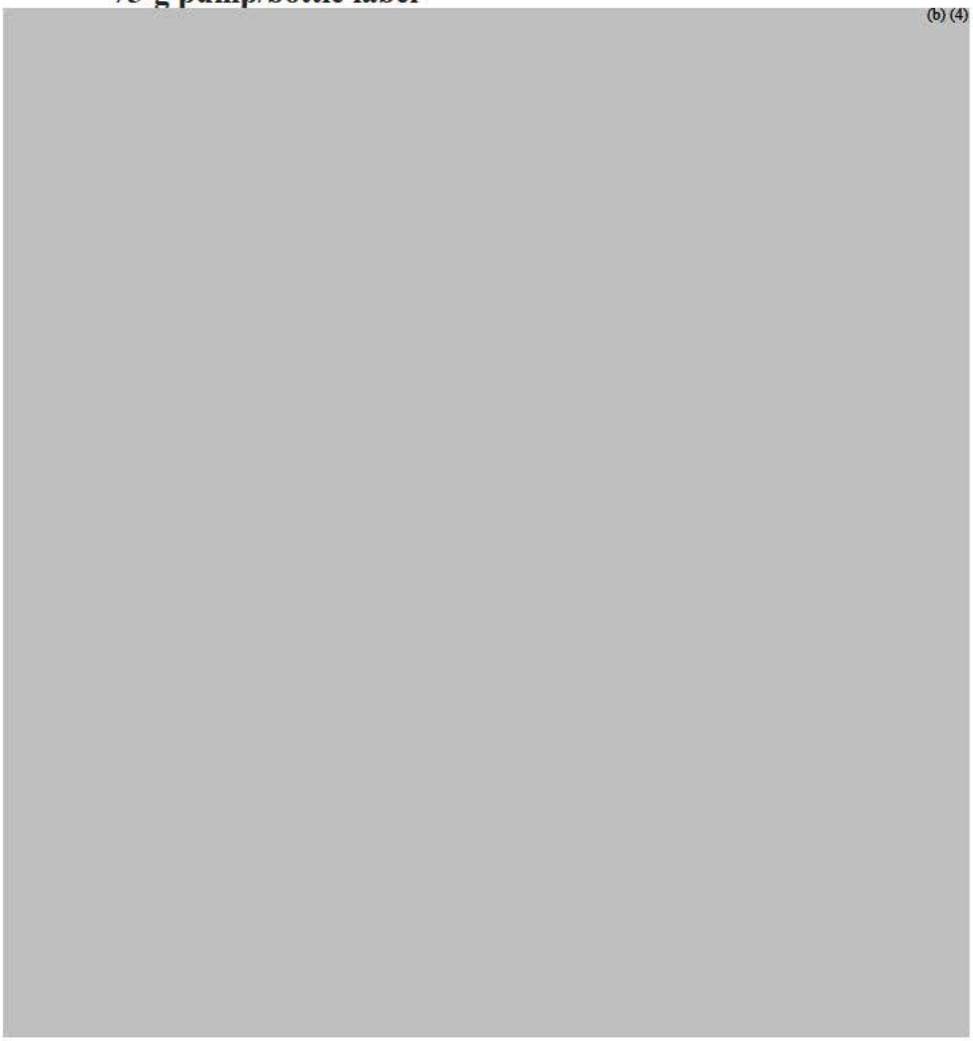
(b) (4)

45-g pump/bottle label

(b) (4)

75-g pump/bottle label

(b) (4)



QUALITY ASSESSMENT

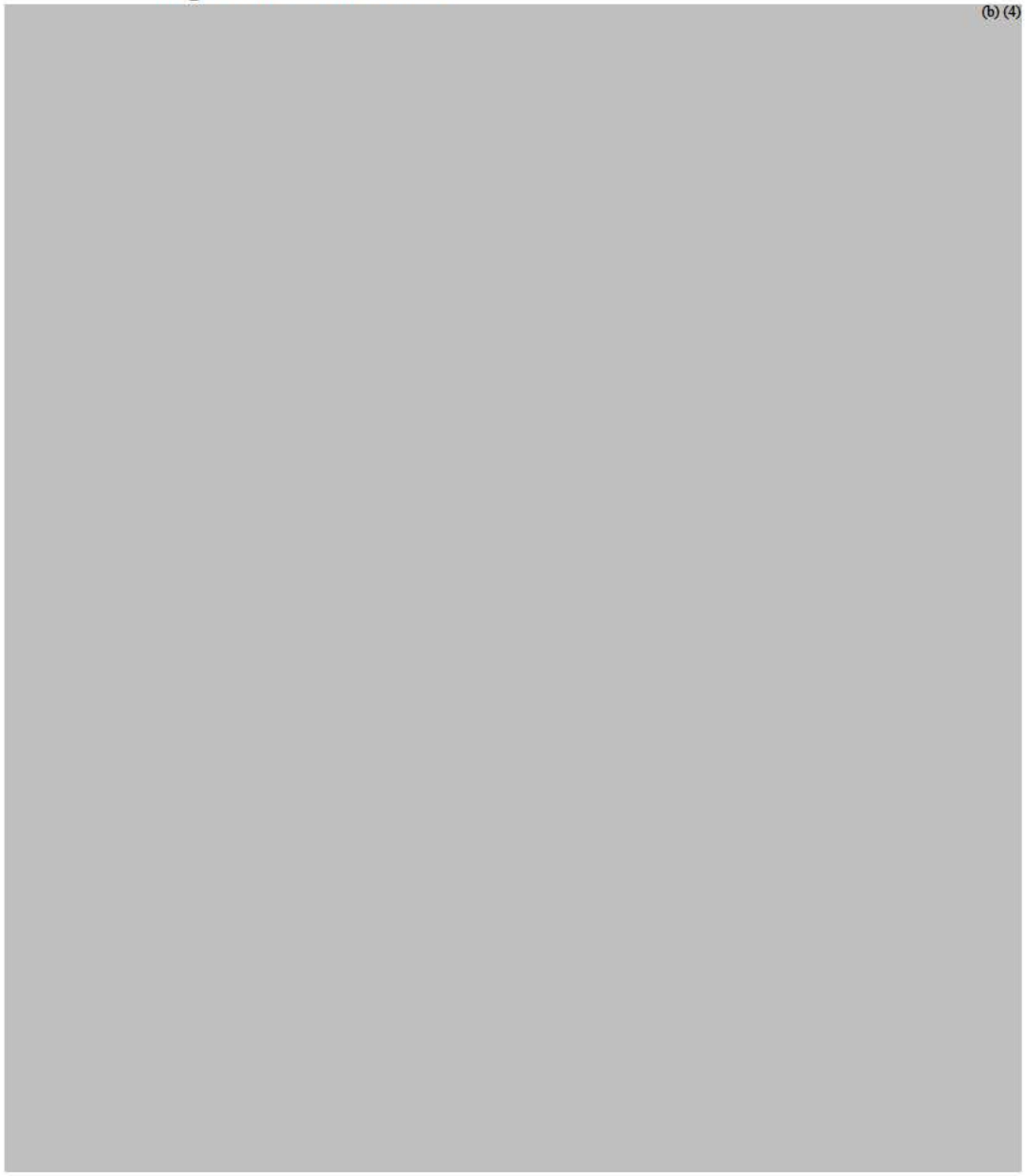
Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4)	Provided. **Satisfactory**
Dosage strength	(b) (4)	Provided but its incorrect. The strength should changed to 0.005% **Unsatisfactory**
Net contents	(b) (4) NET WT 30g NET WT 45g NET WT 75g	Provided. **Satisfactory**
"Rx only" displayed prominently on the main panel	Displayed.	Provided. **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed on each packaging configuration.	Provided. **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	The location for lot number and expiration is displayed.	Provided. **Satisfactory**
Storage conditions	Displayed: Storage: Store at a controlled room temperature of 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86°F).	Provided. **Satisfactory**
Bar code (21CFR 201.25)	Location for barcode is displayed.	Provided???? **Satisfactory**
Name of manufacturer/distributor	Displayed: Marketed by: GALDERMA LABORATORIES, L.P. 14501 North Freeway Fort Worth, TX 76177 USA Made in Canada	Provided. **Satisfactory**
And others, if space is available	For topical use only Not for oral, ophthalmic or intravaginal use. Usual dosage: Apply a thin layer to affected areas of the face and/or trunk once a day. See package insert for complete prescribing information.	Provided. **Satisfactory**

