1. NAME OF THE MEDICINAL PRODUCT

STAQUIS 2% (20 mg/g) ointment

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The medicinal product contains 2% crisaborole (w/w) in an ointment.

One gram of ointment contains 20 mg of crisaborole.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white ointment.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

STAQUIS is indicated for topical treatment of mild to moderate atopic dermatitis in patients 3 months of age and older (see section 5.1).

4.2. Posology and method of administration

Posology

Adults
STAQUIS is to be applied as a thin layer twice daily to affected areas.

STAQUIS can be used on all skin areas, including the face, neck, and intertriginous areas. The use of STAQUIS on the scalp has not been studied.

STAQUIS ointment can be used continuously for up to 28 days per treatment course. The efficacy for continuous use beyond 28 days has not been studied in a controlled trial. Multiple treatment course over 48 weeks have been studied in an open-label extension trial.

Pediatric population
For children and adolescents (3 months to 17 years of age) the posology is the same as for adults. The safety and effectiveness of STAQUIS in pediatric patients below the age of 3 months have not been established.

Special populations
Clinical trials with hepatic or renal impaired subjects have not been conducted. However, dosage adjustment is not expected to be necessary in subjects with mild to moderate hepatic impairment or in subjects with renal impairment.

Clinical studies of STAQUIS did not include sufficient numbers of subjects 65 years of age and over to determine whether they respond differently from younger subjects. However, dosage adjustment is not expected to be necessary in this patient population.

Method of administration

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

STAQUIS has not been studied under occlusion. However, clinical experience available for use of the ointment under occlusion (i.e., diapers/nappies or clothing) has not shown the necessity for any dosage adjustment.

Patients should be instructed to wash their hands after applying STAQUIS, unless it is their hands that are being treated. If someone else applies STAQUIS to the patient, they too should wash their hands after application.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

STAQUIS is not for oral, ophthalmic, or intravaginal use. In cases of accidental exposure to these areas, the ointment should be thoroughly wiped off and/or rinsed with water.

Available data indicate that local skin reactions, such as burning or stinging, may be more likely to occur on sensitive skin areas (such as the face and neck).

Hypersensitivity

Hypersensitivity, including contact urticaria, has 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.

4.5. Interaction with other medicinal products and other forms of interaction

Neither crisaborole nor its 2 main metabolites are expected to cause drug interactions by induction or inhibition of cytochrome P450 (CYP) enzymes based on *in vitro* and *in vivo* data (see section 5.2).

Based on *in vitro* data, concomitant administration of STAQUIS and CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir) or CYP1A2 inhibitors (e.g., ciprofloxacin, fluvoxamine) can increase systemic crisaborole concentrations (see section 5.2).

STAQUIS has not been evaluated in combination with other cutaneous medicinal products including emollients to treat mild to moderate atopic dermatitis.

4.6. Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of STAQUIS in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at maternally non-toxic doses (see section 5.3). Because animal reproduction studies are not always predictive of the human response, as a precautionary measure, the mother's clinical benefit of STAQUIS along with any potential risk on the fetus should be considered.

Breast-feeding

Animal studies on milk excretion after topical application were not conducted and the use of STAQUIS in breast-feeding women has not been studied. STAQUIS is systemically absorbed. It is unknown whether crisaborole/metabolites are excreted in human milk following topical application of STAQUIS or the effects of the medicinal product on the breastfed infant or on human milk production. 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 breast-feeding 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.

To avoid unintentional ingestion by the newborn, STAQUIS should not be applied to the breast.

Fertility

Reproduction studies in male or female rats using oral administration of crisaborole revealed no effects on fertility (see section 5.3).

4.7. Effects on ability to drive and use machines

No studies with STAQUIS on the effect of the ability to drive or use machines have been performed, therefore STAQUIS has no known influence on the ability to drive or use machines.

4.8. Undesirable effects

The most common adverse drug reactions from completed STAQUIS clinical trials (Trials 1 and 2) were application site reactions (5.6% and 3.6% for STAQUIS and vehicle groups, respectively) and most were classified as mild. Of these drug-related application site reactions, application site pain (e.g., burning or stinging) was the only adverse drug reaction that showed a clinically relevant difference in rates between the treatment groups (4.4% and 1.2% for STAQUIS and vehicle groups, respectively). Generally, application site pain was noted early in the treatment period and was transient in nature, resolving spontaneously.

