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APPLICATION NUMBER:

207695Orig1s000

SUMMARY REVIEW

Deputy Division Director Summary Review for Regulatory Action

Date	13 December 2016
From	Jill A Lindstrom, MD
Subject	Deputy Division Director Summary Review
NDA #	207695
Applicant	Anacor Pharmaceuticals, Inc.
Date of Submission	7 January 2016
PDUFA Goal Date	7 January 2017
Proprietary Name	Eucrisa
Non-Proprietary Name	crisaborole
Dosage Form	Ointment
Strength	2% (w/w)
Applicant Proposed Indication(s)/Population(s)	Topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.
Recommended Action for NME:	<i>(Approval vs. Complete Response)</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Melinda McCord, MD
Statistical Review	Matthew Guerra, PhD
Pharmacology Toxicology Review	Kumar Mainigi, PhD
OPQ Review	Joseph Leginus, PhD; Bhavishya Mittal, PhD; Kejun Cheng, PhD; Vipulchandra Dholakia, PhD; Vidula Kolhatkar, PhD; Samata Tiwari, PhD; Maria Cowan; Raanan Bloom, PhD; Yichun Sun, PhD
Clinical Pharmacology Review	Chinmay Shukla, PhD
QT Interdisciplinary Review	Jiang Liu, PhD

Pediatric and Maternal Health Consult	Erica Radden, MD; Jane Liedtka, MD
DPP Consult	Jean Kim, MD, MA
Labeling	Nancy Xu, MD
Project Management	Omolara Laiyemo, PhD
OPDP	Tara Turnher, PharmD, MPH
DMPP	Sharon R. Mills, BSN, RN, CCRP
OSI	Roy Blay, PhD
OSE/DMEPA	Carlos Mena-Grillasca, RPh
OSE/DRISK	Jacqueline Sheppard, PharmD
CDTL Review	Snezana Trajkovic

OND=Office of New Drugs

OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

CDTL=Cross-Discipline Team Leader

DPMH=Division of Pediatric and Maternal Health

DPP=Division of Psychiatry Products

OSE= Office of Surveillance and Epidemiology

DMPP= Division of Medical Policy and Practices

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease that predominantly affects the children but also occurs in adults. Clinical manifestations include erythematous papules and plaques with oozing, scale, crust, excoriations, and lichenification. The face and flexures are areas of predilection. Pruritus is the primary symptom. AD is associated with multiple comorbidities, and impairs both individual and family quality of life. Eucrisa (crisaborole) ointment, 2% is proposed for topical administration twice daily for the treatment of mild to moderate AD in patients 2 years of age and older. Crisaborole, the active ingredient in Eucrisa, is a phosphodiesterase-4 (PDE-4) inhibitor.

The current therapeutic armamentarium for mild to moderate AD includes a variety of topical corticosteroids, topical calcineurin inhibitors, and device creams. Topical corticosteroids are associated with adverse reactions (AR) such as hypothalamic-pituitary-adrenal (HPA) axis suppression, atrophy, striae, telangiectasia, and others. Topical calcineurin inhibitors are indicated as second-line therapy and are labeled with a boxed warning for risk of skin malignancy and lymphoma. Efficacy of the device creams is modest. Because of these limitations, despite the number of available therapies, there is need for additional therapeutic options, particularly with a favorable safety profile.

Two pivotal trials (AN2723-AD-301 and AN2728-AD-302), identical in design, enrolled 1522 subjects 2 years of age and older with AD affecting at least 5% of the body surface area (BSA) and a score of mild (2) or moderate (3) on a 5-grade investigator static global assessment scale (ISGA) that rated erythema, induration/papulation, and oozing/crusting. The primary efficacy endpoint was the proportion of subjects who achieved success in ISGA, defined as a score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline, at Day 29 in the crisaborole-treated group compared to the vehicle-treated group. A significantly greater proportion of subjects treated with crisaborole ointment, 2% achieved success compared to vehicle; the magnitudes of the treatment effect in the two studies were 7.4% and 13.4%, respectively. These results demonstrate modest efficacy of Eucrisa in the treatment of mild to moderate AD.

