CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209305Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	Decemeber 14, 2017
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 209305
Product Name and Strength:	Eskata (hydrogen peroxide) Topical Solution, 40%
Applicant/Sponsor Name:	Aclaris Therapeutics
Submission Date:	Decemeber 4, 2017
OSE RCM #:	2017-399-2
DMEPA Safety Evaluator:	Carlos M Mena-Grillasca, BS Pham
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMO

The Division of Dermatology and Dental Products (DDDP) requested that we review the revised container labels and carton labeling for Eskata topical solution 40% (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling reviews.[ab]

2 CONCLUSION

The Applicant responded that it was not possible to include the bar code to the tube and sleeve labels due to space limitations. We note that the tube and sleeve labels comply with the minimum requirements for small labels per 21 CFR 201.10(i), which require at a minimum the proprietary name, established name, strength, lot number, expiration date, and name of manufacturer, packer, or distributor. Therefore, we agree with the Applicant and find the tube and sleeve labels acceptable. All of DMEPA's recommendations have been addressed by the Applicant and we find all labels and labeling acceptable.

DMEPA defers to OPQ regarding the technical feasibility to add a bar code to the lidding label as the Applicant contends.

[a] Mena-Grillasca C. Label and Labeling Review for Eskata (NDA 209305). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Oct 10. RCM No.: 2017-399

[b] Mena-Grillasca C. Label and Labeling Review Memo for Eskata (NDA 209305). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Nov 17. RCM No.: 2017-399-1

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/s/

CARLOS M MENA-GRILLASCA
12/14/2017

SARAH K VEE
12/14/2017

505(b)(2) ASSESSMENT

Application Information		
NDA # 209305	NDA Supplement #: S- NA	Efficacy Supplement Type SE- NA
Proprietary Name: Eskata Established/Proper Name: hydrogen peroxide Dosage Form: solution Strengths: 40%		
Applicant: Aclaris Therapeutics		
Date of Receipt: February 24, 2017		
PDUFA Goal Date: December 24, 2017	Action Goal Date (if different): December 10, 2017 (DDDP Target Date)	
RPM: Strother D. Dixon		
Proposed Indication(s): For the treatment of seborrheic keratosis		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
published literature	Nonclinical toxicology, Section 13 (genotoxicity and fertility)

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

Per the Clinical Pharmacology filing review, "Via the 505(b)(2) regulatory pathway, the applicant has used literature data to support some of the Pharmacology-Toxicology information. Comparative bioavailability studies were deemed not necessary."
The sponsor is relying upon several publications that describe the effects of hydrogen peroxide on fertility in animals and the genotoxic potential of hydrogen peroxide, which support the current language in labeling Subsection 13.1. The sponsor also relied on one publication to describe the ocular irritation potential of hydrogen peroxide, which supports the current language in labeling Subsection 5.1. The data described in the submitted literature is scientifically relevant to the proposed product because the studies used the same active pharmaceutical ingredient as contained in the sponsor's drug product, and the doses used in the reported animal studies are scientifically relevant to the proposed human dose.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

☐ NO ☒ YES

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

☐ NO ☐ YES

NOTE: European Commission document (cited as relied upon by the applicant) is not essential for approval of the application and supportive only in nature (and thus not invoking 505(b)(2) related concerns).

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO ☒

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

☐ YES ☐ NO

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

☐ YES ☐ NO

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

☐ YES ☐ NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

☐ NO ☒

YES

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

☐ NO ☐

YES

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ ☐ NO ☐

YES

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

☐ NO ☒

YES

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

☐ NO ☐

YES

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ ☐ NO ☐

YES

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

☐ NO ☐

YES

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

☐ YES ☐ NO

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

☐ YES ☐ NO

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

STROTHER D DIXON
12/14/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 17, 2017
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 209305
Product Name and Strength:	Eskata (hydrogen peroxide) Topical Solution, 40%
Applicant/Sponsor Name:	Aclaris Therapeutics
Submission Date:	November 14, 2017
OSE RCM #:	2017-399-1
DMEPA Safety Evaluator:	Carlos M Mena-Grillasca, BS Pham
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMO

The Division of Dermatology and Dental Products (DDDP) requested that we review the revised container labels and carton labeling for Eskata topical solution 40% (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. The container labels should include the NDC number per 21 CFR 207.35(3)(i). The linear bar code is missing from multiple labels and labeling.

We recommend the following be implemented prior to approval of this NDA.

[a] Mena-Grillasca C. Label and Labeling Review for Eskata (NDA 209305). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Oct 10. RCM No.: 2017-399

3 RECOMMENDATIONS FOR PROMIUS PHARMA

A. General (all container labels and carton labeling)

1. Ensure all labels and labeling include a linear bar code in accordance with 21 CFR 201.25(c)(2). Provide adequate orientation and white space around the bar code to facilitate scanning.

B. All tube labels

1. Delete the dosing statement 'See package insert for dosing information'. This statement is not required in small labels per 21 CFR 201.10(i).
2. Add the NDC number in accordance with 21 CFR 207.35(3)(i).

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

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/s/

CARLOS M MENA-GRILLASCA
11/17/2017

SARAH K VEE
11/17/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: September 19, 2017 **Date consulted:** March 29, 2017

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

To: Division of Dermatology and Dental Products (DDDP)

Drug: Eskata (hydrogen peroxide topical solution 40%)

Drug Class: Miscellaneous Dermatologic Agents

NDA: 209305

Applicant: Aclaris Therapeutics, Inc
Subject: Pregnancy and Lactation Labeling (PLLR)

Indication: Treatment of seborrheic keratosis lesions

Materials Reviewed:

- DPMH consult request dated March 29, 2017 in DARRTS (Reference ID 4076900)
- Applicant's submission for original NDA 209305 and Prescribing Information (PI) for Eskata (hydrogen peroxide) topical solution, 40%, dated February 24, 2017.
- Applicant's Response to FDA Request for Information of August 7, 2017

Consult Question:
DDDP requests DPMH assistance with reviewing the applicant's Pregnancy and Lactation Labeling section to comply with PLLR format.