Treatment-emergent adverse events reported by ≥1% of subjects from either treatment group, based on the pooled safety population (Trial 1 and Trial 2) are listed in Table 1.

Table 1: Treatment-Emergent Adverse Events Reported in ≥1% of Subjects in a Treatment Group through Day 29 by Decreasing Frequency in the Crisaborole Group, Trial 1 and Trial 2 (Pooled, Safety Population)

Adverse Event (Pooled data from Trial 1 and Trial 2)	**Crisaborole 2% Twice Daily (N = 1012)**	**Vehicle Twice Daily (N = 499)**
Application site pain	45 (4.4%)*	6 (1.2%)
Upper respiratory tract infection	30 (3.0%)	15 (3.0%)
Pyrexia	19 (1.9%)	7 (1.4%)
Nasopharyngitis	18 (1.8%)	6 (1.2%)
Vomiting	15 (1.5%)	5 (1.0%)
Cough	12 (1.2%)	8 (1.6%)
Headache	11 (1.1%)	1 (0.2%)
Oropharyngeal pain	11 (1.1%)	2 (0.4%)
Dermatitis atopic	7 (0.7%)	8 (1.6%)
Application site pruritus	5 (0.5%)	6 (1.2%)
Staphylococcal skin infection	1 (0.1%)	5 (1.0%)

* Application site pain is the only treatment-related adverse event (ADR)

Uncommon (<1%) adverse reactions in subjects treated with STAQUIS included contact urticaria (see section 4.4).

The safety profile from a completed STAQUIS open-label clinical trial (Trial 3) in which STAQUIS was applied intermittently in 28 day treatment courses for up to 48 weeks was consistent with that of Trial 1 and Trial 2 (see section 5.1).

Table 2: Treatment-Emergent Adverse Events Reported by ≥2% of Subjects, Long-Term Open Label Trial 3, by Decreasing Frequency (Safety Population)

Adverse Event	**Crisaborole 2% Twice Daily (N = 517)**
Dermatitis atopic	58 (11.2 %)
Upper respiratory tract infection	53 (10.3%)
Nasopharyngitis	40 (7.7%)
Cough	35 (6.8%)
Pyrexia	29 (5.6%)
Sinusitis	25 (4.8%)
Pharyngitis streptococcal	20 (3.9%)
Oropharyngeal pain	19 (3.7%)
Application site infection	18 (3.5%)
Dermatitis contact	16 (3.1%)
Asthma	16 (3.1%)
Vomiting	15 (2.9%)
Eczema	13 (2.5%)
Diarrhea	12 (2.3%)
Application site pain	12 (2.3%)
Ear infection	12 (2.3%)
Pharyngitis	12 (2.3%)
Influenza	12 (2.3%)
Seasonal allergy	11 (2.1%)
Otitis media	11 (2.1%)
Headache	11 (2.1%)
Viral infection	11 (2.1%)

Pediatric clinical trial

In a multicenter, open-label, uncontrolled trial, 137 pediatric subjects aged 3 months to less than 2 years were treated with STAQUIS twice daily for 4 weeks. Overall, the safety profile of STAQUIS in this age group was consistent with that of Trials 1 and 2 in subjects 2 years of age and older.

Post-market reported adverse reactions

The following adverse reactions have been identified during post-approval 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:

- Application site reactions.

4.9. Overdose

There has been no experience of overdose with STAQUIS. Overdose following topical administration is unlikely. If too much STAQUIS has been applied, the excess can be wiped off.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of action

Crisaborole is an anti-inflammatory benzoxaborole phosphodiesterase-4 (PDE4) inhibitor that suppresses the secretion of certain cytokines, such as tumor necrosis factor-α (TNF-α), interleukins (IL-2, IL-4, IL-5), and interferon gamma (IFNγ), and improves skin barrier function as measured by transepidermal water loss (TEWL). Crisaborole applied on atopic dermatitis lesions of patients reduces expression of atopic inflammation associated chemokines including CCL17, CCL18, and CCL22.