Change the strength to 0.005%.

2. CARTON LABELS:

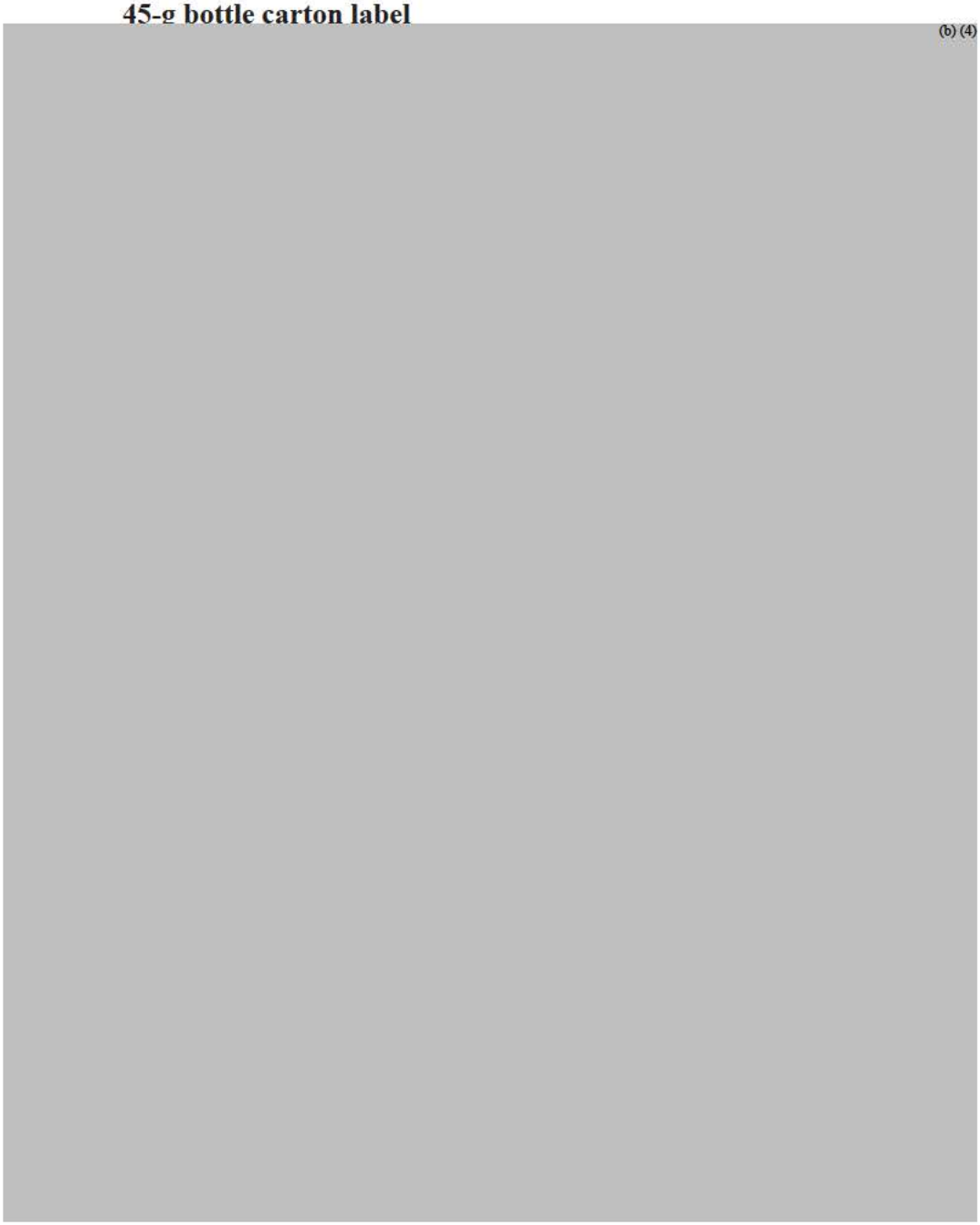
30-g bottle carton label

(b) (4)