INTRODUCTION
On February 24, 2017, the applicant, Aclaris Therapeutics, Inc., submitted an original NDA 209305 for Eskata (hydrogen peroxide) topical solution, 40% indicated for the treatment of seborrheic keratosis lesions.

The Division of Dermatology and Dental Products (DDDP) consulted the Division of Pediatric

and Maternal Health (DPMH) on March 29, 2017, to provide input for appropriate labeling of the pregnancy and lactation subsections of Eskata (hydrogen peroxide ($H_2O_{2)}$) topical solution, 40%, to comply with the Pregnancy and Lactation Labeling Rule format.

This review provides recommended revisions and structuring of information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.

BACKGROUND

Regulatory History

On February 24, 2017, the applicant submitted this NDA 209305 under a 505(b)(2) pathway and relies, in part, on published literature for nonclinical information. The proposed indication for Eskata topical solution, 40% is for the treatment of seborrheic keratosis lesions.

Eskata Drug Characteristics

- Eskata is an oxidizing agent.
- Following application of Eskata in patients with seborrheic keratosis lesions, H_2O_2 rapidly dissociates into water and reactive oxygen species. Indirect assessment of reactive oxygen species in patients with seborrheic keratosis lesions did not demonstrate any systemic absorption of H_2O_2.[1]
- H_2O_2 is a product of cellular metabolism and present in biological systems, including blood, and is excreted in urine.
- H_2O_2 has a molecular weight of 34.01 Daltons and a half-life of 1-4 days.

Background on Seborrheic keratosis (SK)

Seborrheic keratosis (SK) is one of the most common skin tumors in humans. These benign epithelial skin tumors are most commonly seen in older individuals, increase in prevalence with increasing age, and affect men and women roughly equally. SK are most commonly located on the trunk - particularly the upper back, the neck, face, and extremities and may occur on all non-glabrous skin - sparing the palms, soles, and mucous membranes. Lesions are biologically benign and typically asymptomatic. Currently, no specific treatment for SK is approved by the Food and Drug Administration (FDA). Numerous treatment options exist, and include destructive/ablative modalities such as liquid nitrogen cryotherapy, electrodessication, lasers of various wavelengths (ablative and non-ablative), radiofrequency ablation, and surgical removal by curettage or surgical excision.[2]

Other H_2O_2 uses[3]

- Commonly used in household goods including chlorine-free bleaches, general-purpose cleaning products, and disinfectants.
- H_2O_2 has been used as the oxidizing component in hair dyes, and in oral hygiene products and tooth-whitening systems for many years.
- H_2O_2 is used at low concentrations (e.g., 3% to 6%) as a wound irrigant and topical antiseptic/disinfectant since 1858.

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[1] From 12.3 Pharmacokinetics of the proposed labeling for Eskata. For further details, refer to the Clinical Pharmacology Review by Yanhui Lu, Ph.D.

[2] Jackson JM, Alexis A, Berman B, Berson DS, Taylor S, Weiss JS. Current understanding of seborrheic keratosis: prevalence, etiology, clinical presentation, diagnosis, and management. J Drugs Dermatol. 2015;14(10):1119-1125

[3] Dailymed, NIH, National Library of Medicine and accessed on October 10, 2017

REVIEW OF PREGNANCY DATA

Nonclinical

As per the nonclinical reviewer Daivender Mainigi, Ph.D., hydrogen peroxide has been found to exhibit positive results in in vitro tests for genotoxicity, but has not exhibited positive results in in vivo tests for genotoxicity, presumably due to the rapid metabolism of hydrogen peroxide.

Literature Review

Neither the applicant nor DPMH identified any publications on hydrogen peroxide and pregnancy in PubMed and Google Scholar. Review of the Reprotox database in Micromedex Solutions also failed to produce any evidence of adverse developmental outcomes with use of hydrogen peroxide during pregnancy. There is no information in either GG Briggs *et. al*, *Drugs in Pregnancy and Lactation*[4] or C. Schaefer *et. al., Drugs During Pregnancy and Lactation*.[5]

Review of Clinical Trial Data

During the drug development program, there was one pregnancy reported in a healthy woman who had a history of 3 spontaneous abortions. She was discontinued from the trial on Day 21 because of the pregnancy. She subsequently had a spontaneous abortion.

Discussion

Hydrogen peroxide is not absorbed systemically following topical administration, and maternal use is not expected to result in fetal exposure to the drug. The labeling language in 8.1 Pregnancy will reflect the language prescribed in the regulation (21 CFR 201.57(c)(9)(i) (B)).

REVIEW OF LACTATION DATA

No published information was identified by the applicant or the DPMH reviewer regarding hydrogen peroxide and breastfeeding. Review of LactMed and the Reprotox database in Micromedex Solutions also failed to produce any information with use of hydrogen peroxide during lactation. There is no information in either GG Briggs[4], *Drugs in Pregnancy and Lactation*, or C. Schaefer *et. al., Drugs During Pregnancy and Lactation*[5] or TW Hale, *Medications and Mothers' Milk*.[6]

Hydrogen peroxide as an endogenous substance is present in breast milk.[7,8] There are no data on the effects of hydrogen peroxide on the milk production or the breastfed infant.

Discussion

Hydrogen peroxide is not absorbed systemically by the mother following topical administration, and breastfeeding is not expected to result in exposure of the child to hydrogen peroxide. The labeling language in 8.2 Lactation will reflect the language prescribed in the regulation (21 CFR 201.57(c)(9)(ii)(A)(1)).