The safety database was adequate to characterize the safety profile of Eucrisa. In the two pivotal trials, 1012 subjects received the proposed dose of crisaborole. The most frequently reported adverse reaction was application site pain. Contact urticarial was reported in 2 subjects in the crisaborole group and 3 subjects in the vehicle; although the precipitant in these cases is not known, butylated

hydroxytoluene has been implicated in other cases of contact and generalized urticarial and is an excipient in the product. The risk for hypersensitivity is addressed in patient and professional labeling.

Prescription and patient labeling and routine pharmacovigilance are adequate to manage the risks of Eucrisa in the post market milieu; a Risk Evaluation and Mitigation Strategy (REMS) is not needed. Recommended post marketing studies include a pediatric safety and pharmacokinetic (PK) study.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<ul style="list-style-type: none"> • Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease that affects children (predominantly) and adults. Clinical manifestations include erythematous papules and plaques with oozing, scale, crust, and lichenification. The face and flexures are areas of predilection. Pruritus is invariably present and xerosis is common. • In the US, overall prevalence is 6% and prevalence in children is 11%. Disease onset is typically in childhood: 60% of patients develop skin manifestations by 1 year of age and 85% by five years of age. Of those who develop AD in childhood, in approximately one third the disease will persist into adulthood. Approximately one third of patients report mild disease and one half report moderate disease. • Comorbidities include sleep impairment (associated with behavioral deficits and neurocognitive impairment), asthma, allergic rhinitis, food allergies, cutaneous infections, extracutaneous infections, and various psychiatric comorbidities. • Quality of life is impaired for both patients and their families. 	<p>Mild to moderate atopic dermatitis is a common inflammatory skin disease with significant impact on patients and their families due the cutaneous manifestations, accompanying pruritus, co-morbidities, and impairment of quality of life.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Current Treatment Options</p>	<ul style="list-style-type: none"> • Available therapy for mild to moderate AD includes topical corticosteroid products, topical calcineurin inhibitor products, and cleared device creams. • Topical corticosteroid products approved for the treatment of AD (alone or as a subset of the indication of corticosteroid responsive dermatoses) include: fluticasone propionate cream, 0.05%; hydrocortisone butyrate cream, 0.1%; mometasone furoate cream, 0.1%; mometasone furoate lotion, 0.1%; halobetasol propionate 0.05%; desonide gel, 0.05%; desonide foam, 0.05%; fluocinonide cream, 0.1%. • Topical corticosteroid products are associated with local and systemic adverse reactions (AR). Local AR include skin atrophy, striae, telangiectasia, irritation, folliculitis, acneiform eruptions, hypopigmentation, allergic contact dermatitis, and secondary infections. Systemic AR include hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing’s syndrome, hyperglycemia and unmasking of latent diabetes mellitus. • Pimecrolimus cream, 1% is a topical calcineurin inhibitor approved as a second-line therapy for the treatment of mild to moderate AD in patients who have failed other topical treatments. Tacrolimus ointment, 0.03% and 0.1%, is indicated as second-line therapy for patients with moderate to severe AD who have failed other topical treatments. • Labeling for both TCIs include boxed warning regarding reports of skin malignancies (e.g., basal cell carcinoma; squamous cell carcinoma; malignant melanoma) and lymphomas. • Device creams that are 510-k cleared for treatment of AD include 	<p>There are a number of FDA-approved or cleared treatment options for mild to moderate AD. However, because of the potential for adverse reactions or incomplete or lack of response, additional therapeutic options are needed.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Atopiclair, Eleton , EpiCeram, and Mimex. Efficacy is modest.	
Benefit	<ul style="list-style-type: none"> Two pivotal trials (AN2723-AD-301 and AN2728-AD-302), identical in design, enrolled 1522 subjects 2 years of age and older with AD affecting at least 5% of the body surface area (BSA) and a score of mild (2) or moderate (3) on a 5-grade investigator static global assessment scale (ISGA) that rated erythema, induration/papulation, and oozing/crusting. Subjects were randomized to receive crisaborole ointment, 2%, or vehicle ointment, applied twice daily to affected skin for 28 days. The primary efficacy endpoint was the proportion of subjects who achieved success in ISGA, defined as a score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline, at Day 29 in the crisaborole-treated group compared to the vehicle-treated group. A significantly greater proportion of subjects treated with crisaborole ointment, 2% achieved success compared to vehicle; the magnitudes of the treatment effect in the two studies were 7.4% and 13.4%, respectively. 	<p>The data submitted by the applicant meet the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled, and demonstrated modest efficacy for crisaborole ointment, 2%</p>
Risk	<ul style="list-style-type: none"> The overall safety database in AD, based on subjects who received crisaborole at concentrations from 0.3 to 5%, includes data from 1340 subjects, 1150 of whom were <17 years of age. The primary safety database for AD, comprised of pooled data from the Phase 3 trials, includes data from 1012 subjects who received crisaborole and 499 subjects who received vehicle. The size of the safety database is adequate to characterize adverse events. The most frequently reported adverse reaction was application site 	<p>The safety profile of crisaborole ointment has been adequately characterized. The most significant risk is for hypersensitivity or contact urticaria; the most common adverse reaction is application site pain. At this time, the safety profile appears more favorable than topical corticosteroids or calcineurin inhibitors but less favorable than device creams.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>pain.</p> <ul style="list-style-type: none"> Application site (contact) urticaria was reported in 2 subjects in the crisaborole treatment group and three subjects in the vehicle group. Exposure to butylated hydroxytoluene, an excipient in the product, is known to precipitate both contact urticaria and generalized urticaria. The risk for hypersensitivity reactions, including contact urticaria, is addressed in labeling. 	
<p>Risk Management</p>	<ul style="list-style-type: none"> Labeling: Prescription labeling adequately addresses the risks identified during product development. A Patient Package Insert was proposed; patient labeling is appropriate to inform patients about the risk for hypersensitivity. A REMS is not recommended. 	<p>Prescription labeling, patient labeling and routine pharmacovigilance are adequate to manage the risks of the product.</p> <p>Prescription labeling adequately addresses the potential risks with crisaborole use.</p>

