

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

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

### 2 DOSAGE AND ADMINISTRATION

Apply a thin layer of EUCRISA twice daily to affected areas. Once clinical effect is achieved, consider reducing application to once daily [see *Clinical Studies (14)*].

EUCRISA is for topical use only and not for ophthalmic, oral, or intravaginal use.

### 3 DOSAGE FORMS AND STRENGTHS

Ointment: 20 mg of crisaborole per gram (2%) of white to off-white ointment.

### 4 CONTRAINDICATIONS

EUCRISA is contraindicated in patients with known hypersensitivity to crisaborole or any component of the formulation. [see *Warnings and Precautions (5.1)*]

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Hypersensitivity Reactions

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

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

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.

In two double-blind, vehicle-controlled clinical trials (Trial 1 and Trial 2), 1012 subjects 2 to 79 years of age with mild to moderate atopic dermatitis were treated with EUCRISA twice daily for 4 weeks. The adverse reaction reported by  $\geq 1\%$  of EUCRISA-treated subjects is listed in Table 1.

**Table 1: Adverse Reaction Occurring in  $\geq 1\%$  of Subjects in Atopic Dermatitis Trials through Week 4**

Adverse Reaction	EUCRISA Twice Daily N=1012 n (%)	Vehicle Twice Daily N=499 n (%)
Application site pain <sup>a</sup>	45 (4)	6 (1)

<sup>a</sup> Refers to skin sensations such as burning or stinging.

Less common ( $<1\%$ ) adverse reactions in subjects treated with EUCRISA included contact urticaria [see *Warnings and Precautions (5.1)*].

In one double-blind, vehicle-controlled trial including an initial open-label period (Trial 3), 497 subjects 3 months of age and older with mild to moderate atopic dermatitis received EUCRISA twice daily for up to 8 weeks. This was followed by a double-blind period, during which 135 subjects out of 270 randomized

subjects received EUCRISA and 135 subjects received vehicle once daily for 52 weeks or until they developed a flare. The adverse reactions observed in the open-label period were similar to the known safety profile of twice daily treatment with EUCRISA. The adverse reactions observed with once daily treatment were similar to vehicle [see *Clinical Studies (14)*].

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of EUCRISA. 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:

*Skin and Subcutaneous:* allergic contact dermatitis

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Available data from case reports with EUCRISA use in pregnant women are insufficient to inform a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, there were no adverse developmental effects observed with oral administration of crisaborole in pregnant rats and rabbits during organogenesis at doses up to 3 and 2 times, respectively, the maximum recommended human dose (MRHD) (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies carry some risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects in the U.S. general population is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

#### Data

##### *Animal Data*

Rat and rabbit embryo-fetal development was assessed after oral administration of crisaborole. Crisaborole did not cause adverse effects to the fetus at oral doses up to 300 mg/kg/day in pregnant rats during the period of organogenesis (3 times the MRHD on an area under the curve (AUC) comparison basis). No crisaborole-related fetal malformations were noted after oral treatment with crisaborole in pregnant rats at doses 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 administered twice daily in this age group is supported by data from two 28-day adequate, vehicle-controlled safety and efficacy trials (1,313 pediatric subjects ages 2 years to 17 years of whom 874 received EUCRISA), a 28-day open-label, safety and pharmacokinetics (PK) trial (137 subjects ages 3 months to less than 2 years who received EUCRISA), and another trial with an open-label period of up to 8 weeks (327 pediatric subjects ages 5 months to less than 18 years who received EUCRISA) [see *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

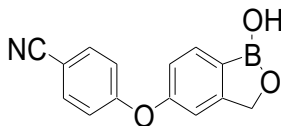
Clinical studies of EUCRISA did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

## 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  $C_{14}H_{10}BNO_3$  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  $\pm$  SD body surface area (BSA) involvement of  $49 \pm 20\%$  (range 27% to 92%). In this study, subjects applied approximately 3 mg/cm<sup>2</sup> 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  $\pm$  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  $127 \pm 196$  ng/mL and  $949 \pm 1240$  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  $\pm$  SD  $C_{\max}$  and  $AUC_{0-12}$  for crisaborole were  $188 \pm 100$  ng/mL and  $1164 \pm 550$  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] of mild (2), and 61.5% had an ISGA of moderate (3), 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 (0) or almost clear (1) with a 2-grade or greater improvement from baseline, comparing EUCRISA-treated subjects to vehicle-treated subjects.

