CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209305Orig1s000

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: **December 14, 2017**
From: **Yichun Sun, Ph.D.**
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

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

To: CMC Review #1 of NDA 209305

Subject: Final Approval Recommendation for NDA 209305

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

Label/Labeling

On December 13, 2017, the NDA applicant submitted an amendment providing the finalized package insert (PI), and the container, sleeve, blister lidding and carton labels. All the labels/labeling issues are now satisfactorily resolved. The CMC sections of the final package insert, and mock up container, sleeve, blister lidding and carton labels are attached (**Attachment - 1**).

Recommendation:

The revised package insert and mock-up container, sleeve, blister lidding and carton labels are now satisfactory from the CMC perspective. Therefore, from the OPQ's perspective, this NDA is recommended for **APPROVAL** with an expiration dating period of 24 months for the drug products when stored at room temperature.

Application Technical Lead's Assessment and Signature

The NDA is recommended for approval from a quality perspective.

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
12/14/2017

Attachment - 1 (CMC Sections of the Finalized Labeling and Container Label)

1. Package Insert

(a) "Highlights" Section

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

——————DOSAGE FORMS AND STRENGTHS——————
Topical solution: 40% (w/w) hydrogen peroxide (3)

(b) "Full Prescribing Information" Section

#3. Dosage Form and Strength

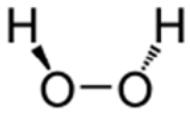
3. DOSAGE FORMS AND STRENGTHS
ESKATA topical solution is a clear, colorless solution containing 40% (w/w) hydrogen peroxide.

#11. Description

11. DESCRIPTION
ESKATA (hydrogen peroxide) topical solution, 40% (w/w) is a clear, colorless solution for topical administration, which contains the active ingredient, hydrogen peroxide.

The chemical name of hydrogen peroxide is dihydrogen dioxide.

The molecular formula of hydrogen peroxide is H_2O_2 and the molecular weight is 34.01. Hydrogen peroxide is represented by the following structural formula:



ESKATA contains 40% (w/w) hydrogen peroxide in an aqueous solution of isopropyl alcohol and water.

#16. How Supplied/Storage and handling

16. HOW SUPPLIED/STORAGE AND HANDLING
ESKATA (hydrogen peroxide) topical solution, 40% (w/w) is a clear, colorless solution and is supplied in a unit dose package. The available carton packages are presented below:

Dosage Strength	Fill Volume	Deliverable Volume	Number of unit dose packages per carton	NDC#
40% (w/w)	1.5 mL	0.7 mL	1	71180-001-01
			3	71180-001-03
			12	71180-001-12
	2.2 mL	1.3 mL	1	71180-002-01
			3	71180-002-03
			12	71180-002-12

Store ESKATA at controlled room temperature of 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59° F and 86° F).

2. Labels

Tube Label (0.7 mL)

(b) (4)

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

Yichun Sun

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Moo Jhong Rhee

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QUALITY ASSESSMENT

Recommendation:

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

NDA 209305
Review # 1

Drug Name/Dosage Form	ESKATA™ (hydrogen peroxide) topical solution
Strength	40% (w/w)
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Aclaris Therapeutics, Inc.
US agent, if applicable	Christopher Powala 101 Lindenwood Drive Malvern, PA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	02-24-2017	All
Amendment	04-12-2017	Facility
Amendment	05-04-2017	Quality microbiology
Amendment	07-05-2017	Drug product manufacturing process
Amendment	07-21-2017	Device - CDRH
Amendment	08-04-2017	Device - CDRH
Amendment	08-11-2017	Drug product
Amendment	09-13-2017	Drug product manufacturing process
Amendment	10-12-2017	Drug product
Amendment	10-16-2017	Drug product manufacturing process

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Jeffrey Medwid	Branch II/Division of New Drug API
Drug Product	Sarah Ibrahim	Branch V/Division of New Drug Products II
Process	James Norman	Branch V/Division of Process Assessment III
Microbiology	Jennifer Sykora	Branch I/Division of Microbiology Assessment
Facility	Brian Ryan	Branch III/Division of Inspection Assessment
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Bamidele (Florence) Aisida	Branch I/Division of Regulatory and Business Management I/Office of Program and Regulatory Operations
Application Technical Lead	Yichun Sun	Branch V/Division of New Drug Products II

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Hydrogen Peroxide (b) (4)	1	October 10, 2017	Adequate

Action codes for DMF Table:

1 – DMF Reviewed.