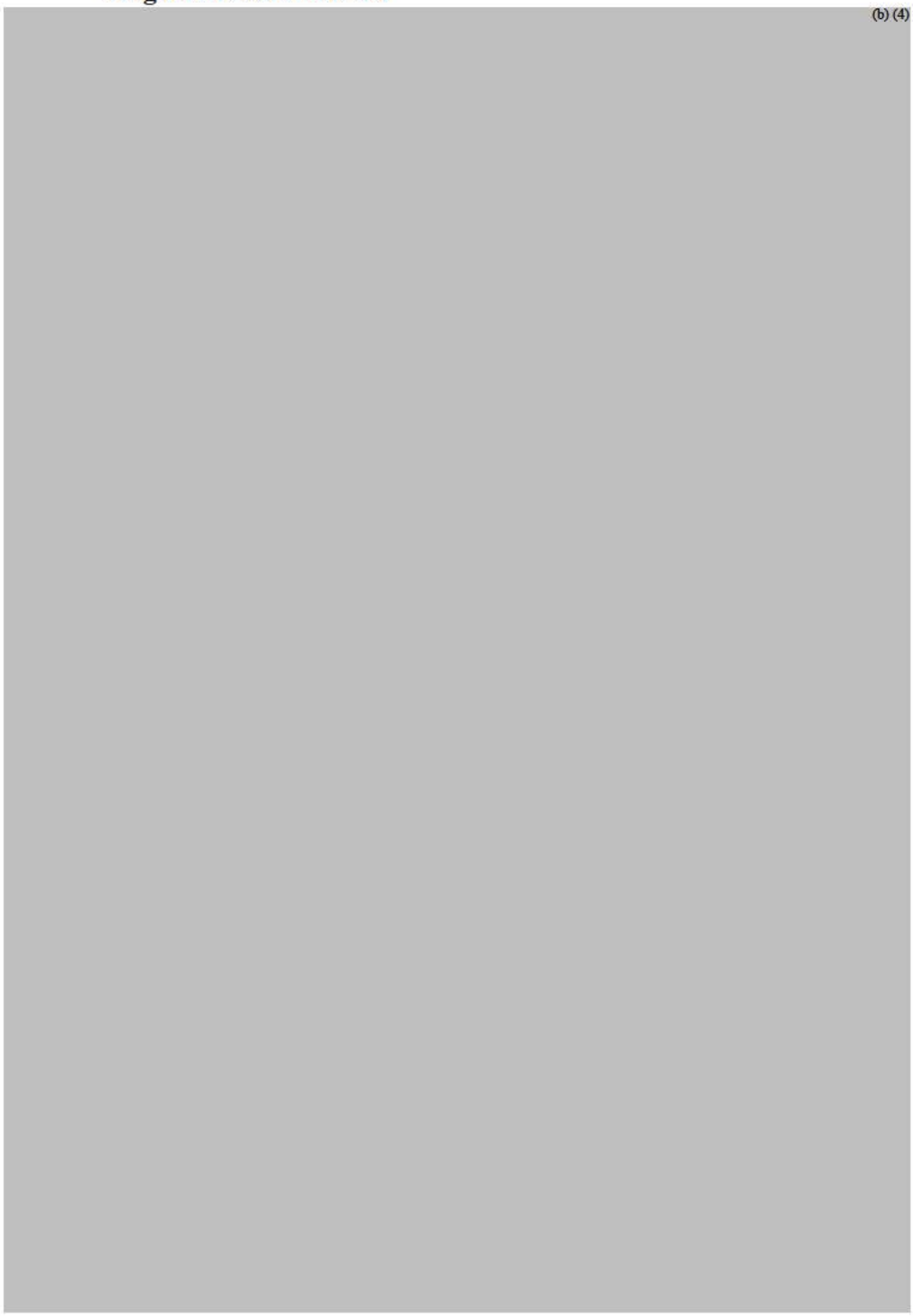
45-g bottle carton label

(b) (4)



75-g bottle carton label

(b) (4)



QUALITY ASSESSMENT

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name (font size and prominence (21 CFR 201.10(g)(2))	Displayed.	Provided. **Satisfactory**
Dosage strength	(b) (4)	Provided but it is incorrect. The strength should be changed to 0.005%. **Satisfactory**
Net contents	30g 45g 75g	Provided. **Satisfactory**
"Rx only" displayed prominently on the main panel	Displayed	Displayed. **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed	Displayed. **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	The location on the carton where the lot number and expiration will be placed has been designated.	Provided. **Satisfactory**
Storage conditions	Store at a controlled room temperature of 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86°F).	Provided. **Satisfactory**
Bar code (21CFR 201.25)	Not displayed.	Not provided. **Unsatisfactory**
Name of manufacturer/distributor	Mar k e t ed by: GALDERMA LABORATOR I ES, L.P. 14501 North Freeway Fort Worth, TX 76177 USA Made in Canada	Displayed. **Satisfactory**
And others, if space is available	For topical use only Not for oral, ophthalmic or intravaginal use. Apply a thin layer to affected areas of the face and / or trunk once a day. See package insert for complete prescribing information.	Provided. **Satisfactory**

Add barcode to all packaging cartons and correct the strength to 0.005%

III. LIST OF DEFICIENCIES:

A. Regarding PI

Highlights

Revised the Title to "AKLIEF® (trifarotene) cream for topical use". Revised the Dosage Form and Strength section to "Cream: 0.005% trifarotene".

Full Prescribing Information

#3: Dosage Forms and Strengths

The following revision is recommended:

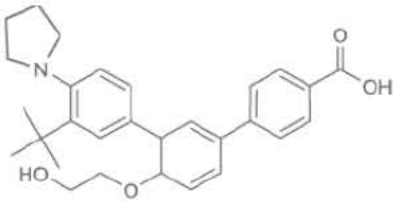
Cream: 0.005%. Each gram of AKLIEF contains 50 mcg of trifarotene in a white cream".

#11: Description

The following revision is recommended:

AKLIEF Cream for topical administration contains (b) (4) (mcg/g) trifarotene. Trifarotene is a terphenyl acid derivative (b) (4) (b) (4)

The chemical name of trifarotene is 3"-tert-Butyl-4'-(2-hydroxy-ethoxy)-4"-pyrrolidin-1-yl-[1,1',3',1"]terphenyl-4-carboxylic acid. Trifarotene has the molecular formula of C29H33NO4, the molecular weight of 459.58, and the following structural formula:



Trifarotene is a white to off-white to slightly yellow powder with the melting of 245°C It is practically insoluble in water with pKa1 of 5.69 and pKa2 of 4.55.

AKLIEF (trifarotene) Cream, (b) (4) contains the following inactive ingredients: (b) (4)

#16: How Supplied/Storage and Handling

The following revision is recommended:

AKLIEF Cream, 0.005% is provided as a white cream supplied in the following packaging configurations with corresponding NDC numbers:

(b) (4)

- 30 gram pump NDC 0299-5935-30
- 45 gram pump NDC 0299-5935-45
- 75 gram pump NDC 0299-5935-75

Storage and handling
- Store at 20 to 25˚C (68 to 77˚F) with excursions permitted to 15°to 30°C (59° to 86°F).

