CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209305Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	November 27, 2017
From	Snezana Trajkovic, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	209305
Applicant	Aclaris Therapeutics, Inc.
Date of Submission	February 24, 2017
PDUFA Goal Date	December 24, 2017
Proprietary Name / Established (USAN) names	Eskata/ hydrogen peroxide
Dosage forms / Strength	Solution/ 40%
Proposed Indication(s)	Treatment of seborrheic keratoses
Recommended:	*Approval*

1. Introduction

Eskata solution, 40% is a drug product for which the applicant seeks approval under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act for the topical treatment of seborrheic keratosis.

ESKATA is to be administered by a health care provider. The proposed dosing regimen for Eskata solution, 40% is as follows:

During a single in-office treatment session, apply Eskata to seborrheic ketosis lesions 4 times, approximately 1 minute apart. If the treated lesions have not completely cleared approximately 3 weeks after treatment, another treatment may be administered following the same procedure.

2. Background

The active ingredient, hydrogen peroxide (H_2O_2), is an oxidizing agent that can induce lipid and membrane peroxidation, protein oxidation, and lead to apoptosis and necrotic cell death. Hydrogen peroxide is continuously generated endogenously during cell lipid metabolism and is rapidly degraded to water and oxygen anion by the built-in complex antioxidant system (e.g. catalases, superoxide dismutase, etc.) and released from cellular peroxisomes. Thus, the nontoxic intracellular (basal) concentration of hydrogen peroxide is tightly controlled under the normal physiological conditions.

At a concentration of 3%, hydrogen peroxide is marketed in the United States under tentative final monograph as an oral health care debriding agent.

Eskata was developed under the IND 117635 by Aclaris Therapeutics, Inc. During their development program, the applicant interacted with the Agency as follows:

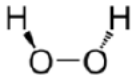
End-of-Phase 2 meeting (held on May 6, 2015)
The following advice was conveyed to the sponsor:

- The Agency advised submitting information and a sample of the delivery device prior to initiation of Phase 3 trials. A different device was used in Phase 2 trials.
- The sponsor agreed with the Agency's advice to enroll subjects with at least four SK lesions on the trunk, extremities and face and
- The sponsor agreed that primary endpoint should be a complete clearance of all four SK lesions.
- The sponsor clarified intent to limit distribution of the product for in-office use based on need for diagnosis of SK lesions by a healthcare provider.

Pre-NDA meeting (held on September 28, 2016)
The content and format of the proposed NDA submission was discussed.

3. CMC/Device

Drug Substance
ESKATA (hydrogen peroxide) topical solution, 40% is a clear, colorless solution for topical administration that contains the active drug substance, hydrogen peroxide. Hydrogen peroxide is an oxidizing agent that can induce lipid and membrane peroxidation, protein oxidation, and lead to apoptosis and cell death. The chemical structure of hydrogen peroxide is:



Hydrogen peroxide has a molecular formulation of H_2O_2 and molecular weight of 34.01 g/mol. The drug substance is being manufactured by (b) (4).

Drug Product
The drug product of the is hydrogen peroxide topical solution, 40% (w/w). It contains a concentrated aqueous solution of hydrogen peroxide as the drug substance. The composition of the drug product is presented below.

Composition of A-101 (Hydrogen Peroxide) 40% Topical Solution

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

Source: Applicants submission; Section 3.2.P.1 Description and Composition of the Drug Product; page 1.

The drug product is contained in clear, (b) (4) glass ampoules at 1.5 mL or 2.2 mL for the intended minimum delivery volume of 0.7 mL and 1.3 mL, respectively. The ampoules are subsequently assembled into applicators which are packaged for individual use.

Device
The applicant's proposed container applicator encloses HP 40% solution in a glass ampoule. Each applicator consists of a (b) (4) tube, protective cap, (b) (4) tip and paper sleeve on the applicator tube. A clear USP (b) (4) glass ampoule filled with hydrogen peroxide solution 40% (w/w) is placed inside of the applicator. At the time of use, the applicator is squeezed at the labeled area to crush the glass ampoule, and release drug product solution through the (b) (4) applicator tip for topical administration. The photograph of the container applicator is presented below.

Drug Product Applicator Photos

Stability and Shelf-life
The registration stability studies were conducted at 5°C, 25°C/60%RH, and 40°C/75%RH. The stability data submitted is sufficient to support the proposed expiration dating period of 24 months when stored at room temperature.