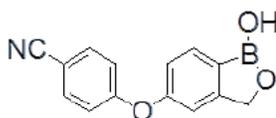
2. Background

Eucrisa (crisaborole) ointment, 2% is a topical drug product for which the applicant seeks approval under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the indication of treatment of mild to moderate atopic dermatitis (AD) in patients 2 years of age and older. Crisaborole is a phosphodiesterase-4 (PDE-4) inhibitor. Crisaborole is not currently marketed in the US or other jurisdictions for any indication. Crisaborole will be the third moiety in the class of PDE-4 inhibitors approved for marketing, and the first topical PDE-4 inhibitor product. The proposed dose is application of a thin layer to affected skin twice daily.

AD is a chronic, pruritic inflammatory skin disease that predominantly affects the pediatric population but also occurs in adults. Clinical manifestations include erythematous papules and plaques with oozing, scale, crust, excoriations, and lichenification. The face and flexures are areas of predilection (distribution varies by age), but involvement can be generalized. Xerosis is common. Pruritus is the primary symptom. Associated comorbidities include sleep loss and psychosocial stress. For mild to moderate disease, therapeutic options include i) nonpharmacologic measures such as bathing practices, moisturizers and device creams, and ii) topical drug products such as corticosteroids and calcineurin inhibitors. Phototherapy and systemic products, including immunosuppressant products used off-label, are generally reserved for moderate to severe disease that is refractory to optimized topical therapy.

3. Product Quality

The drug substance, crisaborole, is a low molecular weight benzoxaborole phosphodiesterase-4 (PDE-4) inhibitor, which has a physical appearance of a white to pale yellow powder. The chemical name is 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-[2,1]-benzoxaborole; the molecular formula is $C_{14}H_{10}BNO_3$ and the molecular weight is 251.1 g/mol. The chemical structure of crisaborole is:



The drug product, Eucrisa ointment, is white to off-white in color and contains 2% (20mg/gm) of crisaborole. The composition of the drug product is described in the following table:

Ingredient	Function	Concentration (%w/w)
Crisaborole	Active	2.0000
White petrolatum	Ointment base	(b) (4)
Propylene glycol	(b) (4)	(b) (4)
Mono- and di-glycerides	(b) (4)	(b) (4)
Paraffin	(b) (4)	(b) (4)
Butylated hydroxytoluene	(b) (4)	(b) (4)
Edetate calcium disodium	(b) (4)	(b) (4)

Source: Adapted from Quality Assessment Review 1, archived 8/17/16, p41.