(b) (4)

- Keep out of reach of children.
- Keep away from heat.

(b) (4)

B. Regarding of the Container/Carton Labels:

1) **Immediate Container Label:**

   Correct drug product strength to 0.005% on all container labels

2) **Carton Label:**

   Add barcode to all packaging cartons.

   Correct the drug product strength to 0.005% on all carton labels.

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

- Multiple PI labeling deficiencies have been noted.
- The carton labels require revisions.

Recommendation:

From the ONDP perspective, this application is ***not*** recommended for approval per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name:

Hamid Shafiei, Ph.D.

Reviewer, Branch V
DNDP II/ONDP/OPQ

Secondary Reviewer Name:

I concur with Dr. Shafiei's assessment and his recommendation that the labels and labeling are ***not*** ready for approval in its present form per 21 CFR 314.125 (b)(6) from the ONDP perspective.

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

Hamid Shafiei

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Moo Jhong Rhee

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

DATE: **September 3, 2019**

FROM: **Hamid R. Shafiei, Ph.D.**
Review Chemist (Branch V/DNDP II/ONDP)

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

TO: **Package Insert (PI) and Immediate Containers/Cartons Labeling/Labels review # 1 for NDA 211527**

SUBJECT: **Final ONDP Recommendation from the Labeling/Labels Review Perspective**

In the review # 1 of NDA 211527, this application was not recommended for approval in the form it was presented due to the CMC deficiencies noted in PI labeling and immediate containers (pumps)/cartons labels.

The CMC labeling-label deficiencies identified during the review # 1 have been satisfactorily addressed in the amendment submitted by the applicant on August 12, 2019 (**Attachment I**).

Recommendation: This application is now recommended for **approval** from the ONDP labeling-labels perspective.

Attachment I: Final PI and Labels

A. PI

a) Highlight Section

AKLIEF® (trifarotene) cream, for topical use
Initial U.S. Approval: 2019

----------DOSAGE FORMS AND STRENGTHS----------
Cream: 0.005% trifarotene. (3)

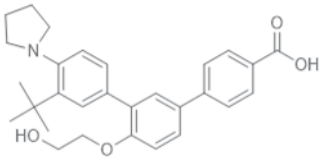
b) Full Prescribing Information

#3: Dosage Forms and Strengths

Cream: 0.005%. Each gram of AKLIEF Cream contains 50 mcg of trifarotene in a white cream.

#11: Description

AKLIEF Cream for topical administration contains 0.005% (50 mcg/g) trifarotene. Trifarotene is a terphenyl acid derivative and is a retinoid. The chemical name of trifarotene is 3”-tert-Butyl-4’-(2-hydroxy-ethoxy)-4”-pyrrolidin-1-yl-[1,1’,3’,1”]terphenyl-4-carboxylic acid. Trifarotene has the molecular formula of C29H33NO4, the molecular weight of 459.58, and the following structural formula:



Trifarotene is a white to off-white to slightly yellow powder with the melting point of 245°C. It is practically insoluble in water with pKa1 of 5.69 and pKa2 of 4.55.

AKLIEF (trifarotene) Cream 0.005% contains the following inactive ingredients: allantoin, copolymer of acrylamide and sodium acryloyldimethyltaurate, dispersion 40% in isohexadecane, cyclomethicone, 5% ethanol, medium-chain triglycerides, phenoxyethanol, propylene glycol, purified water.

#16: HOW SUPPLIED/STORAGE AND HANDLING

AKLIEF Cream, 0.005% is provided as a white cream supplied in the following packaging configurations with corresponding NDC numbers:

- 30 gram pump NDC 0299-5935-30
- 45 gram pump NDC 0299-5935-45

- 75 gram pump NDC 0299-5935-75

Storage and handling

- Store at 20 to 25˚C (68 to 77˚F) with excursions permitted to 15°to 30°C (59° to 86°F).

- Keep away from heat.

- Keep out of reach of children.

B. <u>Container/Carton Labels:</u>

a. Immediate container labels:

30-gram pump label

(b) (4)

45-gram pump label

(b) (4)

