

FOR THE TREATMENT OF MILD-TO-MODERATE ATOPIC DERMATITIS IN PATIENTS 3 MONTHS AND OLDER

Results seen in a real-world patient using EUCRISA



Case report: 18-year-old Hispanic female with mild-to-moderate atopic dermatitis



All patients may not respond to treatment with EUCRISA. Individual results may vary. Photos by Jason Smith, MD (Dermatologist - Rome, GA).

INITIAL PRESENTATION	AREAS AFFECTED	MEDICATION PRESCRIBED	CLINICAL COURSE
Skin rash	Left neck and jawline	EUCRISA (crisaborole) ointment, 2%, twice daily	Patient experienced clinical improvement

EUCRISA was not studied for use with concomitant moisturizers on the affected skin; however, these were allowed on non-affected areas.

Indication

EUCRISA is indicated for topical treatment of mild-to-moderate atopic dermatitis in adult and pediatric patients 3 months of age and older.

IMPORTANT SAFETY INFORMATION (continued on back)

Contraindications

EUCRISA is contraindicated in patients with known hypersensitivity to crisaborole or any component of the formulation.

Please see Full Prescribing Information inside pocket.

Warnings and Precautions

Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with EUCRISA and should be suspected in the event of severe pruritus, swelling, and erythema at the application site or at a distant site. Discontinue EUCRISA immediately and initiate appropriate therapy if signs and symptoms of hypersensitivity occur.

Case report: 14-year-old African-American female with mild-to-moderate atopic dermatitis



BEFORE: DAY 1



AFTER: DAY 21

INITIAL PRESENTATION	Skin rash
AREAS AFFECTED	Right antecubital fossa
MEDICATION PRESCRIBED	EUCRISA (crisaborole) ointment, 2%, twice daily
CLINICAL COURSE	Patient experienced clinical improvement

All patients may not respond to treatment with EUCRISA. Individual results may vary.
Photos by Megan Kera, PA (Montclair, NJ).

EUCRISA was not studied for use with concomitant moisturizers on the affected skin; however, these were allowed on non-affected areas.

EUCRISA has a proven clinical efficacy and safety profile

In pivotal trials of patients 2 years and older

EFFICACY DATA

Significantly more EUCRISA patients achieved success in ISGA* at Day 29 in two clinical trials¹⁻³

- EUCRISA (n=503) 32.8%, Emollient-rich Vehicle (n=256) 25.4%; $P=0.038$ in Trial 1
- EUCRISA (n=513) 31.4%, Emollient-rich Vehicle (n=250) 18.0%; $P<0.001$ in Trial 2

SAFETY DATA

The most common adverse reaction occurring in $\geq 1\%$ of patients in pivotal trials was application site pain (EUCRISA, n=1012; Emollient-rich Vehicle, n=499)^{††}

- Occurred in 4% (n=45) of patients treated with EUCRISA vs 1% (n=6) for Emollient-rich Vehicle¹
 - Application site pain resolved within 1 day for 77.6% of patients who reported it²
- Discontinuation rates due to adverse events were 1.2% for both EUCRISA and Emollient-rich Vehicle in a pooled analysis²

STUDY DESIGN^{1,2}

Two multicenter, randomized, double-blind, vehicle-controlled trials (Trial 1 and Trial 2) treating 1522 patients (1016 EUCRISA; 506 vehicle) 2 to 79 years of age, with mild-to-moderate atopic dermatitis. Patients were instructed to apply EUCRISA or vehicle twice daily for 28 days. Efficacy and safety endpoints were evaluated at Days 1 (baseline), 8, 15, 22, and 29. The primary efficacy endpoint was success in ISGA at Day 29.

*Success in ISGA, a stringent metric, is defined as Clear (0) or Almost Clear (1) **AND** at least a 2-grade improvement from baseline at Day 29.¹

^{††}Refers to stinging or burning.¹

The specific mechanism(s) of action of crisaborole in atopic dermatitis is not well defined.