Recommendation
The product quality review team made the following conclusion: "The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product."

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

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

4. Nonclinical Pharmacology/Toxicology

Under the original IND 117635, in 4-week dermal studies (vehicle and sham controls, 25%, 32.5% and 40% hydrogen peroxide) in rats and minipigs, animals received four weekly applications of test solutions, followed by 2- week recovery period.

In a 4-week rat study, immediately following the first application, white patches were observed in most high-dose of the animals; these lesions completely disappeared by day four. In addition, flaky skin and scabbing was observed on the dorsal anterior or posterior regions of some the same females. No dermal reactions were observed at the end of the recovery period.

In rats, the mean average pre-dose plasma (basal) level of H_2O_2 on day 1 was 0.62μM (0.352-0.887μM). On the same day, plasma peroxide levels after treatment with 25% and 32.5% remained within the basal range at all-time points. In 40% animals, the concentration doubled to 1.2μM at 10 minutes returning to basal range within 30 minutes. After the second weekly dose, the plasma level at 10 minutes was 1.3μM and 1.5μM at 1 hour, returning to basal level at 6.5 hour.

In a 4-week minipig study, histologically, transient skin reactions were more pronounced in H_2O_2 treated animals, including degeneration of superficial collagen fiber, vacuolation of superficial dermis, perivascular inflammatory infiltrate, epidermal bullae and attenuation, basal cell hyperplasia, and occasional epidermal necrosis. At recovery, 3/6 high-dose animals still exhibited these lesions.

The pre-dose basal plasma concentration of H_2O_2 ranged between 0.05 to 3.255μM. Irrespective of the gender; dose level; duration of treatment; or blood sampling time, the plasma concentration of peroxide did not exceed the basal range.

In 12-week rat study, 40% hydrogen peroxide was well tolerated locally and systemically following weekly topical applications. Dose-dependent (32.5% and 40%) reversible lesions (blanched skin, edema, scabs etc.) were confined to applications sites. At the end of the recovery period of 28 days, histological findings were similar in drug and vehicle treated groups.

In the 12-week minipig study, a 45% concentration of H_2O_2 was applied to 2.5% of BSA. This higher concentration of H_2O_2 for 12 weeks did not cause systemic toxicity, indicating none or negligible absorption. The completely reversible local toxicity was confined to skin irritation reactions such as minimal to slight capillary ectasia/congestion and inflammation of the superficial dermis, minimal to slight epidermal hyperplasia and epidermal vacuolation. Local lesions were similar to those observed in minipigs receiving 40% hydrogen peroxide.

Because no systemic toxicity was observed in rat and minipig studies, and no penetration occurred through the dermatomed minipig and human skins (Franz pump), no safety pharmacology studies were deemed necessary.

For *in vitro* and *in vivo* genotoxicity studies, the applicant relied on published literature.

Because of high cytotoxicity of H_2O_2, *in vitro* genotoxicity studies were positive in terms of reverse mutation assays, gene mutation, chromosomal aberration, DNA strand break, unscheduled DNA synthesis, and DNA damage and sister chromatid exchange. However, *in vivo* genotoxicity studies were negative, due to lack of translation, rapid catabolism of peroxide to its basal nontoxic level, and buffering/detoxifying systems in plasma not permitting this level to elevate above the endogenous concentration.

Consistently generated peroxide in all internal organs including gonads is rapidly disposed. Hydrogen peroxide is not absorbed through the skin and is rapidly degraded into water and oxygen by skin catalases. Because of short duration of treatment, lack of any dermal absorption and lack of systemic toxicity, negative non-mutagenic and non-clastogenic behavior in *in vivo* genotoxicity studies, carcinogenicity studies with hydrogen peroxide are not warranted.

Based on the same biological rationale, there is no need to conduct reproductive and developmental studies with hydrogen peroxide.

Local lymph node assay in mice established that hydrogen peroxide formulation is not a sensitizer.

After comprehensive evaluation of ocular studies conducted with various H_2O_2 formulations (consumer products), the European Commission opinion SCCP/1129/07 in 2007 declared hydrogen peroxide as an ocular irritant with a threshold level for human eye ranging from 0.03 to 0.1 percent.