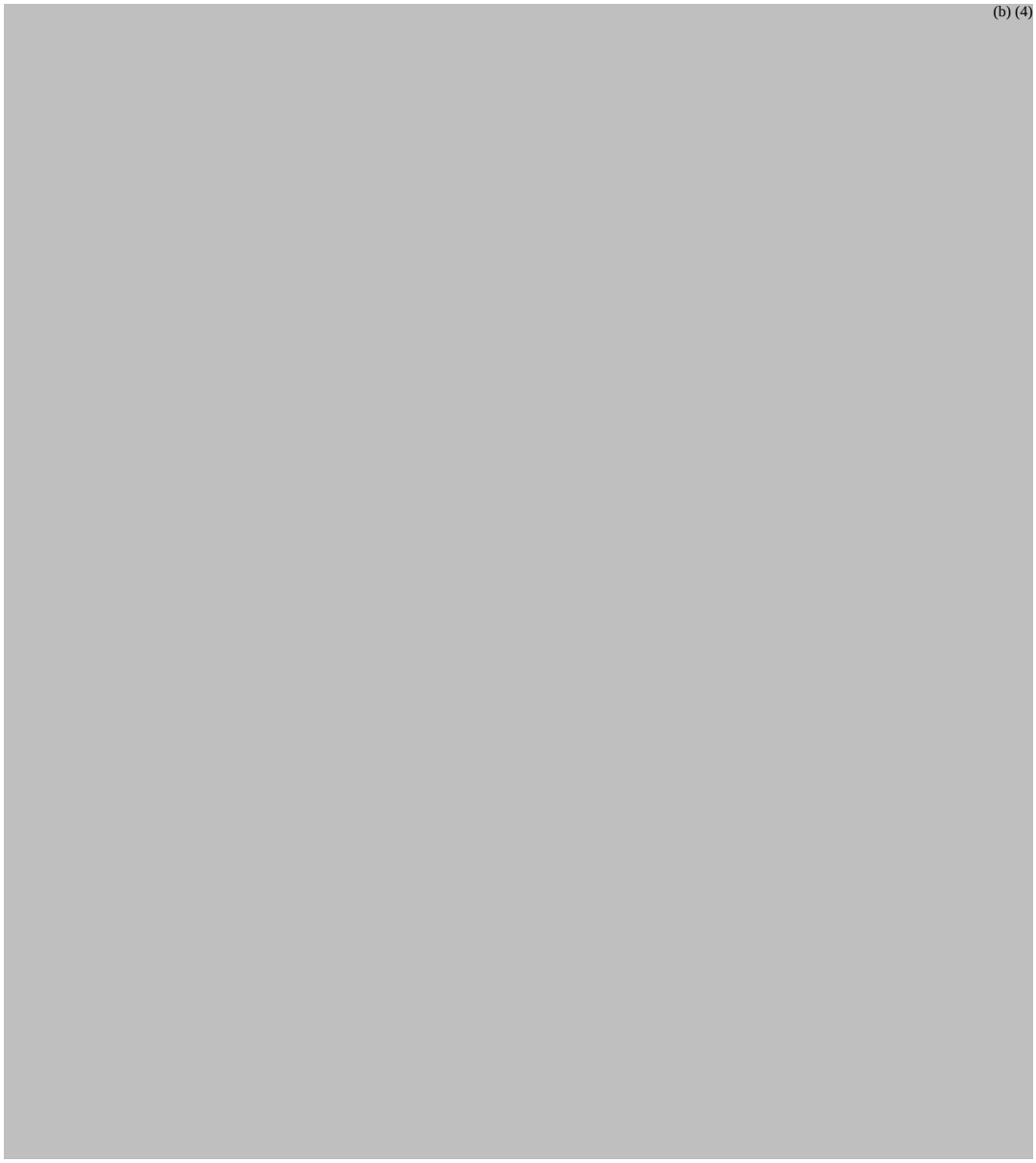
75-gram pump label

(b) (4)

b. Carton Label:

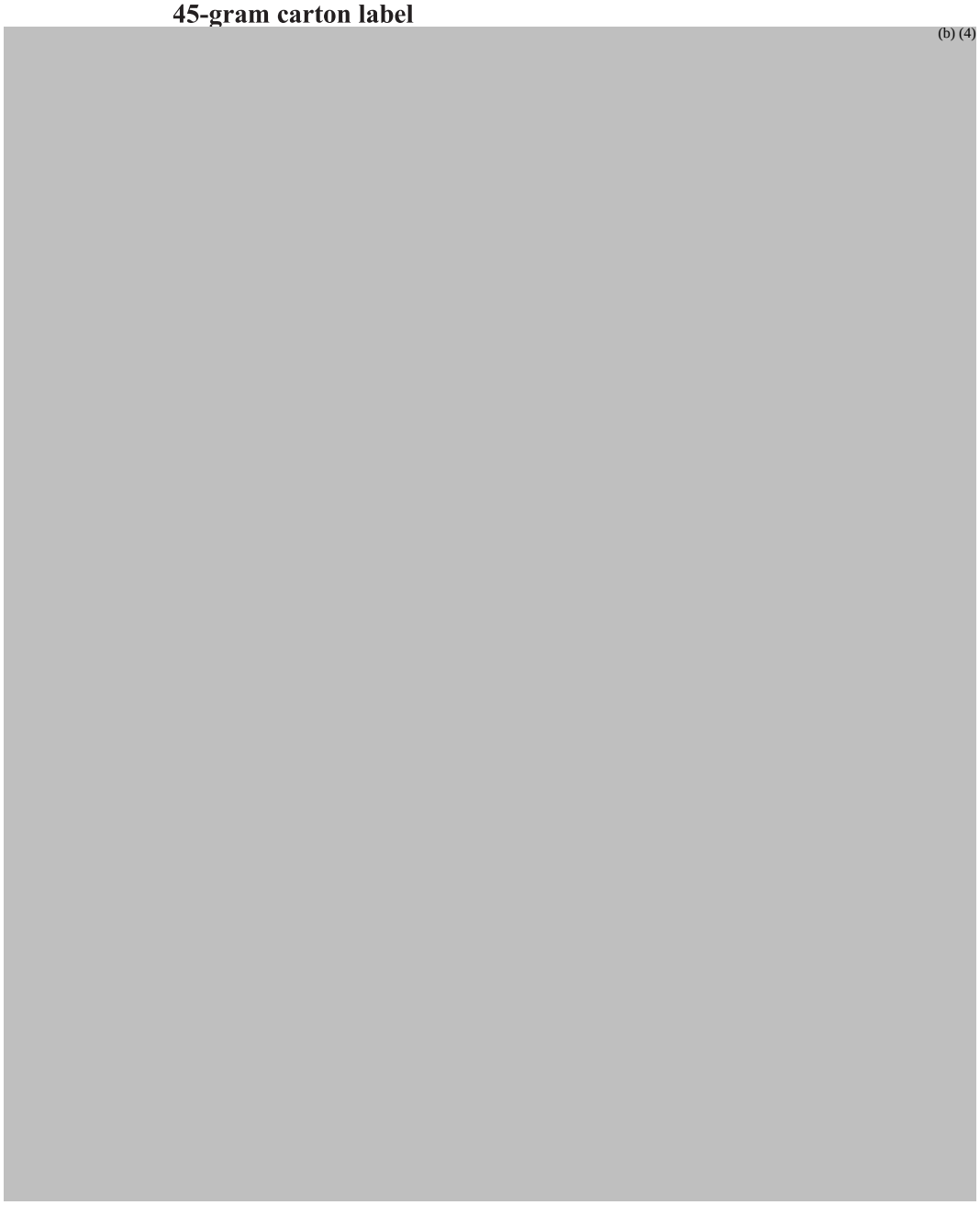
30-gram carton label

(b) (4)