REVIEW OF DATA ON FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

The effects of hydrogen peroxide on fertility have not been evaluated. No published information exists. Hydrogen peroxide at increased concentrations in vitro, during sperm preparation techniques for assisted reproductive technologies (ART), has been associated with effects on

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[4] Briggs GG and Freeman RK. Drugs in Pregnancy and Lactation, Tenth Edition, Wolters Kluwer, Philadelphia, 2015

[5] Schaefer C, Peters P, Miller RK. Drugs During Pregnancy and Lactation, Second Edition, Elsevier, San Diego, 2007

[6] Hale TW. Medications and Mothers' Milk. Seventeenth Edition. Springer, New York, 2017

[7] Clark RM, Ross SA, Hill DW, Ferris AM. Within-day variation of taurine and other nitrogen substances in human milk. J Dairy Sci. 1987;70:776-80

[8] Al-Kerwi EA, Al-Hashimi AH, Salman AM. Mother's milk and hydrogen peroxide. Asia Pac J Clin Nutr. 2005;14:428-31

sperm function.[9] In vivo, no effect of hydrogen peroxide on sperm function has been demonstrated in animals as per the nonclinical reviewer Daivender Mainigi, Ph.D. No human studies have been conducted.

Summary
In vivo animal data does not support an adverse effect on fertility by hydrogen peroxide. Hydrogen peroxide is not absorbed systemically by the mother following topical administration. Therefore, there is no need for contraception prenatally or pregnancy testing prior to initiating treatment with Eskata. There is no information to be relayed in the labeling about infertility, pregnancy testing or contraception, and subsection 8.3 Females and Males of Reproductive Potential is omitted.

CONCLUSIONS
No safety concerns for Eskata use during pregnancy and lactation have been identified.

DPMH revised sections 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR. The below recommendations reflect discussion with the DDDP Nonclinical and Clinical teams as well as the Clinical Pharmacology team. DPMH refers to the final NDA action for final labeling.

The Pregnancy and Lactation sections of Eskata labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of Eskata labeling was formatted in the PLLR format to include: "Risk Summary".
- **Lactation, Section 8.2**
  - The "Lactation" section of Eskata labeling was formatted in the PLLR format to include the "Risk Summary" sections.
- **Females and Males of Reproductive Potential, Section 8.3**
  - Females and Males of Reproductive Potential section of Eskata labeling was omitted because there is nothing to report.

[9] Du Plessis SS, McAllister DA, Luu A, Savia J, Agarwal A, Lampiao F. Effects of H2O2 exposure on human sperm motility parameters, reactive oxygen species levels and nitric oxide levels. Blackwell Verlag GmbH Æ Andrologia 2010;42, 206–210

RECOMMENDATIONS

DPMH has the following recommendations for Eskata labeling.

FULL PRESCRIBING INFORMATION: CONTENTS

USE IN SPECIFIC POPULATIONS

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Hydrogen peroxide is not absorbed systemically following topical administration, and maternal use is not expected to result in fetal exposure to the drug.

8.2 Lactation

Risk Summary

Hydrogen peroxide is not absorbed systemically by the mother following topical administration, and breastfeeding is not expected to result in exposure of the child to hydrogen peroxide

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/s/

CHRISTOS MASTROYANNIS
10/11/2017

TAMARA N JOHNSON
10/11/2017

LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 10, 2017
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 209305
Product Name and Strength:	Eskata (hydrogen peroxide) Topical Solution, 40%
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Aclaris Therapeutics
Submission Date:	February 24, 2017 and August 7, 2017
OSE RCM #:	2017-399
DMEPA Safety Evaluator:	Carlos M Mena-Grillasca, BS Pharm
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

This review responds to a request from the Division of Dermatology and Dental Products (DDDP) to evaluate the proposed container label, carton, and Prescribing Information labeling for Eskata, submitted by the applicant under NDA 209305.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing to market Eskata in 0.7 and 1.3 mL applicators in 1 unit, 3 unit, and 12 unit cartons. The different size applicators provide for treatment of different size areas or number of lesions. Therefore, we find their proposed applicator sizes adequate.

We reviewed the container and sleeve labels, lidding and carton labeling and noted areas for improvement. The established name uses light condensed font, therefore, we find it is not at least ½ the size of the proprietary name and does not meet CFR 201.10(g)(2). Not all labels and labeling include the route of administration statement or the NDC number on the top third of the label as required.

4 CONCLUSION & RECOMMENDATIONS

We find the proposed 0.7 mL and 1.3 mL applicator sizes acceptable. We recommend the following label and labeling revision be implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR PROMIUS PHARMA

A. General Comments (all container labels and carton labeling)

1. Revise the presentation of the established name to ensure that it is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). As currently presented the typography used for the proprietary name (bold font) versus the typography used for the established name (light condensed font) we find they are not commensurate in prominence.

2. Add or relocate the NDC number to comply with CFR 207.35 (3) (i) which states that "the NDC number shall appear prominently in the top third of the principal display panel of the label on the immediate container and of any outside container or wrapper."

B. Container (Tube) and Sleeve Label (0.7 mL and 1.3 mL)

1. Add the route of administration statement 'For Topical Use Only'.

C. Lidding Labeling (0.7 mL and 1.3 mL)

1. Add a linear bar code in accordance with 21 CFR 201.25(c)(2).
2. Increase the prominence of the route of administration statement 'For Topical Use Only' and decrease the prominence of the 'Rx Only' statement. The route of administration is more important information and therefore should be more prominent than the Rx Only statement.

D. Carton Labeling (1 unit; 0.7 mL and 1.3 mL)

1. Increase the prominence of the route of administration statement 'For Topical Use Only' and decrease the prominence of the 'Rx Only' statement. The route of administration is more important information and therefore should be more prominent than the Rx Only statement.
2. Relocate the ingredient list to a side or back panel. As currently presented the ingredient list on the principal display panel is crowding and distracting from more relevant information.