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

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
End-of-Phase 2 Meeting Minutes	117635	Discussions of development plan for hydrogen peroxide topical solution, 40%.
Pre-NDA Meeting Minutes	117635	Discussions of the content and format of the proposed NDA submission.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	----	N/A	----	----
Pharmacology/Toxicology	----	N/A	----	----
CDRH	Complete	Approval	8/31/2017	Janice L. Ferguson
Clinical	----	N/A	----	----
Other	----	N/A	----	----

Executive Summary

I. Recommendations and Conclusion on Approvability

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

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

The consult review on the applicator of the drug product has been conducted by the Office of Device Evaluation, Center for Devices and Radiological Health (CDRH). The device constituent part of this combination product is recommended for approval by CDRH.

However, the issues on labels/labeling are ***not*** completely resolved at this time.

Therefore, from the OPQ perspective, this NDA is ***not*** ready for approval in its present form per 21 CFR 314.125(b)(6) until the aforementioned issues are satisfactorily resolved (See the **List of Deficiencies** on pp. 13-14).

II. Summary of Quality Assessments

A. Product Overview

The NDA of ESKATA™ (hydrogen peroxide) topical solution, 40% (w/w) is submitted as a 505 (b)(2) application by Aclaris Therapeutics, Inc.

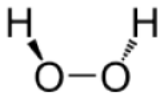
The indication and recommended dose of the drug product are summarized in the following Table.

Proposed Indication(s) including Intended Patient Population	ESKATA™ (hydrogen peroxide) topical solution, 40% (w/w) is indicated for the treatment of seborrheic keratosis lesions.
Duration of Treatment	ESKATA™ topical solution, 40% (w/w) single-use applicator should be activated and the solution applied directly to the targeted lesion(s) up to 4 times, approximately 1 minute apart, during a single in-office treatment session. This product is intended for application by a healthcare professional; it is not intended for application by patients.
Maximum Daily Dose	The safety of more than 4 ESKATA™ treatments has not been determined.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

The active pharmaceutical ingredient (API) used in the drug product, ESKATA™ (hydrogen peroxide) topical solution 40% (w/w), is hydrogen peroxide. Hydrogen peroxide is an oxidizing agent that can induce lipid and membrane peroxidation, protein oxidation, and lead to apoptosis and necrotic cell death. The chemical name for hydrogen peroxide is dihydrogen dioxide. The chemical structure of hydrogen peroxide is:



It has a molecular formula of H_2O_2 and a molecular weight of 34.01 g/mol. The drug substance is being manufactured by (b) (4). Hydrogen peroxide is supplied as (b) (4) (w/w) water solution, which is a clear, colorless solution with a pungent odor.

Detailed CMC information of hydrogen peroxide for this NDA is referred to DMF # (b) (4). The DMF has been reviewed and found adequate to support the **approval** of this NDA. The review on the CMC information of the drug substance has been conducted by Dr. Jeffrey B. Medwid (See **CHAPTER I: Review of Drug Substance**).

Drug Product

The drug product of the NDA is hydrogen peroxide topical solution, 40% (w/w). It contains a concentrated aqueous solution of hydrogen peroxide as the drug substance. The drug product also contains isopropyl alcohol and water as inactive ingredients. The drug product is filled into clear USP (b) (4) glass ampoules at 1.5 mL or 2.2 mL for the intended minimum delivery volume of 0.7 mL and 1.3 mL, respectively. The ampoules are subsequently assembled into applicators which are packaged for individual use. The package for the drug product is an ergonomically designed, single use hand-held applicator, and designed to deliver no less than 0.7 mL (for a 1.5 mL fill) and no less than 1.3 (for a 2.2 mL fill) of drug product solution. Each applicator consists of a (b) (4) tube, protective cap, (b) (4) filter, and a (b) (4) flocked flow-through (b) (4) tip and paper sleeve on the applicator tube. At the time of use, the applicator is squeezed at the labeled area to crush the glass ampoule, and release drug product solution through the in-line filter and through the holed flocked applicator tip for topical administration. The drug product is deemed to be a combination of drug and device.

Specification for ESKATA™ topical solution is adequate to ensure the identity, strength, purity, and quality of the drug product during its expiration dating period. The registration stability studies were conducted at 5°C, 25°C/60%RH, and 40°C/75%RH. The stability data submitted is sufficient to support the proposed expiration dating period of 24 months when stored at room temperature.