Clinical efficacy

Two multicenter, randomized, double-blind, parallel-group, vehicle-controlled trials (Trials 1 and 2), which were identical in design, included a total of 1,522 subjects 2 to 79 years of age. Of these, 61.9% subjects were 2-11 years old, 24.4% of subjects were 12-17 years old, 13.3% of subjects were 18-64 years old, and 0.5% of subjects were 65 years of age or older; the number of subjects ≥18 years of age was limited. The treatable body surface area (BSA) ranged from 5% to 95% (mean = 18.3%, standard deviation [SD] = 17.8%; 9.6% of subjects had >40% treatable BSA); the trials did not include sufficient numbers of subjects with >40% treatable BSA to determine the safety and efficacy of STAQUIS in this subpopulation. At baseline (pooled study data), 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 an ISGA grade of Clear (score of 0) or Almost Clear (score of 1) with at least a 2-grade improvement from baseline, comparing STAQUIS-treated subjects to vehicle-treated subjects. In both trials, a statistically significantly greater percentage of subjects achieved this endpoint in the STAQUIS-treated group compared with the vehicle-treated group.

The secondary efficacy endpoints were the proportion of subjects at Day 29 with an ISGA grade of Clear or Almost Clear and the time to achieve an ISGA grade of Clear or Almost Clear with at least a 2-grade improvement from baseline.

The safety and efficacy of STAQUIS on sensitive skin areas (such as the face and neck) compared to non-sensitive skin areas (such as the arms and legs) were not separately assessed in the clinical trials.

Efficacy results from the two trials are summarized in Table 3.

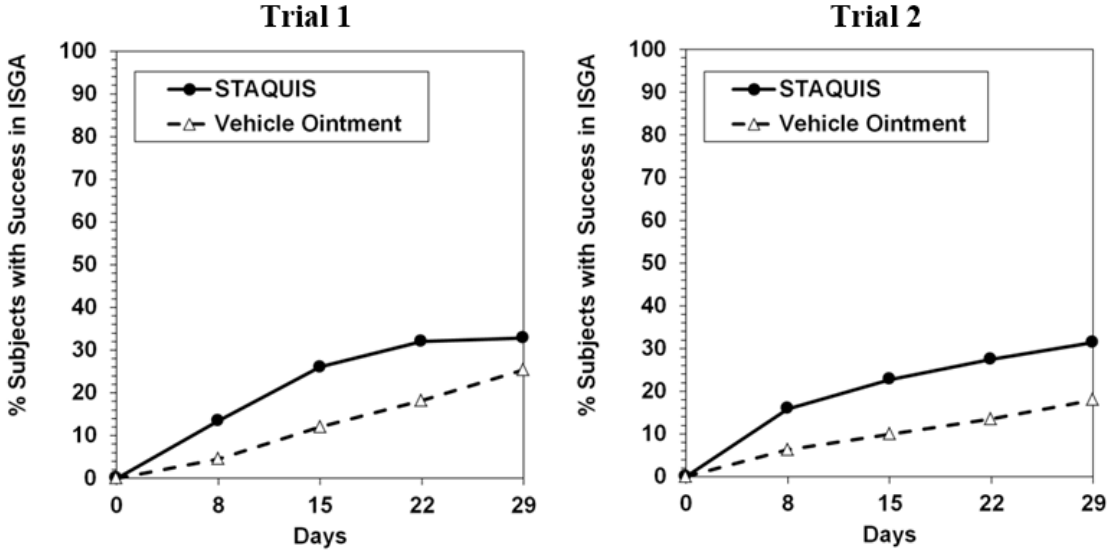
Table 3: Efficacy Outcomes in Subjects with Mild to Moderate Atopic Dermatitis at Day 29

	Trial 1		**Trial 2**	
	STAQUIS (N=503)	**Vehicle (N=256)**	**STAQUIS (N=513)**	**Vehicle (N=250)**
ISGA[a]	32.8%	25.4%	31.4%	18.0%
p-value	0.038[b]		<0.001[b]	
ISGA of Clear or Almost Clear[c]	51.7%	40.6%	48.5%	29.7%
p-value	0.005[d]		<0.001[d]	
Time to ISGA[a,e]	NC[f]	NC[f]	NC[f]	NC[f]
p-value	<0.001[g]		<0.001[g]	