E. Carton Labeling (3 units and 12 units; 0.7 mL and 1.3 mL)

1. Add and/or increase the prominence of the route of administration statement 'For Topical Use Only' consistently across all carton labeling and decrease the prominence of the 'Rx Only' statement. The route of administration is more important information and therefore should be more prominent than the Rx Only statement. We note the 1.3 mL 3 unit carton labeling includes the route of administration statement within the image of the applicator. However, the 1.3 mL 12 unit carton and 0.7 mL 3 unit and 12 unit carton labeling are missing the route of administration statement.
2. Relocate the ingredient list to a side or back panel. As currently presented the ingredient list on the principal display panel is crowding and distracting from more relevant information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Eskata that Aclaris Therapeutics submitted on August 7, 2017.

Table 2. Relevant Product Information for Eskata	
Initial Approval Date	N/A
Active Ingredient	Hydrogen peroxide
Indication	Treatment of seborrheic keratosis lesions.
Route of Administration	Topical
Dosage Form	Solution
Strength	40%
Dose and Frequency	Application directly to the targeted lesion(s) up to 4 times, approximately 1 minute apart, during a single in-office treatment session. Should be administered by a healthcare provider.
How Supplied	1.3 mL and 1.5 mL applicators; packs of 3 and 12 units
Storage	Room temperature (15-25°C).
Container Closure	Glass ampules in applicator

APPENDIX B. PREVIOUS DMEPA REVIEWS

N/A

APPENDIX C. HUMAN FACTORS STUDY

N/A

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F. OTHER SOURCES

N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Eskata labels and labeling submitted by Aclaris Therapeutics on February 24, 2017.

- Container labels
- Carton labeling
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images (not to scale)

Proposed Container Labels (not to scale)

Tube Labels

(b) (4)

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

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

CARLOS M MENA-GRILLASCA
10/10/2017

SARAH K VEE
10/10/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 05, 2017
To:	Kendall Marcus, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lynn Panholzer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ESKATA (hydrogen peroxide)
Dosage Form and Route:	topical solution, 40%
Application Type/Number:	NDA 209305
Applicant:	Aclaris Therapeutics

1 INTRODUCTION

On February 24, 2017, Aclaris Therapeutics submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 209305 for ESKATA (hydrogen peroxide) topical solution, 40%. The proposed indication for ESKATA (hydrogen peroxide) topical solution is for the treatment of seborrheic keratosis.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on March 20, 2017, and March 13, 2017, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ESKATA (hydrogen peroxide) topical solution.

2 MATERIAL REVIEWED

- Draft ESKATA (hydrogen peroxide) topical solution PPI received on February 24, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 26, 2017.
- Draft ESKATA (hydrogen peroxide) topical solution Prescribing Information (PI) received on February 24, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 26, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
10/05/2017

LYNN M PANHOLZER
10/05/2017

BARBARA A FULLER
10/06/2017

LASHAWN M GRIFFITHS
10/06/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 5, 2017

To: Melissa Reyes, M.D.
Division of Dermatology and Dental Products (DDDP)

Strother D. Dixon, Regulatory Project Manager, (DDDP)

Nancy Xu, Associate Director for Labeling, (DDDP)

From: Lynn Panholzer, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew J. Falter, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for Eskata (hydrogen peroxide) topical solution, 40%

NDA: 209305

In response to DDDP's consult request dated March 13, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for Eskata (hydrogen peroxide) topical solution, 40%.

PI and PPI: OPDP's comments on the proposed PI are based on the draft PI received by electronic mail from DDDP (Strother Dixon) on September 26, 2017, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 24, 2017, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
10/05/2017

Clinical Inspection Summary

Date	October 3, 2017
From	Bei Yu, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Strother D. Dixon, Regulatory Project Manager Melissa Reyes, Clinical Reviewer David Kettl, Clinical Team Leader Division of Dermatology and Dental Products (DDDP)
NDA #	NDA 209305
Applicant	Aclaris Therapeutics, Inc.
Drug	Eskata (hydrogen peroxide 40%) Topical Solution
NME	No
Review Priority	Standard Review
Proposed Indication	Treatment of Seborrheic Keratosis
Consultation Request Date	March 30, 2017
Summary Goal Date	October 6, 2017
Action Goal Date	December 12, 2017
PDUFA Date	December 24, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Smith and Pollack were inspected in support of this NDA. The final classification of the inspection of Dr. Smith is Voluntary Action Indicated (VAI), while the final classification of the inspection of Dr. Pollack is No Action Indicated (NAI).

Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. While regulatory violations were observed at Dr. Smith's site, they do not have a significant impact on data reliability.

2. BACKGROUND

The Applicant submitted this NDA to support the use of hydrogen peroxide topical solution 40% in the treatment of seborrheic keratosis (SK) lesions.

Inspections were requested for two identical pivotal study protocols in support of this application:

Protocols A-101-SEBK-301 and **A-101-SEBK-302**, both entitled "A Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study of the Safety and Effectiveness of H008-A-101 Solution 40% in Subjects with Seborrheic Keratosis on the Trunk, Extremities, and Face"

These were two identical randomized, double-blind, vehicle-controlled, and parallel-group studies. During these studies, the investigator identified 4 eligible SK target lesions on each subject on the trunk, extremities and face. Subjects who met eligibility criteria were randomly assigned in a 1:1 ratio to receive treatment with either hydrogen peroxide topical solution 40% or vehicle. The target lesions were treated by an investigational staff member (other than the evaluating investigator) a maximum of two times. The primary efficacy endpoint was proportion of subjects with all 4 target lesions clear (Physician's Lesion Assessment, PLA = 0) at Visit 8 (Day 106).

Study 301 was conducted at 17 U.S. sites between February and November 2016. A total of 450 subjects were enrolled.