The drug product is recommended for **approval** from the drug product perspective. The review on the CMC information of the drug product has been conducted by Dr. Sarah Ibrahim (See **CHAPTER II: Review of Drug Product**). **Note:** An addendum was added for reviewing the updated stability data submitted by the applicant on October 12, 2017.

Device (Applicator)

Each applicator consists of a (b) (4) tube, protective cap, (b) (4) filter, and a (b) (4) flocked flow-through (b) (4) tip and paper sleeve on the applicator tube. A clear USP (b) (4) glass ampoule filled with hydrogen peroxide solution 40% (w/w) is placed inside of the applicator. At the time of application, the ampoule is crushed to release the topical solution and the applicator is used to apply the solution.

Uniformity of dosage units is determined according to USP<905>, acceptance criterion for the 1.5 ampoule is a minimum deliverable volume of no less than 0.7 mL, and for the 2.2 mL fill ampoule is a minimum of no less than 1.3 mL. The applicant provided verification/validation of the essential performance of the drug applicator. All of the performance characteristics met the acceptance criteria that were established. The acceptance criterion (b) (4) for the largest glass particles (b) (4) (b) (4) of the glass particles test is deemed justified by the NDA applicant. There is no potential safety concern for extractables/leachables, either metal or organic, as they are below any safety concern threshold for a topical drug product solution based on the analytical evaluation threshold values in the (b) (4) Extractable Report provided by the applicant. Tests of dispensing accuracy, applicator activation force, applicator expression force and outer tube/sheath puncture force are included in the drug product specification. The stability data for the 1.5 mL fill and 2.2 mL fill applicators provided in the submission are deemed acceptable.

The most significant risk to the product at these various stages is exposing the product to temperatures that are outside of the recommended range or physical damage to the applicator that could lead to decomposition and/or leakage of the applicator contents, respectively. To minimize the risk, the final packaged drug products are transported, stored and delivered by qualified carriers and approved warehouses under strict temperature conditions and only handled at the treatment sites by trained medical personnel.

The device constituent part of this product in the NDA is recommended for **approval** from the device perspective. The review on device constituent part of the drug product has been conducted by Mrs. Janice Ferguson (See **CHAPTER III: Review of Drug Product Applicator**).

Labeling and Labels

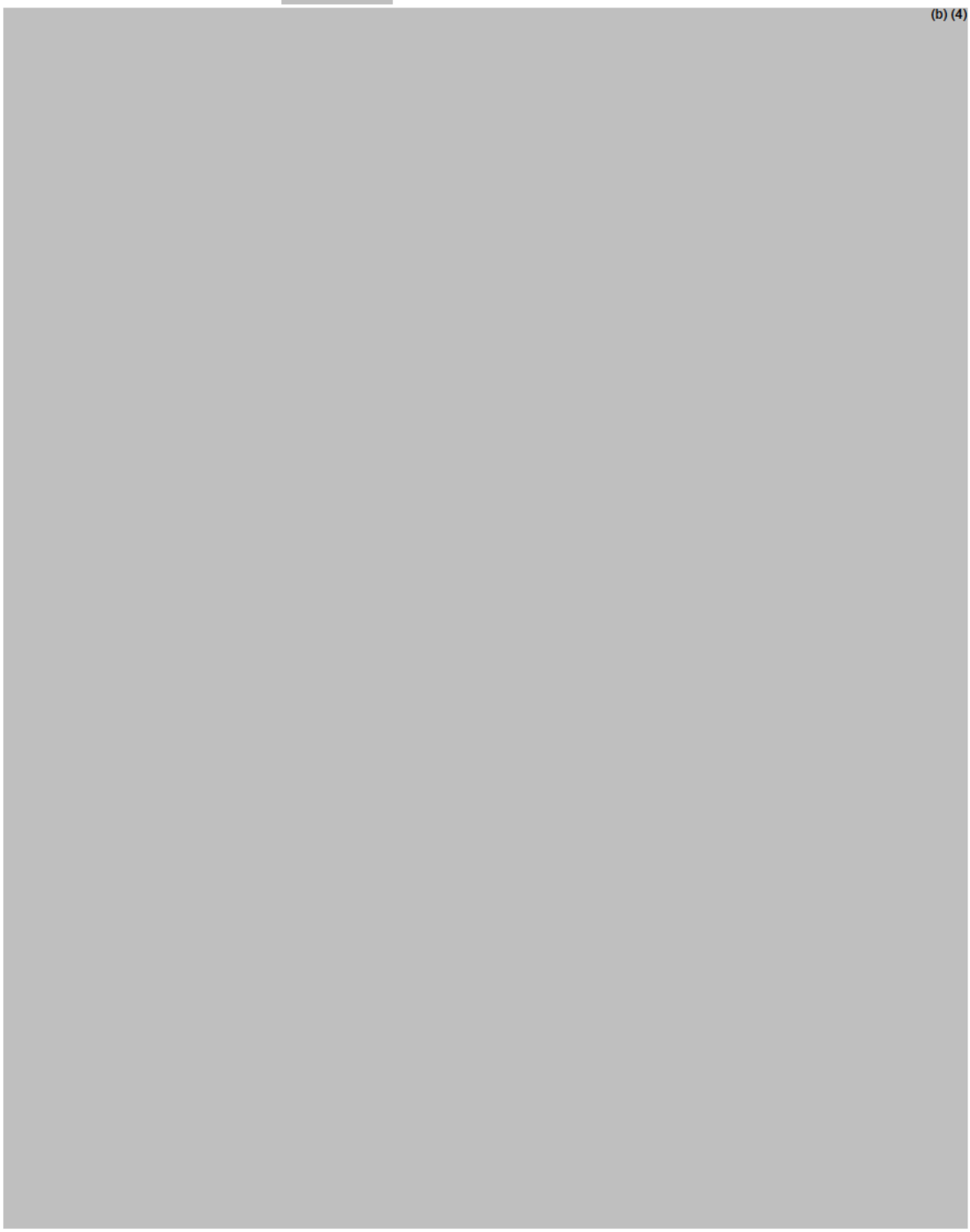
The sections of the Package Insert related to CMC, and container labels of the drug product of the NDA have been reviewed by Dr. Dr. Sarah Ibrahim. Labeling