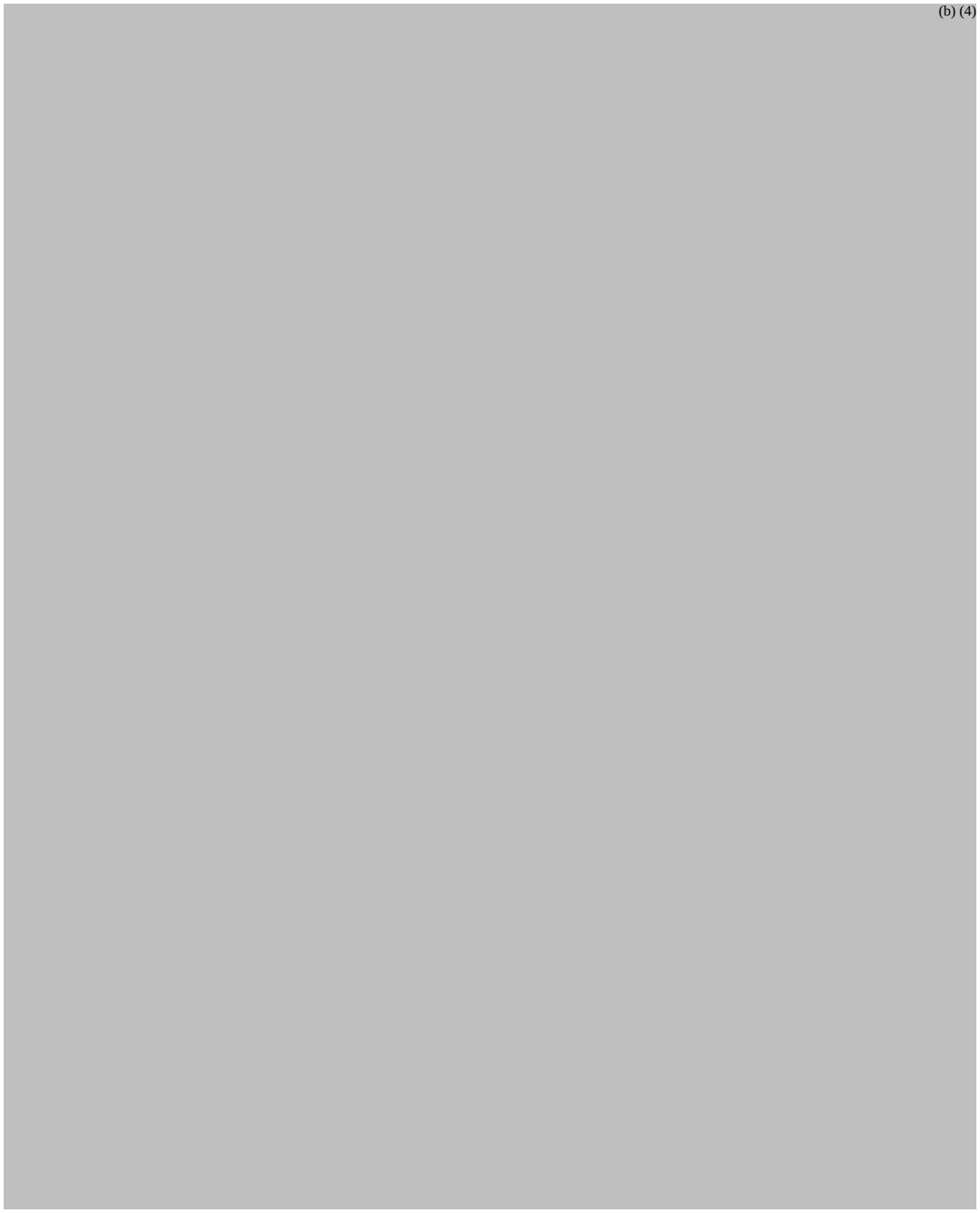
45-gram carton label

(b) (4)



75-gram carton label

(b) (4)



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Moo Jhong Rhee

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BIOPHARMACEUTICS

Product Background: ORIG-1

The current submission is for the approval of Trifarotene, at a concentration of 50 µg/g in a cream vehicle, indicated for the topical treatment of Acne vulgaris [(b) (4)] in patient 9 years of age and older.

NDA: 211527

Drug Product Name / Strength: Trifarotene (CD5789) Cream 50µg/g

Route of Administration: Topical

Applicant Name: Galderma Research and Development LLC.

Review Summary: Adequate

The Applicant submitted in vitro drug release (IVRT) method for Trifarotene Cream drug product and has proposed in vitro release specification as the QC tool. The review is focused on evaluation of proposed IVRT method and acceptance criterion. The Applicant has developed and validated an IVRT method using In Vitro Release Workstation automated system of cells diffusion. The Applicant's proposed drug release acceptance criterion is between [(b) (4)] and [(b) (4)] µg/cm^2/ h$^{1/2}$. The Applicant will conduct IVRT as a routine quality control test at release and only on the three commercial batches in stability studies. The in vitro release method and acceptance criterion are adequate.

Approved IVRT Method and Acceptance Criterion:

Equipment	Membrane	Receptor Medium	Water Bath Temperature	Sampling Times	Magnetic stirring speed	Acceptance criterion
In Vitro Release Workstation	HVHP 0.45µm PVDF Hydrophobic	water/ isopropanol 50/50 v/v	32.5°C ± 1°C	1, 2, 3, 4, 5, 6 hours	600 rpm	[(b) (4)] - [(b) (4)] µg/cm^2/ h$^{1/2}$

In addition to IVRT, there was a minor change in the manufacturing process described later in this review. However, it was believed not to have any clinical impact. Therefore, no further *in vivo* and/or *in vitro* evaluation is warranted at this point.

List Submissions being reviewed:

10/04/2018	NDA 211527/Sequence 0001/Original Submission
03/25/2019	NDA 211527/Sequence 0012/Response to Information Request
05/10/2019	NDA 211527/Sequence 0017/Response to Information Request
06/14/2019	NDA 211527/Sequence 0020/Response to Information Request

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: None

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

IVRT method development:

(b) (6)