Study 302 was conducted at 17 U.S. sites between January and October 2016. A total of 487 subjects were enrolled.

Rationale for Site Selection

Dr. Smith's and Pollack's sites were selected for inspection mainly due to a high site efficacy effect and the fact that these investigators had no prior history of GCP inspections.

3. RESULTS (by site):

Site #/ Name of CI/ Address	**Protocol # / # of Subjects Enrolled**	**Inspection Dates**	**Classification**
Site #14 Smith, Stacy 561 Saxony Place, Suite 102 Encinitas, CA 92024	A-101-SEBK-301 Subjects: 23	24-26 July 2017	VAI
Site# 14 Pollack, Andrew 501 Office Center Drive, Suite 195 Fort Washington, PA 19034	A-101-SEBK-302 Subjects: 43	18-24 July 2017	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

1. Stacy R. Smith, M.D.

For Protocol A-101-SEBK-301, a total of 25 subjects were screened and 23 subjects were enrolled, all of whom completed the study.

Informed consent forms (ICFs) for all 25 screened subjects were reviewed to ensure that subjects were properly consented. Study records for all 23 randomized subjects were reviewed, including, but was not limited to, financial disclosure, training, protocol deviations, monitor/IRB communications, and test article control. Source documents were compared with Case Report Forms (CRFs) and the data listings provided in the inspection assignment.

An FDA Form 483, Inspectional Observations, was issued at the conclusion of the inspection because the investigation was not conducted in accordance with the signed statement of the investigator and with the investigational plan. Specifically, one subject (#14-021) did not meet the inclusion criterion in the study protocol stating that to be eligible for treatment target lesions must have a length between 5 and 15 mm. For this subject, the target lesion was documented with a length of 19 mm at screening and 18 mm at baseline.

Dr. Smith responded to the inspectional findings in a letter dated August 3rd, 2017. His response was adequate.

OSI has discussed these findings with the clinical reviewer for this application. Subject 14-021 was in the active arm, so the impact of the data from this subject on the results of this study, if any, would be to slightly decrease the efficacy signal for the study drug. Therefore, the data generated by Dr. Smith's site appear acceptable in support of the respective indication.

2. Andrew Pollack, M.D.

For Protocol A-101-SEBK-302, 45 subjects were screened and 43 subjects were enrolled, all of whom completed the study.

ICFs for all 45 screened subjects were reviewed to ensure that subjects were properly consented. Study records for all 43 randomized subjects were reviewed, including, but was not limited to, financial disclosure, training, protocol deviations, CRFs, monitor/IRB communications, and safety reports. The enrolled subjects met eligibility criteria, and the primary endpoint data were verifiable. There was no evidence of under reporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

{See appended electronic signature page}

Bei Yu, Ph.D.
Senior Staff Fellow
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm. / NDA 209305
DDDP /Medical Team Leader/David Kettl
DDDP /Project Manager/Strother D. Dixon
DDDP/MO/Melissa Reyes
OSI/DCCE/ Division Director/ Ni Khin
OSI/DCCE/Branch Chief/ Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Bei Yu
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague

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/s/

BEI YU
10/03/2017

PHILLIP D KRONSTEIN
10/03/2017

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: August 31, 2017

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Strother D. Dixon, RPM
DDDP

Subject: QT-IRT Consult to NDA 209305

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 05/19/2017 regarding the sponsor's QT/QTc study waiver request. The QT-IRT reviewed the following materials:

- Sponsor's QT/QTc study waiver request submitted to Sequence 0006;
- CSR for maximal use study A-101-SEBK-205; and
- Highlights of clinical pharmacology and cardiac safety submitted to Sequence 0008.

1. QT-IRT Responses

We agree to a waiver for a thorough QT/QTc study for 40% hydrogen peroxide solution (ESKATA™).

2. Internal Comments to the Division

A thorough QT/QTc study for 40% hydrogen peroxide solution is not needed for the following reasons:

- *The recommendations in ICH E14 may not apply to products with highly localized distribution and those administered topically and not absorbed.*

- *Hydrogen peroxide (H_2O_2) is an endogenous ubiquitous product of cellular metabolism with endogenous levels in the micromolar range (circulating levels of <1 to 35 μM as per different literature sources).*
- *No significant changes in basal systemic levels of hydrogen peroxide in blood were observed after A-101 treatment for subjects in the maximal use study A-101- SEBK-205. While there is a possibility that there could be changes in exposure <0.3 μM (LLOD for assay sensitivity), it will not significantly alter the physiological systemic concentration of H_2O_2 under maximum use conditions.*
- *The nonclinical data does not suggest potential for hERG inhibition (in fact, supra-physiological concentrations of hydrogen peroxide accelerated the activation of the hERG current resulting in an effective increase in current). A shortening of the cardiac action has been reported in guinea pig myocytes and whole heart. As per the sponsor, these effects were observed at concentrations of 100 μM to 10 mM and considered only reflective of potential local pathophysiological levels attained under conditions of ischemia/reperfusion.*
- *The dosing for this drug is a single in-office treatment (application by a healthcare professional; not intended for application by patients), so there is no potential for chronic exposure.*

3. BACKGROUND

Product Information

ESKATA™ (A-101) is hydrogen peroxide 40% w/w topical solution, indicated for the treatment of seborrheic keratosis (SK) lesions. ESKATA™ is applied directly to the targeted lesion(s) up to 4 times, approximately one minute apart, during a single in-office treatment session. This product is not intended for application by patients and is contraindicated for oral or ophthalmic use.

Sponsor's position related to their request for waiver of formal QT/QTc study

Topical application of hydrogen peroxide to treat SK lesions is considered to achieve topical concentrations of superoxide. The topical application of supra-physiologic concentrations of hydrogen peroxide is considered to achieve topical concentrations achieving direct oxidation of organic tissues, generation of reactive oxygen species, and local lipid peroxidation and generation of local concentrations of oxygen that are toxic to the abnormal lesional (seborrheic keratosis) cells. These reactions take place on the surface of the skin while the defense mechanisms in the skin do not allow hydrogen peroxide to permeate into the circulation.