and label issues have ***not*** been resolved satisfactorily as of this review (See **CHAPTER IV: Review of Labeling and Labels**).

Drug Product Manufacturing Process

The manufacturing process of hydrogen peroxide 40% (w/w) topical solution consists of the following (b) (4):

(b) (4)



(b) (4)

The manufacturing process is adequately developed. The NDA is recommended for **approval** from the perspective of drug product manufacturing process. The review on the drug product manufacturing process has been conducted by Dr. James Norman (See **CHAPTER V: Review of Drug Product Manufacturing Process**).

Biopharmaceutics

N/A

Quality Microbiology

The drug product, Eskata™ (hydrogen peroxide) 40% (w/w) topical solution, is a clear, colorless liquid filled into clear USP (b) (4) glass ampoules with either 1.5 or 2.2 mL volume for single-use. It contains 40% (w/w) of hydrogen peroxide and (b) (4) isopropyl alcohol and sterile water (b) (4). Hydrogen peroxide and (b) (4) are deemed to limit microbial growth. The drug product manufacturing process is adequate for a topical, nonsterile product. The applicant provided sufficient information regarding the microbiological tests and sampling frequency for the stability program. This strategy is deemed sufficient to monitor the microbiological attributes for this preservative-free formulation over its shelf life.

The NDA is recommended for **Approval** from the perspective of quality microbiology. The review on microbiology controls of the drug product of the NDA has been conducted by Dr. Jennifer Sykora (See **CHAPTER VI: Review of Quality Microbiology**).

Facilities

The active ingredient, hydrogen peroxide (b) (4) is manufactured by (b) (4) (FEI: (b) (4)) located in the (b) (4) (b) (4) is a manufacturer and distributor of bulk hydrogen peroxide for various uses in many different industries. (b) (4)

(b) (4)

C. Special Product Quality Labeling Recommendations
N/A

D. Final Risk Assessment (Attachment I)

E. List of Deficiencies (Attachment II)

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Risk Assessment for NDA 209305 [ESKATATM (hydrogen peroxide), Topical Solution 40%(w/w)]