There are no novel excipients. Because the product has (b) (4), it does not support microbial growth and needs no preservative/s.

The drug product is packaged into 100gm, 60gm and 2.5gm (physician sample) (b) (4) tube sleeves with (b) (4) tube heads with (u) (4) seals and (b) (4) caps. Stability data support an expiry of 24 months shelf life for the commercial sizes (100gm, 60gm) and 22 months for the physician sample (2.5 gm). The applicant committed to place a minimum of one production lot for each presentation on stability each year.

The facility review team completed facilities inspections and issued an overall “Acceptable” recommendation.

The applicant’s claim of categorical exclusion based on “no extraordinary circumstances” was deemed acceptable.

The Application Technical Lead, Dr. Yichun Sun, concluded that the applicant provided sufficient information to assure the identity, strength, purity and quality of the drug substance and drug product, and did not recommend any postmarketing commitments.

4. Nonclinical Pharmacology/Toxicology

Crisaborole was found to inhibit phosphodiesterase 4, which results in increased intracellular cyclic adenosine monophosphate (cAMP) levels and blocks the signal for release of proinflammatory cytokines.

Oral and dermal repeat-dose toxicity studies, in rat and minipig, respectively, identified no systemic toxicity and only sporadic dermal lesions in all groups attributed to trauma. Crisaborole was found to be a low-potency HERG channel blocker; in an oral single-dose cardiovascular safety study in dogs no ECG effects were noted.

Crisaborole was not genotoxic as assessed by the Ames assay, an in vitro chromosome aberration assay of human peripheral blood lymphocytes, and an in vivo rat micronucleus assay. A two-year dermal carcinogenicity study in mice did not find evidence of crisaborole-induced tumors, but a two-year oral carcinogenicity study in rats found an increased incidence of benign granular cell tumors in the high dose group, the clinical relevance of which is unknown.

The applicant conducted 6-month oral (rat) and 9-month dermal (minipig) repeat-dose safety toxicology studies, 2-year oral (rat) and dermal (mouse) carcinogenicity studies, and reproductive and developmental toxicity studies. No systemic toxicity was identified in either the in the 6-month oral repeat-dose toxicity study in rats or the 9-month dermal repeat-dose toxicity study in minipigs; sporadic dermal lesions in all groups were attributed to traumatic abrasions.

Reproductive toxicity studies were conducted in rats and rabbits. In rabbits, in the highest dose group, maternal toxicity, decreased fetal body weight and delayed skeletal ossification was observed. No treatment related fetal malformations were noted in rats or at lower doses in rabbits. Developmental toxicity studies were conducted in rats. Maternal toxicity was seen in the highest dose group and was associated with findings of stillbirths, pup mortality and reduced pup weights. These findings will be conveyed in Section 8.1 Pregnancy of labeling. The Nonclinical Pharmacology/Toxicology reviewer, Dr. Kumar Mainigi, found the application acceptable from a pharmacology/toxicology perspective and recommended approval.

5. Clinical Pharmacology

Eucrisa (crisaborole) ointment will be marketed at a 2% concentration; the route of administration is topical and the dose regimen is application to affected skin twice a day.

The applicant conducted a pharmacokinetic study under maximal use conditions in 33 subjects with atopic dermatitis ages 2 to 17 years. Crisaborole and its metabolites were quantified in serum from all subjects. Steady state was reached by day 8. For crisaborole on day 8, the maximum plasma concentration (C_{max}) was 127 ± 196 ng/mL, and the area under the concentration curve from 0 to 12 hours post dose (AUC_{0-12}) was 949 ± 1240 ng-h/mL.