[a] Defined as an ISGA score of Clear or Almost Clear with at least a 2-grade improvement from baseline.
[b] p-value from a logistic regression (with Firth option) test with factors of treatment group and analysis center. Trial 1 estimates from logistic regression are 29.1% and 22.0% for STAQUIS and vehicle, respectively. Trial 2 estimates from logistic regression are 26.5% and 14.2% for STAQUIS and vehicle, respectively. Values were adjusted for multiple imputation.
[c] At least a 2-grade improvement from baseline was not required.
[d] p-value from a logistic regression (with Firth option) test with factors of treatment group and analysis center. Trial 1 estimates from logistic regression are 49.0% and 37.7% for STAQUIS and vehicle, respectively. Trial 2 estimates from logistic regression are 45.2% and 25.5% for STAQUIS and vehicle, respectively. Values were adjusted for multiple imputation.
[e] Medians computed using Kaplan-Meier methods.
[f] The median time to achieve an ISGA grade of Clear or Almost Clear with at least a 2-grade improvement from baseline could not be calculated (NC), as fewer than 50% of subjects achieved an ISGA grade of Clear or Almost Clear with at least a 2-grade improvement from baseline.
[g] p-value from log-rank test.

A log-rank test showed the STAQUIS-treated group had a statistically significantly earlier time to success in ISGA than the vehicle-treated group in both studies (p-values <0.001).

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.

The pooled primary efficacy results by race category are summarized in Table 4.

Table 4: Summary of Subjects Achieving ISGA Score of Clear or Almost Clear with At Least a 2-Grade Improvement from Baseline at Day 29 by Race Category – Trial 1 and 2 Pooled

	STAQUIS (N = 1016)		Vehicle (N = 506)	
Race Category	**n**	**Rate**	**n**	**Rate**
American Indian or Alaska Native	11	18.0%	5	0.0%
Asian	52	17.7%	27	13.4%
Black or African American	285	32.1%	139	24.6%
Native Hawaiian or Other Pacific Islander	7	42.9%	8	17.0%
White	617	33.5%	306	22.3%
Other	44	31.9%	21	16.3%

N = Number of subjects in each treatment group
n = Number of subjects in each sub-group category by treatment group

The pooled primary efficacy results by age category and baseline percent body surface area (%BSA) are summarized in Table 5.

Table 5: Subjects N (%) achieving ISGA Score of Clear or Almost Clear with at Least a 2-Grade Improvement from Baseline at Day 29 by Age Category and Baseline %BSA – Trial 1 and Trial 2 Pooled

Age Category	BSA 0-11%		BSA 11-<35%		BSA 35-<60%		BSA ≥60%	
	STAQUIS N (%)	Vehicle N (%)	STAQUIS N (%)	Vehicle N (%)	STAQUIS N (%)	Vehicle N (%)	STAQUIS N (%)	Vehicle N (%)
2-6 yrs	146 (30.9)	58 (25.1)	138 (32.3)	80 (23.0)	30 (33.2)	18 (17.7)	21 (12.9)	15 (7.7)
7-11 yrs	138 (39.9)	67 (19.9)	109 (40.2)	62 (26.7)	26 (27.3)	8 (12.9)	19 (5.2)	7 (28.7)

Age	BSA 0-11%		BSA 11-<35%		BSA 35-<60%		BSA ≥60%	
12-17 yrs	131	72	88	41	13	9	15	2
	(25.7)	(19.2)	(36.3)	(17.6)	(23.0)	(34.6)	(42.5)	(0.0)
≥18 yrs	86	41	43	20	9	3	4	3
	(31.0)	(27.4)	(33.3)	(16.9)	(11.4)	(32.1)	(6.1)	(32.1)

This primary endpoint analyses demonstrate overall the favorable treatment benefit of crisaborole compared to vehicle across the various age and %BSA subgroups. Some subgroups may have a less consistent trend of treatment response, but this is probably related to the small sample size of these subgroups and the larger variability observed.