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay (hydrogen peroxide)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	3	27	The assay for hydrogen peroxide content of the drug product is determined by (b) (4) (b) (4) according to USP (b) (4) The content of the drug product is monitored at release and during stability studies. The topical solution is sealed in a glass ampule and the drug product is stored in a temperature controlled warehouse.
pH	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	2	3	18	pH of the drug product is monitored at release and during stability studies. The pH of the ampoule contents is determined according USP <791>. Stability data indicated that the drug product is stable during the proposed expiration dating period.
Leachables (b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	3	27	The leachables of any (b) (4) from the drug product applicator are determined by LC-DAD. (b) (4) of the applicator leached out are monitored by by GC-FID and LC-DAD. There seems to be no potential safety concern for extractables/leachables based on the study report provided.
Microbial Limits (total aerobic	• Formulation	3	3	3	27	Microbial limit tests performed according to USP<61> and

microbial count, total combined yeasts & molds count, ***P. aeruginosa, E. coli, S. aureus, C. albicans, Clostridium sporogenes, Salmonella typhimurium*****)**	• Raw materials • Process parameters • Scale/equipment • Site					USP<62> are included in the drug product specification. Hydrogen peroxide is an antiseptic agent, which should inhibit microbial growth.
Uniformity of Dosage Units	• Process parameters • Scale/equipment • Site	3	3	2	18	The test is performed according to USP <905>. The weight of the filled ampules are checked during the filling process.
Glass Particles	• Container components • Process parameters	3	4	3	36	The number of glass particles in the contents passing through the applicator filter after activation are monitored. The concern is on the large glass particles rangeing from (b) (4) as they may cause harm on patients. The acceptance criteria for the test were set based on data obtained from the pivotal clinical batches with large sample size (b) (4) applicators each and setting the limit of each size range on the average (b) (4) SD). There were no reports of patients being harmed from glass particles that might have slipped through the flocked tip filter during clinical trials.

RPN: Risk Priority Number

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

Low Risk- RPN ≤ 25

Moderate Risk - 25 < RPN ≤ 60

High Risk - RPN > 60

ATTACHMENT II: List of Deficiencies

A. Labeling Deficiencies:

A. **Package Insert**

a) Highlight Section

- The strength, 40 %, should be 40% (w/w) per 201.10(d)(2).

b) Full Prescribing Information

#3: Dosage Forms and Strengths

- "ESKATA™ topical solution is a clear, colorless solution containing 40% hydrogen peroxide (w/w)." should be revised to "ESKATA™ topical solution is a clear, colorless solution containing 40% (w/w) hydrogen peroxide".

#11: Description

- Revise "(b) (4)" to "contains the active ingredient".
- The strength, 40% should be revised to 40% (w/w).
- (b) (4) should be revised to "ESKATA™ topical solution contains 40% hydrogen peroxide in an aqueous solution of isopropyl alcohol and water."
- Revise (b) (4) to "The molecular formula of hydrogen peroxide is H_2O_2 and the molecular weight is 34.01."
- Remove section (b) (4)

#16: How Supplied/Storage and Handling

- Include the statement "The available carton packages are presented below:" before the Table.
- Revise (b) (4) To "Store ESKATA™ topical solution at controlled room temperature of 20°C to 25°C (68°F to 77°F), excursions permitted between 15° and 30°C (59° and 86°F)."

B. Container Label Deficiencies:

- Include "See package insert for dosage information".
- Strength 40% should be 40% (w/w).

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead's Assessment and Signature

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

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
10/20/2017

Yichun Sun

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Moo Jhong Rhee

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LABELING

R. Regional Information

1.14 Labeling

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

ESKATA™ (hydrogen peroxide) topical solution, (b) (4)
Initial U.S. Approval: YYYY

2) DOSAGE FORMS AND STRENGTHS

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	ESKATA™ (hydrogen peroxide) topical solution (b) (4)	Proprietary name proposed is acceptable. The established name "(hydrogen peroxide) topical solution (b) (4) is acceptable. **Satisfactory.**
Dosage form, route of administration	**topical solution, 40%** **• Should be administered by healthcare professional** **• Recommended dose is application directly to the targeted lesion(s) up to 4 times, approximately 1 minute apart, during a single in-office treatment session (2.1)**	The dosage form, topical solution, is described adequately. Route of administration is presented correctly. **Satisfactory.**
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))	Solution (b) (4) 40% hydrogen peroxide	The dosage form is described correctly. The strength, 40 %, should be 40% (w/w). **Satisfactory.**
Whether the drug product is scored		

2. "FULL PRESCRIBING INFORMATION

1) #3: DOSAGE FORM AND STRENGTHS

ESKATA™ topical solution is a clear, colorless solution containing 40% hydrogen peroxide (w/w).