ISGA=Investigator's Static Global Assessment.

IMPORTANT SAFETY INFORMATION (continued)

Adverse Reactions

The most common treatment-related adverse reaction occurring in clinical trials was application site pain, such as burning or stinging.

Please see Full Prescribing Information inside pocket.

References: 1. Eucrisa [Prescribing Information]. New York, NY: Pfizer Inc., April 2020. 2. Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol*. 2016;75(3):494-503.e4. 3. Data on File. Pfizer Inc., New York, NY.

up to 600 mg/kg/day (13 times the MRHD on an AUC comparison basis) during the period of organogenesis. Maternal toxicity was produced at this high dose of 600 mg/kg/day in pregnant rats and was associated with decreased fetal body weight and delayed skeletal ossification. Crisaborole did not cause adverse effects to the fetus at oral doses up to the highest dose tested of 100 mg/kg/day in pregnant rabbits during the period of organogenesis (2 times the MRHD on an AUC comparison basis).

In a prenatal/postnatal development study, pregnant rats were treated with crisaborole at doses of 150, 300, or 600 mg/kg/day by oral gavage during gestation and lactation (from gestation day 7 through day 20 of lactation). Crisaborole did not have any adverse effects on fetal development at doses up to 300 mg/kg/day (3 times the MRHD on an AUC comparison basis). Maternal toxicity was produced at the high dose of 600 mg/kg/day in pregnant rats and was associated with stillbirths, pup mortality, and reduced pup weights.

8.2 Lactation

Risk Summary

There is no information available on the presence of EUCRISA in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production after topical application of EUCRISA to women who are breastfeeding. EUCRISA is systemically absorbed. The lack of clinical data during lactation precludes a clear determination of the risk of EUCRISA to a breastfed infant. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EUCRISA and any potential adverse effects on the breastfed infant from EUCRISA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of EUCRISA have been established in pediatric patients ages 3 months and older for topical treatment of mild to moderate atopic dermatitis. Use of EUCRISA in this age group is supported by data from two 28-day adequate, vehicle-controlled safety and efficacy trials which included 1,313 pediatric subjects ages 2 years to 17 years of whom 874 received EUCRISA. The most commonly reported adverse reaction in subjects 2 years and older was application site pain. Additionally, use of EUCRISA in pediatric patients ages 3 months to less than 2 years was supported by data from a 28-day open-label, safety and pharmacokinetics (PK) trial in 137 subjects. No new safety signals were identified in subjects 3 months to less than 2 years of age *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

The safety and effectiveness of EUCRISA in pediatric patients below the age of 3 months have not been established.

8.5 Geriatric Use

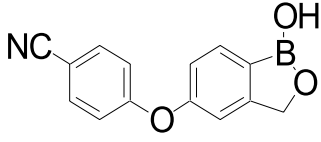
Clinical studies of EUCRISA did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

EUCRISA contains 2% crisaborole (w/w) in a petrolatum-based, white to off-white ointment and is for topical use. The active ingredient, crisaborole, is a phosphodiesterase-4 (PDE-4) inhibitor.

Crisaborole is described chemically as 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-[2,1]-benzoxaborole. The empirical formula is C₁₄H₁₀BNO₃ and the molecular weight is 251.1 g/mol.

The structural formula is represented below:



Crisaborole drug substance is freely soluble in common organic solvents such as isopropyl alcohol and propylene glycol, and insoluble in water.

Each gram of EUCRISA contains 20 mg of crisaborole in an ointment containing white petrolatum, propylene glycol, mono- and di-glycerides, paraffin, butylated hydroxytoluene, and edetate calcium disodium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Crisaborole is a phosphodiesterase 4 (PDE-4) inhibitor. PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate (cAMP) levels. The specific mechanism(s) by which crisaborole exerts its therapeutic action for the treatment of atopic dermatitis is not well defined.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At therapeutic doses, EUCRISA ointment is not expected to prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

The PK of EUCRISA were investigated in 33 pediatric subjects 2 to 17 years of age with mild to moderate atopic dermatitis and a mean ± SD body surface area (BSA) involvement of 49 ± 20% (range 27% to 92%). In this study, subjects applied approximately 3 mg/cm² of EUCRISA ointment (dose range was approximately 6 g to 30 g per application) twice daily for 8 days.