In a multicenter, open-label, uncontrolled trial, 137 pediatric subjects aged 3 months to less than 2 years were treated with STAQUIS twice daily for 4 weeks. The primary endpoint of safety was evaluated through 4 weeks, with support from pharmacokinetic analyses showing similar drug exposure to older subjects. Efficacy was considered an exploratory objective in this study. At Baseline, 38.0% of the subjects had an ISGA score of 2 (Mild), and 61.3% had an ISGA score of 3 (Moderate). At Day 29, 30.2% of subjects achieved an ISGA grade of Clear (score of 0) or Almost Clear (score of 1) with at least a 2-grade improvement. In addition, 47.3% of subjects had achieved an ISGA grade of Clear or Almost Clear. Mean treatable percent BSA affected with atopic dermatitis decreased from 28.1% at Baseline to 12.4% at Day 29. The results on ISGA and treatable percent BSA were comparable to those observed among STAQUIS-treated subjects in Trials 1 and 2.

QT study results

Results from a thorough QT study of STAQUIS applied to 60% BSA in healthy volunteers did not demonstrate QT prolongation. Although healthy volunteers had lower crisaborole concentrations compared to patients with atopic dermatitis, clinical studies of STAQUIS did not identify any cardiac effects including prolongation of QT interval.

5.2. Pharmacokinetic properties

Absorption

The pharmacokinetics (PK) of STAQUIS were investigated in 33 pediatric subjects 2 to 17 years of age with mild to moderate atopic dermatitis and a mean ± standard deviation (SD) 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 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. Systemic levels of crisaborole and its main metabolites were similar between age cohorts of 2 to 5 years, 6 to 11 years, and 12 to 17 years.

Systemic exposure (C_{max} and AUC_{0-12}) of crisaborole and its main metabolites increased with increasing % BSA treated.

A separate PK study evaluated 18 subjects aged 3 months to <2 years of age. Following STAQUIS twice daily administration, large variations in plasma concentrations of crisaborole were observed, with 5 infants exhibiting more than 2-fold higher AUC compared to adults. Sampling methodology errors may have contributed to this result. When excluding values associated with potential sampling errors, results indicated comparable systemic crisaborole exposures in infants and toddlers as observed in older patients at similar treated BSA. However, an actual increase in exposure in infants and toddlers relative to older patients cannot be excluded.

Distribution

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

Biotransformation and elimination

Crisaborole is substantially metabolized into inactive metabolites. The main 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 main 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. Renal excretion of metabolites is the major route of elimination.

Drug interactions

Potential for crisaborole to influence the PK of other drugs
In vitro studies using human liver microsomes indicated that under the conditions of clinical use, crisaborole and metabolite 1 are not expected to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 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 indicate that under the condition 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 UGT1A1, 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 transporters such as P-glycoprotein, breast cancer resistance protein (BCRP) and organic anionic or cationic transporters.

5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenicity, juvenile toxicity, or toxicity to reproduction and development.

The repeated-dose toxicology studies demonstrated that administration of crisaborole by both the dermal and oral routes in mice, rats, and minipigs at plasma exposures up to 11 times that in humans did not result in significant toxicity relevant to its use in humans.

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).

In an oral carcinogenicity study in Sprague-Dawley rats, oral doses of 30, 100, or 300 mg/kg/day crisaborole were administered 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 maximum recommended human dose (MRHD) on an area under the curve (AUC) comparison basis). The clinical relevance of this finding is unknown, however given the tumor type and benign status in a single species and single sex, the relevance to humans is considered to be low.

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 was not found to be a reproductive toxicant nor a teratogen in reproductive toxicology studies at maternally non-toxic doses that examined effects on fertility, embryo-fetal development, and the F1 generation. Maternal toxicity in rats (associated with decreased fetal body weight and delayed skeletal ossification) but no crisaborole-related fetal malformations were noted after oral administration of crisaborole during organogenesis at doses up to 600 mg/kg/day (13 times the MRHD on an AUC comparison basis). 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 administered during the period of organogenesis (2 times the MRHD on an AUC comparison basis).

In a rat prenatal/postnatal development study, 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 findings of stillbirths, pup mortality, and reduced pup weights.

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.

Juvenile rat and minipig studies did not reveal any relevant findings suggestive of a specific risk for use in the pediatric population.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

White Petrolatum
Propylene Glycol
Mono- and Di-glycerides
Paraffin
Butylated Hydroxytoluene
Edetate Calcium Disodium

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Refer to outer carton for expiry date.

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

Multi-layered laminate tube with a high-density polyethylene tube head with a peel seal, and a white polypropylene cap closure.

Tubes of 2.5, 30, 60, and 100 grams.

Not all tube sizes may be marketed.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

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