Hydrogen peroxide is an endogenous substance in the human body, a product of cellular metabolism and consequently tissues are continuously exposed to hydrogen peroxide.

Measurement of changes in blood exposure to hydrogen peroxide following topical application of A-101 40% hydrogen peroxide formulation showed no significant changes in the basal levels of hydrogen peroxide in blood.

Mechanistic electrophysiology studies indicate that high (supra-physiological) levels of hydrogen peroxide do not block the hERG channel providing any risk of QT prolongation but instead promote activation of the current.

It is considered that the ventricular myocardium is continuously exposed to hydrogen peroxide produced by cellular metabolism in cardiac tissue and circulating in blood. There is no evidence that topical administration of A-101 hydrogen peroxide formulations to treat SK lesions elevates blood levels and therefore no risk of cardiovascular effects and in particular effects on QT interval from topical application of 40% hydrogen peroxide solutions. Furthermore, hydrogen peroxide is not associated with hERG channel block and is therefore not considered to be of risk to prolong QT interval.

As A-101 hydrogen peroxide solution is a topical treatment with no evidence of systemic permeation no formal QT/QTc study is considered necessary to support the safety assessment of the product.

Quantification of changes in systemic H_2O_2 levels after maximal use topical application of drug

In Study A-101- SEBK-205, A-101 Solution 40% was administered under maximum use to 24 subjects, each with 10 eligible SK Target Lesions on the trunk, extremities, and face (including at least 1 Target Lesion on the face). Each SK lesion was treated once with 40 % w/w A-101 Solution. The total A-101 solution applied was approximately 1.45 mL of 40% hydrogen peroxide, equivalent to 580 mg of hydrogen peroxide.

If all of the hydrogen applied was absorbed without degradation, distribution, metabolism or excretion and was distributed into a circulating blood volume of 5L then the increase in hydrogen peroxide concentration would be 116,000 ng/mL. The local toxic effects of reactive oxygen species on the skin are mitigated by the presence of a complex antioxidant defense system that includes enzymes such as catalase, glutathione peroxidase, superoxide dismutase, thioredoxin reductase, lipoamine, and lipid peroxidase, as well as non-enzymatic components including ascorbic acid, urates and uric acid, tocopherol, glutathione, ubiquinones, ubiquinol, and other water soluble groups. The local application of supra-physiologic concentrations of hydrogen peroxide may overwhelm the antioxidant defense systems in the skin, allowing hydrogen peroxide to act not only through its direct oxidation of organic tissues, generation of reactive oxygen species, and local lipid peroxidation, but also by the generation of local concentrations of oxygen that are toxic to the abnormal lesional (seborrheic keratosis) cells. The permeation of hydrogen peroxide through the skin into the circulation is considered highly unlikely.

Hydrogen peroxide levels measured in human plasma vary depending on techniques employed with reports of plasma H_2O_2 concentrations < 1 to 34 μM with some tissues such as kidney, bladder, and lung exposed to higher concentrations. These measurements are potentially affected by the stability of H_2O_2 in plasma and the ability of biological systems to generate H_2O_2. In a review of these methods of detection, Tarpey et al (2004) concluded that horseradish peroxidase photometric and fluorescein fluorescence assays can be significantly affected by endogenous substances that affect the assay and react with H2O2. Assessment of the ratio of reduced glutathione (GSH) to oxidise glutathione or glutathione disulfide (GSSG) provides a measure of oxidative stress as reported by Jones (2002), based on the approach of Asensi et al (1999). Serru et al (2001) reported on an assay to determine the GSH/GSSG ratio in whole human blood that has been adapted to detect changes in H_2O_2 exposure, which was refined by Steghens et al (2003) and more recently by Moore et al (2013). GSH can be rapidly converted to GSSG by any superoxide and GSH is continuously regenerated by the action of nicotinamide adenine

dinucleotide phosphate (NADPH)-dependent reductase, although this is a relatively slow process, such that the balance of GSH and GSSG provides a dynamic indicator of oxidative stress (Jones, 2002) and changes in blood H_2O_2 levels.

This assay was established for use with whole human blood to detect potential exposure of blood to the dermally applied A-101 H_2O_2 formulation. Detection of a change in the GSH/GSSG ratio would indicate that H_2O_2 could permeate through the skin, intact and without degradation, and enter the peripheral circulation, resulting in the conversion of GSH to GSSG. The assay was shown to be sensitive to changes in hydrogen peroxide concentration of > 10 ng/mL (equivalent to 0.3 μM hydrogen peroxide), ~0.01% of the hydrogen peroxide applied to each subject.

In Study A-101- SEBK-205 subjects were treated with vehicle on Visit 2 of treatment and hydrogen peroxide on Visit 3 (within 7 days of Visit 2) of treatment. Blood samples were analysed for GSH and GSSG content pre-dose and up to 6 h post application on each visit. GSH and GSSG levels and the calculated GSH/GSSG ratio for each subject from pre-dose to 6.5 hours post-dose at Visit 2 (no treatment) and 6 hours post-dose at Visit 3 (A-101 applied) were determined. The mean (standard deviation) baseline GSH/GSSG ratio was 2036 (877) at Visit 2 and 1933 (948) at Visit 3. There was either no change from baseline or a small reduction of mean GSH/GSSG ratio for all subjects during Visit 2 sampling (-3%), while during Visit 3 there was an overall increase in the GSH/GSSG ratio with a mean peak change of 8%. The mean data show no indication of a decrease in GSH/GSSG ratio on Visit 3, indicating no increase in blood exposure to H_2O_2 that would result in an increase in GSSG levels. Mean peak % reduction in GSH/GSSG ratio was -9.24 at Visit 2 and -4.18 at Visit 3; the peak reduction in GSH/GSSG ratio following application of A-101 Solution 40% was less than when there was no treatment. Comparison of these changes showed no significant difference indicating that A-101 treatment does not significantly change basal levels of H_2O_2 in blood and consequently does not significantly change the GSH/GSSG ratio.