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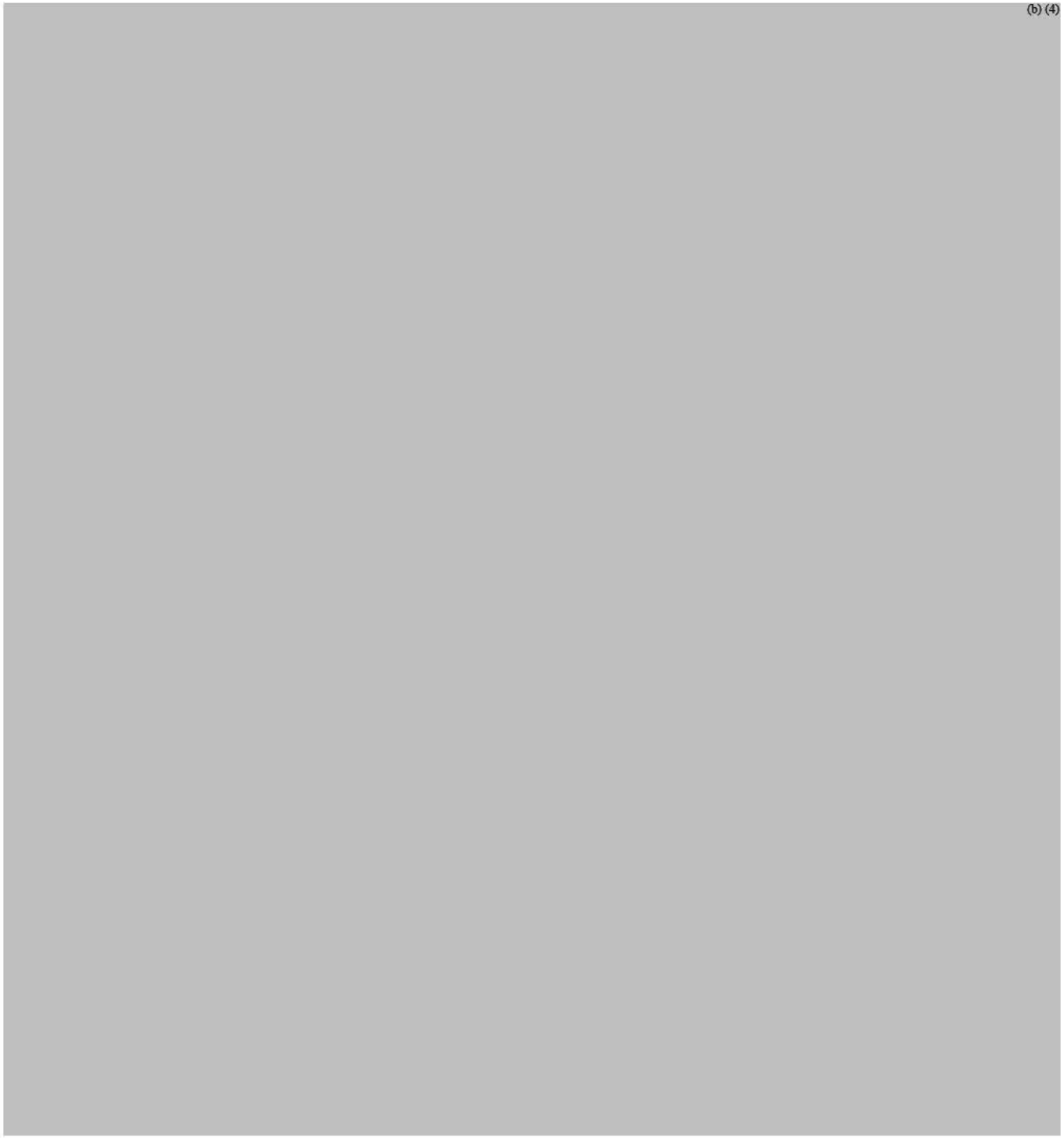
(b) (4)



On June 10, 2019, in an information request, the following was communicated to the Applicant:

1. We note that you have submitted complete in vitro release testing data for Batch 143701 and 143799. Submit additional available in vitro release data for Phase 3 and/or exhibit batches.

2. You proposed to conduct IVRT on the first three commercial batches. IVRT should be conducted as a routine quality control test for all future commercial batches to ensure consistent

performance from batch to batch. We request that you add IVRT testing and the IVRT acceptance criterion to the drug product specifications

On June 14, 2019, in Sequence 0020, the Applicant responded:

Regarding question 1, the Applicant resubmitted the same IVRT data shown above that had previously been submitted in Sequence 0017.

The applicant stated that the proposed limit range of (b) (4) to (b) (4) µg/cm2/h½ for trifarotene release rate was tentatively established, based on data obtained on these three industrial batches and will be confirmed when more information is gained, after testing the first three commercial batches.

Reviewer's comments

Although IVRT data were presented on only one fresh batch, the data from stability batches exhibited a low %RSD. Therefore, using these data to set the acceptance criterion carries a low risk. The IVRT data submitted by the Applicant is adequate.

Regarding question 2, the Applicant stated that they will conduct IVRT as a routine quality control at release and only on the three commercial batches in stability studies.

Reviewer's comments

The proposed product will have IVRT for all batches at release. Also, the stability data presented at various time points on 3 batches showed no significant change in release characteristics over time. The Applicant's response is adequate.

Bridging of Formulations

All batches used in the Phase 3 clinical studies (long-term safety and pivotal Phase 3 studies) were manufactured at the (b) (4) site (b) (4) The clinical batch used for the long-term safety study (Batch 115009, manufactured in May 2014) was manufactured according to the process described in Figure 1 on p.9 of the Pharmaceutical Development Report in Module 3.2.P.2.3. A study was then performed (b) (4) (b) (4) The active batches for pivotal Phase 3 clinical supplies (Trifarotene 50 µg/g cream batch 123648 manufactured in February 2015 and batch 148856, manufactured in February 2017) were manufactured according to (b) (4) process, which is the process intended for the manufacturing of the to-be marketed product, as described in Module 3.2.P.3.3. According to SUPAC-SS guidance, this constitutes a Level 2 process change where bridging by IVRT data is recommended. However, the Applicant did not submit IVRT results for batches 115009, 123648,

and 148856. The Applicant was asked to submit these data in an information request dated May 4, 2019. On May 10, 2019 the Applicant responded by resubmitting IVRT data from other batches; however, the Applicant stated that "No IVRT results for batches 115009, 123648, and 148856 are available." According to Dr. Tapash Ghosh, an expert in reviewing biopharmaceutics of topical dosage forms, with the slight change in the manufacturing process for 2 clinical batches, (b) (4) the exact rate and extent and ultimate clinical impact (efficacy and safety) of this change is unknown. However, all these 3 batches 115009, 123648, and 148856 were evaluated in clinical studies (either in long term safety or pivotal Phase 3 studies). Therefore, the clinical reviewer will be able to compare the safety information from all these batches. If any unusual safety signal arises from any batch, we need to find the root cause. If not, we can say that this minor change in the manufacturing process will carry a very **low safety risk** from the clinical perspective. Accordingly, the clinical reviewer was consulted to opine in this regard.

According to the medical officer Dr. Denise Cook, the clinical reviewer for this NDA, there were no differences in the safety signals from the 12 week pivotal trials and the 52 week long term safety trial. Overall given the nature of the API (low permeability), local effect (not systemic) of the drug product and chronic indication for a non-life threating disease condition, it is believed that overall risk from the product due to this minor manufacturing process change is *very low*. Therefore, no further *in vivo* and/or *in vitro* evaluation is warranted at this point.

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name:

Bryan Ericksen, Ph.D.