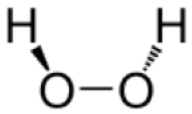
Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	ESKATA™ topical solution is a clear, colorless solution containing 40% hydrogen peroxide (w/w).	"ESKATA™ topical solution is a clear, colorless solution containing 40% hydrogen peroxide (w/w)." should be revised to "ESKATA™ topical solution is a clear, colorless solution containing 40% (w/w) hydrogen peroxide" **Not Satisfactory.**
Strengths: in metric system	40%	The strength 40% should be 40% (w/w). **Not Satisfactory.**
Active moiety expression of strength with equivalence statement (if applicable)		N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	clear, colorless solution	The description is correctly expressed. **Satisfactory.**

2) #11: DESCRIPTION

ESKATA™ (hydrogen peroxide) topical solution, 40% is a clear, colorless solution for topical administration, which contains the active (b) (4) hydrogen peroxide, (b) (4)

The chemical name of hydrogen peroxide is dihydrogen dioxide.

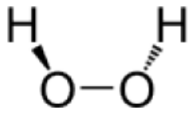
The molecular formula is H_2O_2 and the molecular weight is 34.01. Hydrogen peroxide is represented by the following structural formula:



ESKATA™ (b) (4) contains 40% hydrogen peroxide in an aqueous solution, isopropyl alcohol, and water.

(b) (4)

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	ESKATA™	The drug name "ESKATA" (hydrogen peroxide) topical solution **Satisfactory.**
Dosage form and route of administration	topical solution	The dosage form and route of administration are expressed correctly. **Satisfactory.**
Active moiety expression of strength with equivalence statement (if applicable)	40%	Should be, 40% (w/w) **Not Satisfactory.**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	ESKATATM (b) (4) contains 40% hydrogen peroxide in an aqueous solution, isopropyl alcohol, and water.	The inactive ingredients information is presented correctly however, the statement should be revised to "ESKATA™ topical solution contains 40% (w/w) hydrogen peroxide in an aqueous solution of isopropyl alcohol, and water." **Not Satisfactory.**
Statement of being sterile (if applicable)	NA	**Satisfactory**
Pharmacological/ therapeutic class	(b) (4)	**Satisfactory**
Chemical name, structural formula, molecular weight	The chemical name of hydrogen peroxide is dihydrogen dioxide. The molecular formula of H_2O_2 and the molecular weight is 34.01. Hydrogen peroxide is represented by the following structural formula: 	The chemical names and the structural formula are correctly presented. The molecular weight is included. **Satisfactory.**
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	**NA**	NA

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

ESKATA™ solution is a clear, colorless solution and is supplied in a unit dose package [redacted] (b) (4)

Dosage Strength	Fill Volume	Number of unit dose packages per carton	NDC#
40%	2.2 ml	X	71180-XXX-XX
40%	1.5 ml	X	71180-XXX-XX

Store ESKATA™ topical solution at room temperature [redacted] (b) (4).

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	40%	Should be 40% (w/w) **Not Satisfactory.**
Available units (e.g., bottles of 100 tablets)	2.2 mL 1.5mL	The information provided is Adequate. **Satisfactory.**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	solution is a clear, colorless solution and is supplied in a unit dose packag [redacted] (b) (4)	The information provided is Adequate. **Satisfactory.**
Special handling (e.g., protect from light)	N/A	**Satisfactory.**
Storage conditions	Store ESKATA™ topical solution at room temperature [redacted] (b) (4).	The information provided is Adequate. **Satisfactory.**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Not included in this section but displayed in the #17.	**Satisfactory.**

II. Labels

1. IMMEDIATE CONTAINER

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Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	ESKATA (hydrogen peroxide) topical solution, 40%	**Satisfactory.**
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	40%	Should be 40 % (w/w) **Not Satisfactory.**
Net contents	0.7 mL 1.3 mL	**Satisfactory**
"Rx only" displayed prominently on the main panel	Displayed	**Satisfactory.**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed	**Satisfactory.**
Lot number and expiration date (21 CFR 201.17)	Displayed	**Satisfactory.**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Not Displayed	**Satisfactory.**
Bar code (21CFR 201.25)	Displayed	**Satisfactory.**
Name of manufacturer/distributor	Displayed	**Satisfactory.**
And others, if space is available		

