▼This medicinal product is subject to additional monitoring **in Australia**. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – STAQUIS™ (CRISABOROLE)

1. NAME OF THE MEDICINE

Crisaborole

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

STAQUIS contains 2% (w/w) crisaborole in a paraffin-based, ointment and is for topical use. The active ingredient, crisaborole, is a phosphodiesterase-4 (PDE-4) inhibitor. Each gram of STAQUIS contains 20 mg of crisaborole.

For the full list of excipients, see Section 6.1 – List of excipients.

3. PHARMACEUTICAL FORM

STAQUIS is a white to off-white ointment containing 20 mg of crisaborole per gram (2% w/w) crisaborole.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

STAQUIS is indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.

4.2 Dose and method of administration

Dosage

STAQUIS 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 courses over 48 weeks have been studied in an open-label extension trial. Do not co-apply STAQUIS with other topical atopic dermatitis medicines on the same lesions. The concurrent use of STAQUIS with other topical atopic dermatitis medicines on separate lesions has not been studied.

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 head and face, neck and intertriginous areas. Use on the scalp has not been studied.

Paediatric population

For children and adolescents (2-17 years) the dosage is the same as for adults. The safety and efficacy of STAQUIS in children less than 2 years of age has not been established. No data are available.

Method of administration

STAQUIS is for topical use only and not for oral, ophthalmic, or intravaginal use. If accidentally applied to these areas, the ointment should be thoroughly wiped off and rinsed well with water.

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

STAQUIS is contraindicated in patients with known hypersensitivity to crisaborole or any component of the formulation (see Section 4.4).

4.4 Special warnings and precautions for use

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.

Use in hepatic impairment

Clinical studies with hepatic impaired subjects have not been conducted.

Use in renal impairment

Clinical studies with renal impaired subjects have not been conducted.

Use in the elderly

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

Paediatric use

The safety and effectiveness of STAQUIS have been established in paediatric patients age 2 years and older for topical treatment of mild to moderate atopic dermatitis. Use of STAQUIS in this age group is supported by evidence from two multicentre, randomised, double-blind, parallel-group, vehicle-controlled 28-day trials which included 1,313 paediatric subjects 2 years and older (see Section 5.1 – Clinical trials and Section 4.8 - Adverse effects (Undesirable effects)). The safety and effectiveness of STAQUIS in paediatric patients below the age of 2 years have not been established.

Effects on laboratory tests

No data available.

Class effects of oral PDE-4 inhibitors

Insomnia, anxiety, depression, suicidal ideation and weight loss are observed as risks in patients taking oral PDE-4 inhibitors. Existing data from clinical trials and post marketing experience with topical crisaborole do not show evidence of a similar risk with STAQUIS.

4.5 Interactions with other medicines and other forms of interactions

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.

STAQUIS has not been evaluated in combination with other topical drugs used to treat mild to moderate atopic dermatitis. Emollients may be used on areas of skin other than skin concurrently treated with STAQUIS.

4.6 Fertility, pregnancy and lactation

Effects on fertility

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 maximum recommended human dose (MRHD) on an AUC comparison basis).

Use in pregnancy - Category B1

There are no adequate data from the use of crisaborole in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at maternally non-toxic doses. 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.

In animal reproduction studies, 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 AUC comparison basis). No drug-related fetal malformations were noted after oral administration of 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 the high dose of 600 mg/kg/day in pregnant rats and was associated with findings of 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 findings of stillbirths, pup mortality, and reduced pup weights.

Use in lactation

There is no information available on the presence of crisaborole 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. Crisaborole 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. To avoid unintentional ingestion by the newborn, STAQUIS should not be applied to the breast.

4.7 Effects on ability to drive and use machines

STAQUIS has no known influence on the ability to drive and use machines.

4.8 Adverse effects (Undesirable effects)

Clinical Trials Experience

Two multicentre, randomised, double-blind, parallel-group, vehicle-controlled trials (Studies 301 and 302) included a total of 1,522 subjects 2 to 79 years of age (86.3% of subjects were 2 to 17 years of age) and one multicentre, single-arm, open-label long-term safety trial (Study 303) included a total of 517 subjects 2 to 72 years of age; in all three trials, subjects treated 5% to 95% body surface area.

The number of subjects with at least 4 weeks, 24 weeks, and 48 weeks of cumulative exposure to STAQUIS was 1025, 272, and 20, respectively.

In the 28-day pivotal trials, application site pain (e.g., burning or stinging) was the only treatment-related adverse event that showed a clinically relevantly higher rate in STAQUIS-treated groups versus vehicle-treated groups in subjects with atopic dermatitis. 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 (Studies 301 and 302) 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, Studies 301 and 302 (Pooled, Safety Population)

Adverse Event (Pooled data from 301 and 302 studies)	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 - Special warnings and precautions for use).

Open-label clinical trial experience (exposure up to 48 weeks)

The safety profile from a completed STAQUIS open-label clinical trial (Study 303) in which STAQUIS was applied intermittently in 28 day treatment courses for up to 48 weeks was consistent with that of Studies 301 and 302 (see Section 5.1 – Clinical trials).

Table 2: Treatment-Emergent Adverse Events Reported by ≥2% of Subjects, Long-Term Safety Study 303, 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%)
Diarrhoea	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%)

Post-market experience

The safety profile from post-market experience is consistent with that established through clinical trial experience. No new safety information has been derived from the post-market experience.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

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.

STAQUIS is not for oral use. Oral ingestion may lead to adverse effects associated with systemic administration. If oral ingestion occurs, medical advice should be sought.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Crisaborole is a competitive inhibitor of cyclic adenosine monophosphate (cAMP) at the PDE-4 catalytic site resulting in increased intracellular cAMP levels. As a phosphodiesterase-4 (PDE-4) inhibitor, crisaborole suppresses inflammation and secretion of certain cytokines, such as TNF α, from the peripheral blood mononuclear cells. The specific mechanism(s) by which crisaborole exerts its therapeutic action for the treatment of atopic dermatitis is not well defined.