Effects of hydrogen peroxide on cardiac ion channels

Several published studies on cardiac ion channels and excitation contraction coupling have been conducted with hydrogen peroxide. Of particular interest is the hERG channel is used as a model system for assessing the interaction of compounds with the ventricular the repolarizing potassium current IKr which defines the duration of the cardiac ventricular action potential and consequently the QT interval of the ECG.

Studies have been conducted on the effects of supra-physiological concentrations of hydrogen peroxide on the hERG channel current (Berube et al., 2001, tested at 30, 100 and 1000 μM hydrogen peroxide accelerated the activation of the hERG current resulting in an effective increase in current and allows a greater amount of potassium ions to flow through the channel during the first 150 ms of the plateau phase of the action potential (where IKr is predominant). This effect is translated to a functional impact on the native IKr and is considered to be involved in the action potential duration reduction or action potential shortening observed in cardiomyocytes (Goldhaber & Liu, 1994) and the guinea pig heart following exposure to hydrogen peroxide solutions (Hayashi et al., 1989) although again it should be noted that these observations were made at concentrations of 100 μM to 10 mM hydrogen peroxide.

These data suggest that hydrogen peroxide does not block the hERG channel but instead promotes the activity of the channel at high concentrations. These concentrations are significantly in excess of physiological levels and should therefore be considered to be

associated with pathophysiological conditions and might be attained only under conditions of ischemia/reperfusion.

Preclinical and clinical cardiac safety

Refer to Table 1.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

Table 1: Highlights of clinical pharmacology and cardiac safety

Therapeutic dose and exposure	ESKATA™ is hydrogen peroxide (H_2O_2) 40% w/w topical solution, indicated for the treatment of seborrheic keratosis (SK). ESKATA™ is applied directly to the targeted lesion(s) up to 4 times, approximately one minute apart, during a single in-office treatment session. This product is not intended for application by patients and not indicated for oral or ophthalmic use. The maximum total dose is anticipated to be up to 1.45 mL of 40% H_2O_2 equivalent to 580 mg of H_2O_2. H_2O_2 is a ubiquitous product of cellular metabolism with endogenous levels reported in the micro-molar range (circulating levels of <1 to 35 μM). Application of 40% H_2O_2 under maximum use conditions was shown not to produce a significant change in blood H_2O_2 levels.	
Maximum tolerated dose	40% H_2O_2	
Principal adverse events	Stinging and transient erythema at the site of application where solution is in contact with skin; no drug-related systemic adverse events were noted.	
Maximum dose tested	Single Dose	40% H_2O_2 up to 1.45 mL or ~ 580 mg applied to 10 SK lesions in a maximum use safety and PK study
	Multiple Dose	N/A – (only single doses administered)
Exposures Achieved at Maximum Tested Dose	Single Dose	No increase in endogenous levels detected
	Multiple Dose	N/A
Range of linear PK	N/A	
Accumulation at steady state	N/A	
Metabolites	Metabolites of H_2O_2 are water and oxygen	
Absorption	Absolute/Relative Bioavailability	N/A
	Tmax	N/A N/A
Distribution	Vd/F or Vd	Topically applied H_2O_2 is considered to permeate into the skin but immediately reacts or is metabolized in the skin and does not distribute further. Potential permeation to allow absorption into blood is very unlikely, but in this event H_2O_2 would be rapidly metabolized/catalytically deactivated by enzyme systems such as the antioxidant defense system including catalase, superoxide dismutase, glutathione peroxidase and thioredoxin reductase) These serve to effectively regulate H_2O_2 levels as was evidenced in the maximum use PK study.
	% bound	N/A
Elimination	Route	• Levels of H_2O_2 are measured in urine although this is the elimination of excess, endogenously produced, H_2O_2.

	Terminal t½	• Unknown
	CL/F or CL	Unknown
Intrinsic Factors	Age	N/A
	Sex	N/A
	Race	N/A
	Hepatic & Renal Impairment	N/A
Extrinsic Factors	Drug interactions	N/A
	Food Effects	N/A
Expected High Clinical Exposure Scenario	Topical application of 40% hydrogen peroxide (H_2O_2) formulation has been shown not to result in an increase in systemic levels of hydrogen peroxide	
Preclinical Cardiac Safety	Supra-physiological concentrations of hydrogen peroxide accelerated the activation of the hERG current resulting in an effective increase in current. A shortening of the cardiac action has been reported in guinea pig myocytes and whole heart. These effects were observed at concentrations of 100 μM to 10 mM and considered only reflective of potential local pathophysiological levels attained under conditions of ischaemia/reperfusion.	
Clinical Cardiac Safety	H_2O_2 had been applied topically (as A-101 formulation) on single occasions with no change in endogenous levels detected under maximum use conditions. No evaluation of ECGs was conducted in clinical trials with Eskata/A-101 topical formulation as there was no increase in circulating H_2O_2 levels after A-101 administration under maximum use conditions.	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DHANANJAY D MARATHE
08/31/2017

CHRISTINE E GARNETT
08/31/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209305 BLA# NA	NDA Supplement #: S- NA BLA Supplement #: S- BA	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Eskata Established/Proper Name: hydrogen peroxide Dosage Form: solution Strengths: 40% Route(s) of Administration: topical		
Applicant: Aclaris Therapeutics, Inc. Agent for Applicant (if applicable): NA		
Date of Application: February 24, 2017 Date of Receipt: February 24, 2017 Date clock started after Unacceptable for Filing (UN): NA		
PDUFA/BsUFA Goal Date: December 24, 2017	Action Goal Date (if different): December 22, 2017	
Filing Date: April 25, 2017	Date of Filing Meeting: April 4, 2017	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☒ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): For the treatment of seborrheic keratosis		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)	

Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 117635	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.***	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☒	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		

• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*	☐	☒		

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☒	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included.* ***Forms** include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		September 20, 2017
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	Full Waiver
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) (sponsor included in section 17) ☒ Instructions for Use (IFU) (sponsor added to section 16) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☐ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576 htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☐	☒	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent: CDRH OC and CDRH ODE March 2, 2017; DPMH consult – March 29, 2017; OSI – March 30, 2017***	☒	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** May 6, 2015	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** September 28, 2016	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** NA	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 4, 2017; 2:00 PM

BACKGROUND: NDA 209305 hydrogen peroxide solution, 40% for the treatment of seborrheic keratosis. The IND associated with this NDA is IND 117635. There was a Pre-NDA meeting on September 28, 2016 and an End-of-Phase 2 meeting on May 6, 2015. There is an agreed iPSP for a full waiver dated October 29, 2015.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Strother D. Dixon	Y
	CPMS/TL:	Barbara Gould	N
Cross-Discipline Team Leader (CDTL)	David Kettl, MD		Y
Division Director/Deputy	Jill Lindstrom, MD		Y
	Hon-Sum Ko, MD		Y
Associate Director Labeling	Nancy Xu, PhD		Y
Office Director/Deputy	NA		NA
Clinical	Reviewer:	Melissa Reyes, MD	Y
	TL:	David Kettl, MD	Y
Clinical Pharmacology	Reviewer:	Yanhui Lu	Y
	TL:	Chinmay Shukla, PhD	Y
	Director	Edward Bashaw, PhD	N
Biostatistics	Reviewer:	Kathleen Fritsch, PhD	Y
	TL:	Mohamed Alosh, PhD	Y

Nonclinical Pharmacology/Toxicology)	Reviewer:	Daivender Mainigi, PhD	Y
	TL:	Barbara Hill, PhD	Y
Product Quality (CMC) Review Team:	ATL:	Yichun Sun, PhD	Y
	RBPM:	Bamidele Aisida	N
• Drug Substance	Reviewer:	Sarah Ibrahim	N
• Drug Product	Reviewer:	Jeffrey Medwid	Y
• Process	Reviewer:	James Norman	N
• Microbiology	Reviewer:	Jennifer Sykora	N
• Facility	Reviewer:	Brian Ryan	N
• Biopharmaceutics	Reviewer:	NA	
• Immunogenicity	Reviewer:	NA	
• Labeling (BLAs only)	Reviewer:	NA	
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Susan Redwood	N
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Silvia Wanis	Y
	TL:	Matthew Falter	N
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Carlos Mena-Grillasca	Y
	TL:	Sarah Vee	Y

Bioresearch Monitoring (OSI)	Reviewer:	Bei Yu	N
	TL:	Phillip Kronstein	Y
CDRH	OC Reviewer	Robert Kang	N
	ODE Reviewer	Janice Ferguson	N
Other reviewers/disciplines			
Other attendees	Tri Bui Nguyen		Y
	Angela Brown		Y
	Cecilia Robinson		Y
	Hamid Tabatabai		Y
	Jessica Weintraub		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO Per the Clinical Pharmacology Filing Review: Via the 505(b)(2) regulatory pathway, the applicant has used literature data to support some of the Pharmacology-Toxicology information. Comparative bioavailability studies were deemed not necessary.
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☐ YES ☒ NO ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Jill Lindstrom, MD **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): Mid-cycle July 25, 2017 **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STROTHER D DIXON
05/05/2017

BARBARA J GOULD
05/05/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209305

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Eskata (hydrogen peroxide) solution, 40%

Applicant: Aclaris Therapeutics, Inc.

Receipt Date: February 24, 2017

Goal Date: December 24, 2017

1. Regulatory History and Applicant's Main Proposals

NDA 209305 hydrogen peroxide solution, 40% is an original NDA for the treatment of seborrheic keratosis. The IND associated with this NDA is IND 117635. There was a Pre-NDA meeting on September 28, 2016 and an End-of-Phase 2 meeting on May 6, 2015. There is an agreed iPSP for a full waiver dated October 29, 2015.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

In addition, the following labeling issues were identified:

1. The sponsor combined patient use instructions in section 16.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by May 15, 2017. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

NO 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *Increase the left margin of the HL to 1/2 inch.*

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *The revised date is below the half page portion of the page. Decrease the font or decrease the top header to ensure the entire HL section is one-half page or less.*

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

NO 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *Add a numerical identifier after the statement "The safety of more than 4 ESKATA treatments has not been determined."*

NO 7. Headings in HL must be presented in the following order:

Selected Requirements of Prescribing Information

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

Selected Requirements of Prescribing Information

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

NO 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment: *The RPM will update at time of approval. Will edit to MM/YYYY until time of approval*

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

NO 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: *6.1in the FPI the "s" is missing from Trials; The study number in the 14.2 title is 301 in the TOC and 302 in the FPI*

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *Section 8.3 is not included*

NO 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*."

Comment: *The cross-references in section 2 should refer to the section, followed by a numerical identifier, be in italics and enclosed within brackets.*

Selected Requirements of Prescribing Information

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

NO 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *Add "Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use)" to the beginning of Section 17.*

NO 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *In your label, the Patient Information is a subsection under Section 17 (PATIENT COUNSELING INFORMATION). Provide language for Section 17 and create delineation between Section 17 and the Patient Information labeling. Refer to Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products — Content and Format.*

Appendix: Highlights and Table of Contents Format

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

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STROTHER D DIXON
04/04/2017

BARBARA J GOULD
04/04/2017