2. CARTON LABELS:

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

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	ESKATA (hydrogen peroxide) topical solution, 40%	**Satisfactory.**
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	40%	Should be 40% (w/w) **Not Satisfactory.**
Net quantity of dosage form	Displayed.	Satisfactory.
"Rx only" displayed prominently on the main panel	Displayed	**Satisfactory.**
Lot number and expiration date	Displayed	**Satisfactory.**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Displayed	**Satisfactory.**
Bar code (21CFR 201.25)	Displayed	**Satisfactory.**
NDC number (21 CFR 207.35(b)(3)(i))	Displayed	**Satisfactory.**
Manufacturer/distributor's name	Displayed	**Satisfactory.**
Quantitative ingredient information (injectables)	NA	
Statement of being sterile (if applicable)	Displayed	**Satisfactory.**
"See package insert for dosage information"	Not Displayed	**Not Satisfactory.**
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	N/A	**N/A**

III. LIST OF DEFICIENCIES:

A. **Regarding PI**

a) Highlight Section

The strength, 40 %, should be 40% (w/w) per 201.10(d)(2).

b) Full Prescribing Information
#3: Dosage Forms and Strengths

- "ESKATA™ topical solution is a clear, colorless solution containing 40% hydrogen peroxide (w/w)." should be revised to "ESKATA™ topical solution is a clear, colorless solution containing 40% (w/w) hydrogen peroxide"

#11: Description

- Revise "[redacted (b) (4)]" to "contains the active ingredient".
- The strength, 40% should be revised to 40% (w/w).
- "ESKATATM [redacted (b) (4)] contains 40% hydrogen peroxide in an aqueous solution of isopropyl alcohol, and water." should be revised to "ESKATATM topical solution contains 40% hydrogen peroxide in an aqueous solution of isopropyl alcohol and water."
- Revise "[redacted (b) (4)]" to "The molecular formula of hydrogen peroxide is H_2O_2 and the molecular weight is 34.01."
- Remove section [redacted (b) (4)]

#16: How Supplied/Storage and Handling

- Include the statement "The available carton packages are presented below:" before table.
- Revise "[redacted (b) (4)]." to "Store ESKATATM topical solution at controlled room temperature of 20°C to 25°C (68°F to 77°F), excursions permitted between 15° and 30° (59° and 86° F)."

B. Regarding of the Container/Carton Labels:

- Include "See package insert for dosage information"
- Strength 40% should be 40% (w/w)

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

Overall, labeling and labels have required information, however, they need to be revised before approval.

Therefore, from the ONDP perspective, this application is ***not*** deemed ready for approval until the deficiencies delineated above are satisfactorily resolved.

QUALITY ASSESSMENT

Primary Labeling Reviewer Name and Date:

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

I concur with Dr. Sarah Ibrahim's assessment and recommendation on the labels and labeling from the ONDP perspective.

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

Sarah Ibrahim

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Moo Jhong Rhee

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MICROBIOLOGY

Product Background: -

NDA/ANDA/BLA: NDA 209305

Drug Product Name / Strength: Eskata™ (hydrogen peroxide) 40%, topical solution

Route of Administration: Topical

Applicant Name: Aclaris Therapeutics, Inc., 101 Lindenwood Drive, Suite 400, Malvern, PA 19355, USA

Manufacturing Site: James Alexander Corporation, 845 Route 94, Blairstown, NJ 07854, USA

Method of Sterilization: Not applicable

Review Summary: The submission is recommended for approval.

List Submissions being reviewed: February 24, 2017, May 4, 2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents: Not Applicable

Remarks Section: N/A

P.1 Description of the Composition of the Drug Product

- Description of drug product – The drug product, Eskata™ (hydrogen peroxide) 40% Topical Solution is single-use and filled into clear USP (b) (4) glass ampoules with either 1.5 or 2.2 mL volume.

- Drug product composition –

Ingredient	Content (% w/v)	Function
Hydrogen Peroxide, (b) (4)	80	Active
Isopropyl Alcohol (b) (4) USP	(b) (4)	

Sterile Water	(b) (4) USP	(b) (4)

- Description of container closure system –

Configuration	Component	Description	Manufacturer
1.5 and 2.2 mL	Ampoule	Clear, colorless, (b) (4) glass tubing	(b) (4)

Reviewer's Assessment: The applicant provided sufficient information about the drug product and the container closure system.