In phototoxicity assay, MEC (molar extinction coefficient) of (b) (4) for hydrogen peroxide was considered negligible compared to threshold of 1,000 MEC required to cause any cellular photo damage.

Pharmacology/Toxicology reviewer, Kumar D. Mainigi, Ph.D., recommended the approval of this NDA.

5. Clinical Pharmacology/Biopharmaceutics

The active pharmaceutical ingredient (API) used in the drug product, ESKATA topical solution 40%, is hydrogen peroxide. Hydrogen peroxide is an oxidizing agent that can induce lipid and membrane peroxidation, protein oxidation, and lead to apoptosis and necrotic cell death.

Pharmacokinetics (PK)
The bioavailability of Eskata under maximal use conditions was evaluated in trial A-101-SEBK-205.

Trial A-101-SEBK-205 was an open-label trial in 24 adult subjects who had 10 eligible SK target lesions on the face, trunk and extremities. At baseline, prior to treatment, blood samples were obtained. Subjects' SKs were treated with single application of the study product.

Because HP rapidly degrades into water and oxygen, direct measurement of HP in blood was not possible. Instead, the changes in concentration ratio of glutathione (GSH, reduced form) and glutathione disulfide (GSSG, oxidized form) in blood, were measured following single application of Eskata to SK lesions. The GSH/GSSG ratio in post-treatment blood samples did not change significantly following application of Eskata when compared to pre-dose samples, suggesting no systemic absorption of hydrogen peroxide following topical administration of Eskata.

QT study
The Applicant submitted a waiver from conducting thorough QT/QTc (TQT) study for Eskata on 5/16/2017. The QT Interdisciplinary Review Team reviewed the waiver request and agreed with the applicant that the thorough QT/QTc study 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 (H2O2) 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 H2O2 under maximum use conditions.*
- *The nonclinical data does not suggest potential for hERG inhibition (in fact, supraphysiological 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.*

For more information refer to full review by Dhananjay D. Marathe dated 8/31/2017.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The applicant submitted data from two Phase 3 trials [(A-101-SEBK-301 (Study 301) and A-101-SEBK-302 (Study 302)] to establish the effectiveness of their product in the treatment of actinic keratosis (SK) that are raised. These were identically designed, randomized, multicenter, double-blind, vehicle-controlled, Phase 3 trials that evaluated the safety and efficacy of HP 40% solution for the treatment of raised SK on the face, trunk and extremities. The two trials evaluated in 937 subjects, 18 years and older, with who had four SK target lesions (SKTLs) with at least one target lesion on the face and with at least one target lesion on the trunk or extremities. Each lesion was treated with 4 applications of study drug, at baseline and again at Day 22, if the lesion was still present.

Efficacy was assessed on Day 106. The primary endpoint was the proportion of subjects with clearance of all target SK lesions at Day 106. The pre-specified secondary endpoint was the proportion of subjects who achieved clearance of three or more target lesions at Day 106 compared to baseline.

In both trials, Eskata was statistically superior to vehicle for all endpoints. The efficacy results are presented in Table below.

Table: Results of the Primary and Secondary Endpoints for Trials SEBK-301 and SEBK-302

	Study 301			Study 302		
	Hyd. Per. N=223	Vehicle N=227	P-value	Hyd. Per. N=244	Vehicle N=243	P-value
All 4 lesions clear	9 (4.0%)	0 (0%)	0.002	19 (7.8%)	0 (0%)	<0.001
≥ 3 lesions clear	30 (13.5%)	0 (0%)	<0.001	56 (23.0%)	0 (0%)	<0.001

Source: Statistical review by Kathleen Fritsch, Ph.D., Table 1; page 3.

In the Study 302, the response rate in the hydrogen peroxide arm was nearly twice the response rate observed in the trial Study 301. The higher response rate in Study 302 was driven by the results at a single center, as this center enrolled about 9% of the total subjects, but includes 53% of the subjects who achieved complete clearance. In a sensitivity analyses where the center with the high proportion of responders is removed, the results of Study 302 remain statistically significant.