Plasma concentrations were quantifiable in all the subjects. The mean ± SD maximum plasma concentration (C_{max}) and area under the concentration time curve from 0 to 12 hours post dose (AUC_{0–12}) for crisaborole on Day 8 were 127 ± 196 ng/mL and 949 ± 1240 ng h/mL, respectively. Systemic concentrations of crisaborole were at steady state by Day 8. Based on the ratios of AUC_{0–12} between Day 8 and Day 1, the mean accumulation factor for crisaborole was 1.9.

The PK of EUCRISA were investigated in 13 subjects 4 months to less than 24 months of age. The mean ± SD C_{max} and AUC_{0–12} for crisaborole were 188 ± 100 ng/mL and 1164 ± 550 ng-h/mL, respectively.

Distribution

Based on an in vitro study, crisaborole is 97% bound to human plasma proteins.

Elimination

Metabolism

Crisaborole is substantially metabolized into inactive metabolites. The major metabolite 5-(4-cyanophenoxy)-2-hydroxyl benzylalcohol (metabolite 1), is formed via hydrolysis; this metabolite is further metabolized into downstream metabolites, among which 5-(4-cyanophenoxy)-2-hydroxyl benzoic acid (metabolite 2), formed via oxidation, is also a major metabolite.

PK of metabolites 1 and 2 were assessed in the PK study described above and the systemic concentrations were at or near steady state by Day 8. Based on the ratios of AUC_{0–12} between Day 8 and Day 1, the mean accumulation factors for metabolites 1 and 2 were 1.7 and 6.3, respectively.

Excretion

Renal excretion of metabolites is the major route of elimination.

Drug Interaction Studies

In vitro studies using human liver microsomes indicated that under the conditions of clinical use, crisaborole and metabolite 1 are not expected to inhibit cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4.

In vitro human liver microsomes studies for metabolite 2 showed that it did not inhibit activities of CYP2C19, 2D6, and 3A4; was a weak inhibitor of CYP1A2 and 2B6; and a moderate inhibitor of CYP2C8 and 2C9. The most sensitive enzyme, CYP2C9, was further investigated in a clinical trial using warfarin as a CYP2C9 substrate. The results of this study showed no drug interaction potential.

In vitro studies in human hepatocytes showed that under the conditions of clinical use, crisaborole and metabolites 1 and 2 are not expected to induce CYP enzymes.

In vitro studies showed that crisaborole and metabolite 1 did not inhibit the activities of uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1, 1A4, 1A6, 1A9, 2B7, and 2B15. Metabolite 2 did not inhibit UGT1A4, 1A6, 2B7, and 2B15. Metabolite 2 showed weak inhibition of UGT1A1, however, no clinically significant drug interactions are expected between crisaborole (and its metabolites) and UGT1A1 substrates at therapeutic concentrations. Metabolite 2 showed moderate inhibition of UGT1A9 and may result in a moderate increase of the concentrations of sensitive UGT1A9 substrates.

In vitro studies indicate that under the condition of clinical use, crisaborole and metabolites 1 and 2 are not expected to cause clinically significant interactions with substrates of P-glycoprotein and organic anionic or cationic transporters. Crisaborole and metabolite 1 are not expected to inhibit breast cancer resistance protein (BCRP); metabolite 2 is expected to inhibit BCRP at therapeutic concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In an oral carcinogenicity study in Sprague-Dawley rats, oral doses of 30, 100, or 300 mg/kg/day crisaborole were administered to rats once daily. A crisaborole-related increased incidence of benign granular cell tumors in the uterus with cervix and vagina (combined) was noted in 300 mg/kg/day crisaborole treated female rats (2 times the MRHD on an AUC comparison basis). The clinical relevance of this finding is unknown.

