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

<table>
<thead>
<tr>
<th>INITIAL PRESENTATION</th>
<th>AREAS AFFECTED</th>
<th>MEDICATION PRESCRIBED</th>
<th>CLINICAL COURSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>Left neck and mandible</td>
<td>EUCRISA (crisaborole) ointment, 2%, twice daily</td>
<td>Patient experienced clinical improvement</td>
</tr>
</tbody>
</table>

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.

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.

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.
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

Success in ISGA was achieved by an almost 3 times higher percentage of EUCRISA patients vs Emollient-rich Vehicle at Day 81,3

- EUCRISA (n=1016) 14.7%, Emollient-rich Vehicle (n=506) 5.4% in a pooled analysis from 2 pivotal studies

Safety Data

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

- 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 it1
- Discontinuation rates due to adverse events were 1.2% for both EUCRISA and Emollient-rich Vehicle in a pooled analysis2

Studied as Monotherapy

EUCRISA was studied as a monotherapy in both treatment-naïve and treatment-experienced patients3‡

- Patients were excluded if they were on a TCS or TCI within 14 days of the study, if they had ever previously used biologic therapy, and/or had used systemic corticosteroids or systemic immunosuppressants within 28 days of the study2

Study Design1,2

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
‡Patients in pivotal trials were not required to have received prior treatment for atopic dermatitis. Those who did went through a washout period before starting treatment with EUCRISA.3
The specific mechanism(s) of action of crisaborole in atopic dermatitis is not well defined.

ISGA=Investigator’s Static Global Assessment; TCS=topical corticosteroid; TCI=topical calcineurin inhibitor.

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.

Inactive ingredients: white petrolatum, propylene glycol, mono- and di-glycerides, paraffin, butylated hydroxytoluene, and crisaborole.

What are the ingredients in EUCRISA that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about EUCRISA that is

General information about the safe and effective use of EUCRISA

Store EUCRISA at room temperature, between 68°F and 77°F (20°C and 25°C).

How should I store EUCRISA?
• Store EUCRISA at room temperature, between 68°F and 77°F (20°C and 25°C).
• Keep the tube tightly closed.

General information about the safe and effective use of EUCRISA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EUCRISA for a condition for which it was not prescribed. Do not give EUCRISA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about EUCRISA that is written for healthcare professionals.

What are the ingredients in EUCRISA?
Active ingredient: crisaborole
Inactive ingredients: white petrolatum, propylene glycol, mono- and di-glycerides, paraffin, butylated hydroxytoluene, and edetate calcium disodium.

For more information, call 1-866-EUCRISA [1-866-382-7472] or go to www.EUCRISA.com

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

EUCRISA® (crisaborole) ointment, for topical use
Initial U.S. Approval: 2016

RECENT MAJOR CHANGES

INDICATIONS AND USAGE

EUCRISA is a phosophobenzoxype 4 inhibitor indicated for topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 3 months of age and older.

DOSEAGE AND ADMINISTRATION

• Apply a thin layer twice daily to affected areas. (2)
• For topical use only. (2)
• Not for ophthalmic, oral, or intranasal use. (2)

FULL PRESCRIBING INFORMATION: CONTENTS*

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OSUMMARY OF RECOMMENDED DOSAGE

DOSAGE FORMS AND STRENGTHS

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

DOSEAGE AND ADMINISTRATION

APPLICATION SITE

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

In clinical trials, crisaborole ointment was associated with flushing 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.

ADVERSE REACTIONS

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), 1025 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 in ≥1% of EUCRISA-treated subjects is listed in Table 1.

Table 1: Adverse Reaction Occurring in ≥1% of Subjects in Atopic Dermatitis Trials through Week 4

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EUCRISA n=603 (%)</th>
<th>Vehicle n=600 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site pain</td>
<td>45 (4)</td>
<td>6 (1)</td>
</tr>
</tbody>
</table>

* 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)).

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

Postmarketing Experience

There is no available data with EUCRISA in pregnant women to inform the drug-associated risk for major birth defects and miscarriage. 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 in the U.S. general population is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Clinical Data

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

Distributed by

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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 04/2020
atopic dermatitis is not well defined. The mechanism(s) by which crisaborole exerts its therapeutic action for the treatment of increased intracellular cyclic adenosine monophosphate (cAMP) levels. The specific white petrolatum, propylene glycol, mono- and di-glycerides, paraffin, butylated Each gram of EUCRISA contains 20 mg of crisaborole in an ointment containing 2,1-[benzoxaborole. The empirical formula is C\textsubscript{14}H\textsubscript{10}BNO\textsubscript{3} and the molecular weight is 65 and over to determine whether they respond differently from younger subjects. were identified in subjects 3 months to less than 2 years of age open-label, safety and pharmacokinetics (PK) trial in 137 subjects. No new safety signals pediatric patients ages 3 months to less than 2 years was supported by data from a 28-day adequate, vehicle- compared basis). Maternal toxicity was produced at the high dose of 600 mg/kg/day in pregnant rabbits during the period of ossification. Crisaborole did not cause adverse effects to the fetus at oral doses up to 600 mg/kg/day in pregnant rats and was associated with stilbister, 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 age treated with EUCRISA or vehicle. The safety and efficacy of EUCRISA were studied in 13 subjects 4 months to less than 24 months of age. No new safety signals were identified in subjects 3 months to less than 2 years of age (see Adverse Reactions (6.1)). Crisaborole is substantially metabolized into inactive metabolites. The major metabolite (5-(4-cyanophenoxy)-3,4-dihydrobenzotiazolyl carbamoyl metabolite 1), is formed via hydrolytic. This metabolite is further metabolized into downstream metabolites, among which is 5-(4-cyanophenoxy)-2-hydroxy benzoic acid (metabolite 2) formed, via oxidation, is another major metabolite. PK of metabolites 1 and 2 were assessed in the PK study described above and the potential pharmacokinetic differences were not considered to be clinically relevant. 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, 2C8, 2C9, 2D6, 2C19, 2C9, 2D6, and 3A4. A weak inhibitor of CYP2C9 and 2C8. 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, 1B1, and 2B7 and 2B7. Metabolite 2 did not inhibit UGT1A4, 1A4, 1A6, 1B1, and 2B7. The second major metabolite of crisaborole was a weak inhibitor of UGT1A1, however, no clinically significant drug interactions are expected between crisaborole and its metabolites (and UGT1A1) and substrates at therapeutic concentrations. Metabolite 2 showed moderate inhibition of UGT1A1 and may result in a moderate increase of the concentrations of sensitive UGT1A1 substrates. In vivo studies indicated 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-glycoproteins and organic anion or cation 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 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 primary end point was the proportion of subjects at 31 days. Trial 2

Table 1: Summary of Clinical Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>EUCRISA (mg)</th>
<th>Vehicle (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>N=258</td>
<td>N=250</td>
</tr>
<tr>
<td>Trial 2</td>
<td>N=313</td>
<td>N=260</td>
</tr>
</tbody>
</table>

*Success 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 Over Time in Subjects with Mild to Moderate Atopic Dermatitis

15 HOW SUPPLIED/STORAGE AND HANDLING

15.1 How Supplied EUCRISA is a white to off-white ointment containing 2% crisaborole and is supplied in 60 g and 100 g laminated tubes. 60 g tube: NDC 55724-211-21 100 g tube: NDC 55724-211-11


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