Acceptable

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

Not applicable, container closure integrity is not required for a non-sterile product.

Antimicrobial Effectiveness Testing

N/A. The subject drug product is a single dose.

P.3 Manufacture

P.3.1 Manufacturers

Drug product

James Alexander Corporation
845 Route 94
Blairstown, NJ USA 07825

Release/stability testing

(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls

Overall Manufacturing Operation

(b) (4)

[redacted]

(b) (4) **Additionally, the drug product is composed of hydrogen peroxide and isopropanol which should limit microbial growth. Therefore the applicant's manufacturing process is adequate for a topical, non-sterile product.**

Acceptable

P. 3.5 Process Validation and/or Evaluation

P.5 Control of Drug Product

P. 5.1 Specification

(3.2.P.5.1 – Specficiations.pdf)

Information Request (Apr 20, 2017):

The submission provided microbial specifications using methods described in USP <61> and USP <62>. However studies supporting these methods were not described. Please provide a suitability study that includes detailed protocols for microbial enumeration, protocols that ensure the absence of specified organisms, justification for the chosen methods, controls and acceptance criteria.

Response (May 4, 2017):

The firm described that all validations and subsequent testing was completed on the 40% H_2O_2 product collected from the ampoules and expressed from the applicators. Because of the intrinsic antimicrobial nature of the drug product modifications to the test method were used to demonstrate acceptable microbial recovery from the test product following inoculation with specific organisms. (b) (4) No difference was observed when testing the 40% H_2O_2 solution directly or from the applicators.

Microbial Limits

Total aerobic microbial count: NMT (b) (4) CFU/mL
Total yeast and molds count: NMT CFU/mL

Absence of Specified Organisms: *P. aeruginosa, E. coli, S. aureus, C. albicans, C. sporogenes, S. typhimurium*

Testing is performed per USP <61> and <62>.

Suitability tests were submitted in the IR response from the firm (see 0005 – 3.2.P.5.3). (b) (4)

(b) (4)

(b) (4)

Acceptable

P.5.2 Analytical Procedures - See Section 5.1

P.5.3 Validation of Analytical Procedures – N/A

P.7 Container Closure – See Section P.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(3.2.P.8.1 - Stability Summary and Conclusions.pdf)

Proposed Expiry: 24 months

Testing was performed per USP <61> and <62>.

Microbial Limits

		(b) (4)	
Total aerobic microbial count:	NMT		CFU/mL
Total yeast and molds count:	NMT		CFU/mL

Absence of Specified Organisms: *P. aeruginosa, E. coli, S. aureus, C. albicans, A. brasiliensis, S. typhimurium*

Samples for long-term stability (25 °C/60% RH) for microbiological testing are taken at 1, 3, 6, 9, 12, 18, 24 months. Acceptable results were provided for multiple lots of the drug product in the proposed container-closure system (3.2.P.8.3).

The microbial limits set for long term stability is sufficient to ensure an acceptable, low-risk amount of microorganisms for the shelf-life of this drug product. The suitability tests provided were sufficient to validate these limits.

Reviewer's Assessment: The applicant provided sufficient information regarding the microbiological tests and sampling frequency for the stability program. This strategy is sufficient to monitor the microbiological attributes for this preservative-free formulation over its shelf life.

Acceptable

(b) (4)

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: Not Applicable.

A.2.1 Materials of Biological Origin

Reviewer's Assessment: Not Applicable.

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: Not Applicable.

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: Not Applicable.

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: Not Applicable.

R Regional Information

Executed Batch Records

Executed batch records were provided for multiple lots for both strengths.

Reviewer's Assessment: The applicant provided sufficient information regarding the executed batch records.

Acceptable

Comparability Protocols– No CP was included in the application.

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

2.A. Package Insert

(1.14.1.3)

Storage temperature: (b) (4) ; Route of administration: topical ; Container: Single dose

Reviewer's Assessment: The applicant has provided sufficient information in the drug labeling to ensure the sterility of the drug product.

Acceptable

Post-Approval Commitments: N/A

Lifecycle Management Considerations: N/A

The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows ☐ YES ☐ NO

Major Deficiency ☐ YES ☐ NO

Minor Deficiency ☐ YES ☐ NO

Primary Microbiology Reviewer Name and Date: Jennifer Sykora, Ph.D. 23 May 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Erika Pfeiler, Ph.D.

Jennifer Sykora

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Erika Pfeiler

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