For detailed review of the Phase 3 trials and additional analyses, the reader is referred to the biostatistics review by Kathleen Fritsch, Ph.D.,

8. Safety

The applicant conducted two identical randomized, vehicle controlled, Phase 3 trials (A-101-SEBK-301 and A-101-SEBK-302) in subjects 18 years of age and older, with the raised SK lesions on the face, trunk and extremities. Pooled data from these Phase 3 trials comprise the primary safety database. Safety was also derived from the open-label Phase 3 trial (SEBK-303) and Phase 1 and Phase 2 trials that assessed safety of HP 40% during the development program for the SK indication.

The primary safety population was comprised of subjects who took part in two Phase 3 trials (A-101-SEBK-301 and A-101-SEBK-302) that included a total of 467 subjects who were treated with Eskata solution, 40%

Safety Results
One death (metastatic carcinoma of unknown primary) was reported during the development program for Eskata. The temporal relationship of death to the treatment and the mechanism of action of HP does not support a causal relationship.

In two Phase 3 trials, 10 subjects in each treatment arm experienced non-fatal SAEs. These SAEs were not considered treatment related.

In Phase 2 trials (SEBK-201, SEBK-202, and SEBK-203) an additional 5 non-fatal SAEs were reported. These SAEs were not considered treatment related.

The most frequently reported adverse reactions were local skin reactions. Local adverse reactions were consistent with the mechanism of action of hydrogen peroxide. Systemic adverse reactions were not expected as the drug product is not systemically absorbed.

Table: Percent of Subjects with Local Skin Reactions
Trials SEBK-301 and SEBK-302

	ESKATA N=467	Vehicle N=470
Erythema	99 %	34 %
Stinging	97 %	10 %
Edema	91 %	6 %
Scaling	90 %	33 %
Crusting	81 %	19 %
Pruritus	58 %	8 %
Hyperpigmentation	39 %	1 %
Vesicles	24 %	<1 %
Hypopigmentation	19 %	1 %
Erosion	15 %	1 %
Ulceration	9 %	2 %
Atrophy	4 %	0 %
Scarring	3 %	0 %

Source: Clinical review by Dr. Melissa Reyes.

The type and severity of adverse reactions correlated with time from the treatment.

- Common local skin reactions observed 10 minutes after treatment were: erythema (98%); stinging (93%); edema (85%); pruritus (32%) and vesiculation (18%).

- Common local skin reactions observed one week after the treatment were: scaling (72%); crusting (67%); erosions (9%) and ulcerations (4%).

- At Day 106, local skin reactions occurring in at least 1% of the subjects were: erythema (21%); hyperpigmentation (18%); crusting (12%); hypopigmentation (7%); scarring (1%), and atrophy (1%).

Less common adverse reactions occurring in $\geq$ 0.5% of subjects treated with Eskata were eyelid edema (0.6%) and herpes zoster (0.6%).

9. Advisory Committee Meeting

Not applicable; this application was not presented to the Advisory Committee as the application did not raise novel or controversial issues that would merit outside discussion.

10. Pediatrics

Clinical trials submitted in support of this application were conducted in adult subjects. The Applicant had an Agreed Initial Pediatric Study Plan (iPSP) dated 10/29/2015.

With this NDA, the applicant submitted a request for a waiver from conducting studies in pediatric patients 0 to less than 18 years of age. The reason stated was that, studies would be impossible or highly impracticable, given the low prevalence of SKs in the pediatric population.

Applicant's proposed Pediatric Study Plan was presented to Pediatric Review Committee (PeRC) on September 20, 2017. The PeRC agreed with the plan for a full waiver as studies are impossible of highly impracticable.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

We have completed our review of the proposed proprietary name Eskata and, found to be acceptable.

12. Labeling

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. Professional and patient labeling were reviewed, and negotiations regarding the contents are ongoing at the time of closure of this review.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**: Approval
  I concur with the recommendations of the multi-disciplinary review team for approval of NDA 209305, Eskata Solution, 40% pending agreement by the applicant with the recommended labeling revisions.

- **Risk Benefit Assessment:**
  The risk-benefit assessment supports approval of this product for the treatment of seborrhoeic keratoses that are raised, in patients 18 years of age and older.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**
  No postmarketing risk evaluation and mitigation strategies are recommended for this product.

- **Recommendation for other Postmarketing Requirements and Commitments**

Postmarketing risk management beyond professional labeling, drug administration by healthcare provider, and routine pharmacovigilance, is not needed.

- **Recommended Comments to Applicant**
  None.

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

/s/

SNEZANA TRAJKOVIC
11/27/2017