The applicant conducted in vitro and clinical drug interaction assessments. Neither crisaborole nor major metabolite AN7602 is expected to impact CYP enzymes. Although the downstream metabolite AN8323 was identified as a weak to moderate inhibitor of CYP enzymes in vitro, a clinical study found no drug interaction effect on the most sensitive enzyme, CYP2C9, and thus AN8323 is not expected to produce clinically meaningful inhibition of any CYP enzymes.

To address the impact of crisaborole on repolarization, the applicant conducted a thorough QT study in healthy adults in which crisaborole was applied to 60% of body surface area of subjects in the suprathreshold dose group. No significant prolongation of the QTc interval was identified; however systemic crisaborole exposure in the suprathreshold dose group was lower than that in the maximal use pharmacokinetic trial. Analysis of ECGs obtained during the pivotal trials found no subjects with QTcF >480ms or a change in QTcF from baseline of >30ms. Thus it appears that crisaborole has no clinically significant impact on cardiac repolarization.

The Clinical Pharmacology Reviewer, Dr. Chinmay Shukla, recommended approval of the application from a Clinical Pharmacology perspective.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant submitted data from two pivotal trials, AN2723-AD-301 and AN2728-AD-302 (hereafter 301 and 302), to establish the effectiveness of their product in the treatment of mild to moderate atopic dermatitis. The trials were identical multi-center, prospective, randomized, double-blind, placebo-controlled parallel group studies, conducted concurrently in the US to evaluate the effect of crisaborole ointment, 2%, applied twice daily for 28 days.

The trials enrolled children and adults 2 years of age and older with atopic dermatitis affecting at least 5% of the body surface area (BSA) and a score of mild (2) or moderate (3) on a 5-grade investigator static global assessment scale (ISGA) that rated erythema, induration/papulation, and oozing/crusting. Subjects were permitted to use a bland emollient on uninvolved skin “...but not on or overlapping the treatable AD-involved areas (emphasis original)”. Use of topical or systemic corticosteroids or topical calcineurin inhibitors was prohibited during the study. Subjects on stable regimens of oral antihistamines or inhaled corticosteroids were allowed to continue these treatments. Subjects were randomized 2:1 to active versus vehicle.

The primary efficacy measure was the ISGA. The primary efficacy variable was success in ISGA, defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline. The primary efficacy endpoint was the proportion of subjects who achieved success in ISGA at Day 29 in the crisaborole-treated group compared to the vehicle-treated group. Secondary endpoints included i) the proportion of subjects with an ISGA score of Clear (0) or Almost Clear (1) at Day 29 in the crisaborole-treated group compared to the vehicle-treated group, and ii) time to success in ISGA in the crisaborole-treated group compared to the vehicle-treated group.

The results of the primary and secondary endpoints are presented below:

Endpoints	Trial 301			Trial 302		
	Eucrisa N=503	Vehicle N=256	P- value	Eucrisa N=513	Vehicle N=250	P-value
Primary: Success in ISGA	32.8%	25.4%	0.038	31.4%	18.0%	<0.001
Secondary:						
ISGA 0 or 1	51.7%	40.6%	0.005	48.5%	29.7%	<0.001
Time to Success	NC	NC		NC	NC	

Time to success could not be calculated because fewer than 50% of subjects achieved success in ISGA

Source: adapted from Statistical Review and Evaluation NDA 207695, Matthew Guerra, PhD; archived 8/19/2016, p.3.

In both trials, crisaborole was statistically superior (p-values <0.05) to placebo for the primary endpoint, and also for the secondary endpoint ISGA 0 or 1.

The reader is referred to the biostatistical and clinical reviews by Drs. Matthew Guerra and Melinda McCord, respectively, for further information and additional analyses, including post hoc explorations of the data and sensitivity analyses. I agree with Drs. Guerra and McCord that the data support a determination of efficacy.

8. Safety

The overall safety database in AD, based on subjects with AD who received crisaborole at concentrations from 0.3 to 5%, includes data from 1340 subjects, 1150 of whom were ≤ 17 years of age. The primary safety database for AD, comprised of pooled data from the Phase 3 trials, includes data from 1012 subjects who received crisaborole and 499 subjects who received vehicle. The size of the safety database is adequate to characterize adverse events.