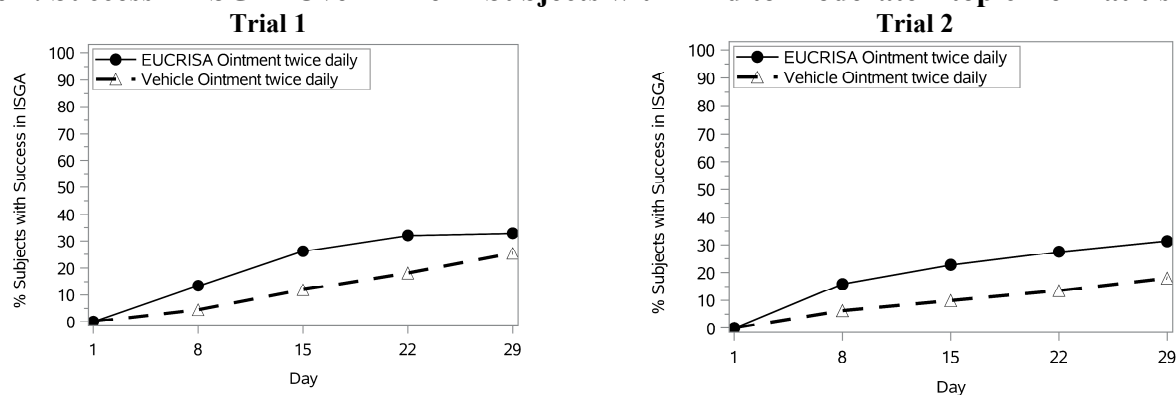
Efficacy results from the two trials are summarized in Table 2.

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

	Trial 1		Trial 2	
	EUCRISA Twice Daily (N=503)	Vehicle Twice Daily (N=256)	EUCRISA Twice Daily (N=513)	Vehicle Twice Daily (N=250)
Success in ISGA <sup>a</sup>	32.8%	25.4%	31.4%	18.0%

<sup>a</sup> Defined as an ISGA 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<sup>a</sup> Over Time in Subjects with Mild to Moderate Atopic Dermatitis**

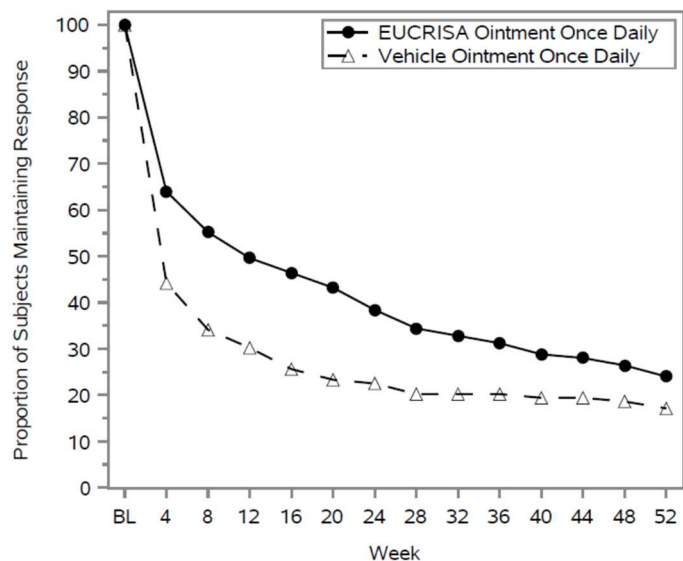
<sup>a</sup> Success is defined as an ISGA of clear (0) or almost clear (1) with a 2-grade or greater improvement from baseline.

One randomized, double-blind, vehicle-controlled trial (Trial 3) assessed the efficacy and safety of EUCRISA once daily over 52 weeks in pediatric (3 months to less than 18 years of age) and adult subjects with mild to moderate atopic dermatitis, who achieved success on EUCRISA twice daily during open-label treatment of up to 8 weeks.

A total of 497 subjects 3 months of age and older with a 2% to 90% treatable BSA, entered into an open-label period to receive EUCRISA twice daily for up to 8 weeks. At baseline, 327 (66%) of subjects were 3 months to less than 18 years of age, 66% of the subjects had an ISGA of moderate (3), and 34% had an ISGA of mild (2), in the overall assessment of atopic dermatitis (erythema, induration/papulation, and oozing/crusting) on a severity scale of 0 to 4.

Of the 497, a total of 254 subjects 3 months of age and older, who achieved both ISGA success (score of clear [0] or almost clear [1] with a  $\geq 2$  grade improvement from baseline) and EASI50 response (at least 50% improvement from baseline in EASI scores) were randomized 1:1 into a double-blind period to receive EUCRISA once daily or vehicle for 52 weeks or until they developed a flare. At the beginning of the double-blind period, 59% of the subjects had an ISGA of almost clear (1) and 41% had an ISGA of clear (0).

Figure 2 presents the percentage of subjects maintaining an ISGA of clear or almost clear through Week 52.

**Figure 2: Percentage of Subjects Maintaining ISGA of Clear or Almost Clear Through Week 52**

## 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 topical 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](http://www.pfizer.com).



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