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

Vidula Kolhatkar, Ph.D.

Tertiary Reviewer Name:

Tapash Ghosh, Ph.D.

APPENDIX 1

IVRT Data Tables

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Bryan Ericksen

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Vidula Kolhatkar

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Tapash Ghosh

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	211527
Assessment Cycle Number	01
Drug Product Name/ Strength	CD5789 Trifarotene Cream / 50 µg/g
Route of Administration	Topical (dermal)
Sponsor Name	Galderma Research and Development, LLC
Therapeutic Classification/ OND Division	N/A
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
1	10/04/2018
18	05/20/2019

List Submissions being assessed (table):

Submit	Received	Review Request	Assigned to Reviewer
10/04/2018	10/04/2018	N/A	05/01/2019
05/20/2019	05/20/2019	N/A	05/20/2019

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

Remarks:
This is an electronic submission.
No comparability protocols are included.
Goal date is 10/04/2019.

Review also contains response to the Agency's 05/08/2019 information request that was provided in the 05/20/2019 submission.

Assessment Summary:
The submission is **recommended** for approval based on sterility assurance.

Concise Description of Outstanding Issues
No outstanding issues remain.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(section 3.2.P.1).

The quantitative composition of the drug product and the role of each ingredient are described below.

Ingredients	Formula (b) (4) 50 µg/g		Function
	% (w/w)	mg/g	
Trifarotene (in-house)	0.005	0.05	Active substance
Purified water, USP	(b) (4)		
Propylene glycol, USP			
Allantoin, USP			
Medium-chain triglycerides, NF			
Phenoxyethanol, Ph. Eur (b) (4)			
Cyclomethicone, NF			
Copolymer of acrylamide and sodium acryloyldimethyltaurate, dispersion 40 % in Isohexadecane, (in-house)			
Ethanol (b) (6) USP			

Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

(section 3.2.P.7).

The proposed container closure systems for Trifarotene 50 µg/g cream consists of:

White (b) (4) bottle system consisting of a (b) (4) bottle (b) (6) and a (b) (6) pump/overcap. The bottle systems are available in (b) (4) 30 mL, 50 mL and 75 mL formats, respectively filled to (b) (4) 30 g, 45 g and 75 g with the drug product.

(b) (4)

Adequate

(b) (4)

(b) (4)

Results

(b) (4)

P.3 MANUFACTURE

P.3.1 MANUFACTURERS

(b) (4)

Adequate

P.3.3 DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS

Overall Manufacturing Operation

(section 3.2.P.3.3).

(b) (4)

(b) (4)

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(b) (4)

P.8 STABILITY

P.8.1 STABILITY SUMMARY AND CONCLUSION

(section 3.2.P.8.1).

Three registration batches each of Trifarotene 50 µg/g cream manufactured were placed on stability under the following storage conditions (studies PSP.0195 and PSP 0232):

- Long-term storage conditions: (25 ± 2 °C/60 ± 5 % RH)
- Accelerated storage conditions: (40 ± 2 °C/75 ± 5 % RH)
- Cold storage conditions: (5 ± 3 °C)
- Cold/warm cycles: (5 ± 3 °C/40 ± 2 °C with 75 ± 5 % RH)
- Freeze/thaw cycles: (-20 ± 3 °C/25 ± 2 °C with 60 ± 5 % RH)

The sponsor proposes a 36-month shelf life for Trifarotene 50 µg/g cream packaged in the proposed container closure system ((b) (4) 30 g, 45 g, or 75 g) based on:

- 36-month formal stability data obtained under long-term conditions for (b) (4) 30 g, 45 g, 75 g (b) (6) pump system (study PSP.0195)
- 18-month formal stability data obtained under long-term conditions for (b) (6) 75 g (b) (6) pump system (study PSP.0232)

Adequate

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

(section 3.2.P.8.2).

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
TAMC	(b) (4) / USP <61> / and USP <62>	NMT (b) (4) CFU/g
TYMC		NMT CFU/g
S. aureus		Absence
P. aeruginosa		Absence
B. cepacia	Not provided	Not provided

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

- **Stability storage conditions:** 25 ± 2 °C/60 ± 5 % RH

Test	Time (Months)								
	0	3	6	9	12	18	24	36	48

TAMC	X		X	
TYMC	X		X	
S. aureus	X		X	
P. aeruginosa	X		X	
B. cepacia	NP		NP	

NP: Not provided (please see below).

Post Approval Stability Commitment

The sponsor commits to complete long term and accelerated stability studies for this submission (reviewer is assuming this is at least three previously describe above). Thereafter, on an annual basis, at least one production lot will be added to the stability program.

Adequate

P.8.3 STABILITY DATA

(section 3.2.P.8.3).

Stability data are provided for 12 batches of the drug product under study PSP 0195 (formal stability study). The 36-month time point provided for all the lots tested indicate that all lots met specification for microbial limit and demonstrated the absence of *S. aureus* and *P. aeruginosa*. No tests were performed for *B. cepacia* complex. Lots also passed [redacted] (b) (6) [redacted] (b) (4) testing performed at the 36-month time point for bacteria, yeast or molds.

The following deficiency was issued in the Agency's 05/08/2019 microbiology information request:

Deficiency: It is acknowledged that acceptable stability data were provided for TAMC, TYMC, absence of S. aureus and P. aeruginosa. Please revise the stability program to include testing to confirm the absence of B. cepacia and provided stability data to demonstrate the presence or absence of B. cepacia in manufactured lots.

Response: The applicant commits to include a test for the absence of *B. cepacia* at release as part of the on-going stability program. Section 3.2.P.8.1 was revised accordingly.

Test	Method	Acceptance Criteria	Time Point (Months)								
			0	3	6	9	12	18	24	36	48
TAMC	[redacted] (b) (4)	NMT [redacted] (b) (4) CFU/g	√							√	
TYMC		NMT [redacted] CFU/g	√							√	
S. aureus		Absence/g	√							√	
P. aeruginosa		Absence/g	√							√	
B. cepacia		Absence/g	√							√	

Adequate

R REGIONAL INFORMATION

Executed Batch Records

(section 3.2.R).

Executed batch records for the 148856.

Adequate

Post-Approval Commitments

None provided.

Adequate

MICROBIOLOGY LIST OF DEFICIENCIES

None

Primary Microbiology Assessor Name and Date:

Eric Adeeku, 05/21/2019

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

Jesse Wells, 05/21/2019

Eric Adeeku

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Jesse Wells

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