No deaths were reported during the development program. Serious adverse events (SAE) were reported in 9 subjects (8 crisaborole and 1 vehicle) during the pivotal trials and 7 subjects during the long-term safety study. None of the SAEs reported in subjects exposed to crisaborole were considered to be related to study drug. Overall adverse event rates were similar across study arms. The most frequently reported adverse reaction was application site pain.

Application site (contact) urticaria was reported in five subjects, 2 of whom were in the crisaborole treatment group and three of whom were in the vehicle group. In the medical literature, butylated hydroxytoluene (an excipient in Eucrisa ointment) has been reported to precipitate both contact urticaria¹ and generalized urticaria^{2,3,4}. The risk for hypersensitivity reactions, including contact urticaria, is addressed in labeling.

Analysis of the impact of crisaborole exposure on body weight did not reveal a correlation, however weight measurement was obtained only at baseline in the pivotal trials and again at weeks 24 and 48 for those subjects who also enrolled in the open-label long-term safety study.

The reader is referred to the clinical review by Dr. Melinda McCord for a full discussion of the safety database.

9. Advisory Committee Meeting

Not applicable, as no Advisory Committee meeting was held for this application because it did not raise controversial issues that would benefit from outside discussion. Although crisaborole is a new molecular entity, it is not first-in-class. The route of administration for crisaborole is topical, whereas the other products in the PDE4-class are oral dosage forms with greater systemic exposure.

¹ Osmundsen PE. Contact urticaria from nickel and plastic additives (butylhydroxytoluene, oleylamide). *Contact Dermatitis*. 1980 Dec;6(7):452-4.

² Goodman DL, McDonnell JT, Nelson HS, Vaughan TR, Weber RW. Chronic urticaria exacerbated by the antioxidant food preservatives, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). *J Allergy Clin Immunol*. 1990 Oct;86(4 Pt 1):570-5.

³ Moneret-Vautrin DA, Bene MC, Faure G. She should not have chewed. *Lancet*. 1986 Mar 15;1(8481):617.

⁴ Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol*. 1981 Apr;104(4):369-81.

10. Pediatrics

The applicant submitted safety and efficacy data for children 2 to 17 years of age. In their pivotal trials, approximately 85% of subjects were pediatric (ages 2 to 17). The applicant conducted their maximum use pharmacokinetic study in pediatric subjects of this age range.

The applicant requested deferral of studies in children 3 mos to <2 years of age in order to allow the FDA to review safety data from pivotal trials in subjects >2 years of age (included in their application) [REDACTED] (b) (4). The applicant proposes [REDACTED] (b) (4) an open-label clinical study to evaluate the safety of crisaborole ointment in 100 subjects ages 3 months to <2 years of age, with PK assessment in a subset of [REDACTED] (b) (4) of the subjects with BSA of $\geq 35\%$.

The applicant requested waiver of studies in children 0 to <3 months of age on the basis that studies are impracticable because the diagnosis of AD is uncommon and often unreliably made before the age of 8 months.

The application was presented to the Pediatric Review Committee (PeRC) on 10 August 2016; PeRC agreed with the Division that the waiver and deferral requests were reasonable.

11. Other Relevant Regulatory Issues

DSI audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted.

12. Labeling

All components of labeling were reviewed.

The proposed proprietary name, Eucrisa, was found acceptable from a safety and misbranding perspective.

The carton and container labels were acceptable

The package insert conforms to the Physicians Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR). Safety information regarding the risk for hypersensitivity reactions, including contact urticaria, was added to the Contraindications and Warnings and Precautions sections of labeling.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

Prescription status, product labeling (including a Medication Guide), and routine pharmacovigilance are sufficient to address the post-marketing safety of the product.

- Other Postmarketing Requirements and Commitments

Conduct an open-label safety trial in ^{(b) (4)} 100 evaluable pediatric subjects with mild to moderate atopic dermatitis ages 3 months to < 2 years and at least 5% treatable percent body surface area (%BSA). Evaluate the pharmacokinetics of crisaborole under maximal use conditions ^{(b) (4)} in 16 evaluable subjects with moderate atopic dermatitis and at least 35% treatable percent body surface area (%BSA).

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/s/

JILL A LINDSTROM
12/13/2016