FULL PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT
STAQUIS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each gram of STAQUIS contains 20 mg of crisaborole.

For the full list of excipients, see *Description*.

3. PHARMACEUTICAL FORM
Ointment

4. INDICATIONS AND USAGE
STAQUIS is indicated for topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 3 months of age and older.

5. DOSAGE AND ADMINISTRATION
Apply a thin layer of STAQUIS twice daily to affected areas.
STAQUIS is for topical use only and not for ophthalmic, oral, or intravaginal use.

6. DOSAGE FORMS AND STRENGTHS
Ointment: 20 mg of crisaborole per gram (2%) of white to off-white ointment.

7. CONTRAINDICATIONS
STAQUIS is contraindicated in patients with known hypersensitivity to crisaborole or any component of the formulation. *[see Warnings and Precautions]*

8. WARNINGS AND PRECAUTIONS
8.1 Hypersensitivity Reactions
Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with STAQUIS. 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 STAQUIS immediately and initiate appropriate therapy.

8.2 The product contains butylated hydroxytoluene that may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

8.3 The product contains Propylene glycol that may cause skin irritation.

9 ADVERSE REACTIONS
9.1 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 STAQUIS twice daily for 4 weeks. The adverse reaction reported by ≥1% of STAQUIS-treated subjects is listed in Table 1.

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

Adverse Reaction	STAQUIS N=1012 n (%)	Vehicle N=499 n (%)
Application site pain[a]	45 (4)	6 (1)

[a] Refers to skin sensations such as burning or stinging.

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

9.2 Postmarketing Experience

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

There is no available data with STAQUIS 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 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.

10.2 Lactation

Risk Summary

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

10.3 Pediatric Use

The safety and effectiveness of STAQUIS have been established in pediatric patients ages 3 months and older for topical treatment of mild to moderate atopic dermatitis. Use of STAQUIS 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 STAQUIS. The most commonly reported adverse reaction in subjects 2 years and older was application site pain. Additionally, use of STAQUIS 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, Clinical Pharmacology, and Clinical Studies]*.

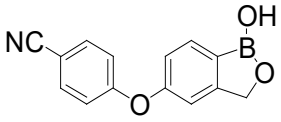
The safety and effectiveness of STAQUIS in pediatric patients below the age of 3 months have not been established.

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

11 DESCRIPTION
STAQUIS 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 STAQUIS 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, STAQUIS ointment is not expected to prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics
Absorption

The PK of STAQUIS 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/cm^2 of STAQUIS 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 STAQUIS 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 STAQUIS 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 STAQUIS-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

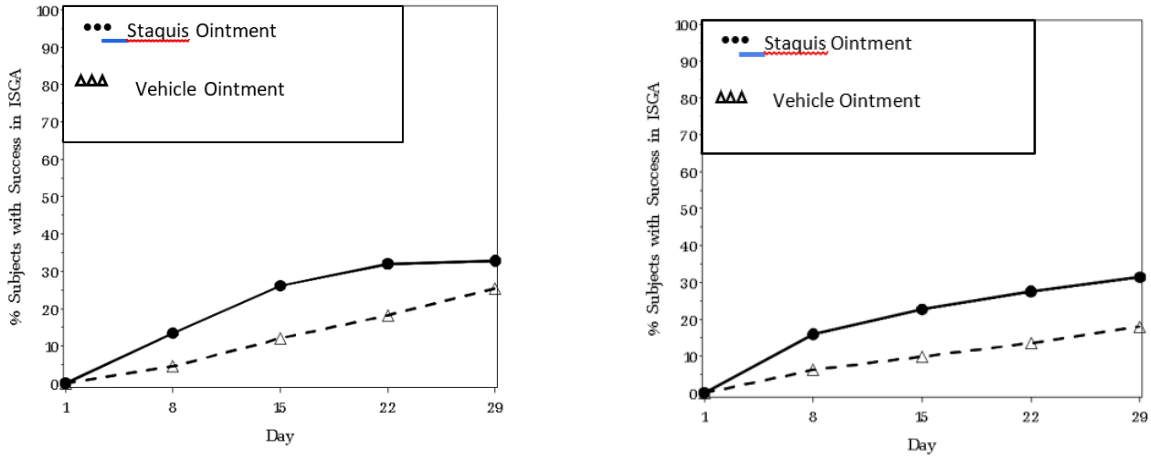
	Trial 1		Trial 2	
	STAQUIS (N=503)	**Vehicle (N=256)**	**STAQUIS (N=513)**	**Vehicle (N=250)**
Success in ISGA[a]	32.8%	25.4%	31.4%	18.0%

[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

Trial 1 **Trial 2**



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

15 HOW SUPPLIED/STORAGE AND HANDLING

15.1 How Supplied

STAQUIS is a white to off-white ointment containing 2% crisaborole and is supplied in 2.5 g, 30 g, 60 g and 100 g laminate tubes.

Not all packaging sizes may be marketed

15.2 Storage and Handling

Store below 25°C

Keep tube tightly closed.

15.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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16 LICENSE HOLDER

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17 LICENSE NUMBER

161-76-35303

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