In a dermal carcinogenicity study in CD-1 mice, topical doses of 2%, 5%, or 7% crisaborole ointment were administered once daily. No crisaborole-related neoplastic findings were noted at topical doses up to 7% crisaborole ointment (1 times the MRHD on an AUC comparison basis).

Crisaborole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay).

No effects on fertility were observed in male or female rats that were administered oral doses up to 600 mg/kg/day crisaborole (13 times the MRHD on an AUC comparison basis) prior to and during early pregnancy.

14 CLINICAL STUDIES

Two multicenter, randomized, double-blind, parallel-group, vehicle-controlled trials (Trials 1 and 2) treated a total of 1522 subjects 2 to 79 years of age (86.3% of subjects were 2 to 17 years of age) with a 5% to 95% treatable BSA. At baseline, 38.5% of the subjects had an Investigator's Static Global Assessment [ISGA] score of 2 (mild), and 61.5% had an ISGA score of 3 (moderate), in the overall assessment of atopic dermatitis (erythema, induration/papulation, and oozing/crusting) on a severity scale of 0 to 4.

In both trials, subjects were randomized 2:1 to receive EUCRISA or vehicle applied twice daily for 28 days. The primary efficacy endpoint was the proportion of subjects at Day 29 who achieved success, defined as an ISGA grade of Clear (score of 0) or Almost Clear (score of 1) with a 2-grade or greater improvement from baseline, comparing EUCRISA-treated subjects to vehicle-treated subjects.

Efficacy results from the two trials are summarized in Table 2.

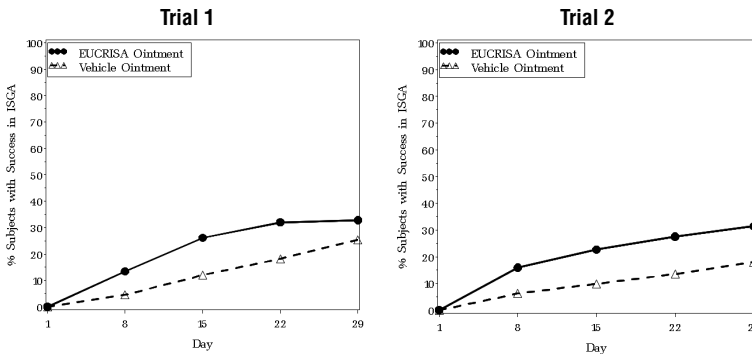
Table 2: Primary Efficacy Outcomes in Subjects with Mild to Moderate Atopic Dermatitis at Day 29

	Trial 1		Trial 2	
	EUCRISA (N=503)	Vehicle (N=256)	EUCRISA (N=513)	Vehicle (N=250)
Success in ISGA^a	32.8%	25.4%	31.4%	18.0%

^a Defined as an ISGA score of Clear (0) or Almost Clear (1) with a 2-grade or greater improvement from baseline.

The success rates over time are presented in Figure 1.

Figure 1: Success in ISGA^a Over Time in Subjects with Mild to Moderate Atopic Dermatitis



^a Success is defined as an ISGA score of Clear (0) or Almost Clear (1) with a 2-grade or greater improvement from baseline.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

EUCRISA is a white to off-white ointment containing 2% crisaborole and is supplied in 60 g and 100 g laminate tubes.

60 g tube: NDC 55724-211-21

100 g tube: NDC 55724-211-11

16.2 Storage and Handling

Store at 20°C–25°C (68°F–77°F); excursions permitted to 15°C–30°C (59°F–86°F). [see USP Controlled Room Temperature].

Keep tube tightly closed.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregivers to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Advise patients to discontinue EUCRISA and seek medical attention immediately if signs or symptoms of hypersensitivity occur *[see Warnings and Precautions (5.1)]*.

Administration Instructions

Advise patients or caregivers that EUCRISA is for external use only and is not for ophthalmic, oral, or intravaginal use.

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.



LAB-0916-5.0