Clinical trials

Two multicentre, randomised, double-blind, parallel-group, vehicle-controlled trials (Studies 301 and 302) treated a total of 1,522 subjects 2 to 79 years of age (86.3% of subjects were 2 to 17 years of age) with a 5% to 95% treatable body surface area. 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 randomised 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. The success rates over time are presented in Figure 1.

In both trials, a statistically significantly greater percentage of subjects achieved the success in ISGA in the STAQUIS-treated group compared with the vehicle-treated group. The proportion of subjects achieving an ISGA score of Clear (0) or Almost Clear (1) at Day 29 in the STAQUIS-treated group compared to the vehicle-treated group was also statistically significant. The secondary efficacy endpoints were the proportion of subjects at Day 29 with ISGA grade of Clear (score of 0) or Almost Clear (score of 1) and the time to success in ISGA. Efficacy results from the two trials are summarised in Table 3.

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

	Study 301		Study 302	
	STAQUIS (N=503)	**Vehicle (N=256)**	**STAQUIS (N=513)**	**Vehicle (N=250)**
Success in ISGA[a]	32.8%	25.4%	31.4%	18.0%
p-value	0.038[b]		<0.001[b]	
ISGA of Clear (0) or Almost Clear (1)[c]	51.7%	40.6%	48.5%	29.7%
p-value	0.005[d]		<0.001[d]	

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

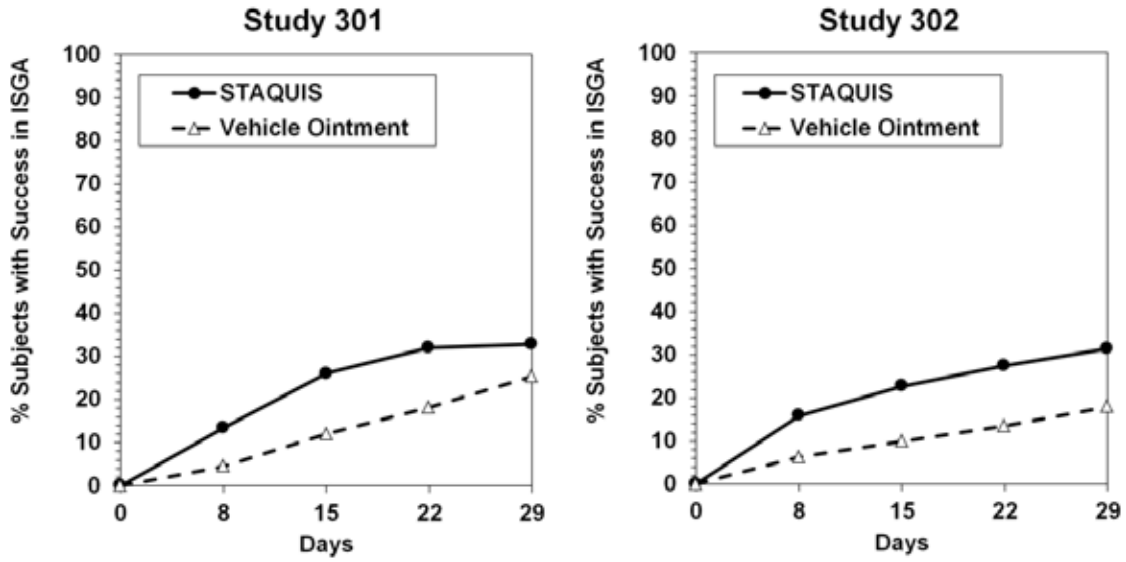
[b] p-value from a logistic regression (with Firth option) test with factors of treatment group and analysis centre. Study 301 estimates from logistic regression are 29.1% and 22.0% for STAQUIS and vehicle, respectively. Study 302 estimates from logistic regression are 26.5% and 14.2% for STAQUIS and vehicle, respectively. Values were adjusted for multiple imputation.

[c] A 2-grade or greater improvement from baseline was not required.

[d] p-value from a logistic regression (with Firth option) test with factors of treatment group and analysis centre. Study 301 estimates from logistic regression are 49.0% and 37.7% for STAQUIS and vehicle, respectively. Study 302 estimates from logistic regression are 45.2% and 25.5% for STAQUIS and vehicle, respectively. Values were adjusted for multiple imputation.

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 incidence of flare and relapse has not been established in controlled trials. Currently, there are no clinical trial data comparing crisaborole to an active comparator.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics (PK) of STAQUIS were investigated in 33 paediatric subjects 2 to 17 years of age with mild to moderate atopic dermatitis and a mean ± SD body surface area 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. When STAQUIS ointment is applied topically, approximately 25% of the crisaborole dose is absorbed. 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 – 5 years, 6 – 11 years, and 12 - 17 years.

Distribution

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

Metabolism

After dermal absorption, crisaborole is substantially and rapidly metabolised into inactive metabolites. The major metabolite 5-(4-cyanophenoxy)-2-hydroxyl benzylalcohol (metabolite 1), is formed via hydrolysis; this metabolite is further metabolised 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.

5.3 Preclinical safety data

Genotoxicity

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).

Carcinogenicity

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 drug-related increased incidence of benign granular cell tumours in the uterus with cervix or vagina (combined) was noted in 300 mg/kg/day crisaborole administered female rats (2 times the MRHD on an AUC comparison basis). Given the tumour type and benign nature 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% and 7% crisaborole ointment were administered once daily. No drug-related neoplastic findings were noted at topical doses up to 7% crisaborole ointment (equal to the MRHD on an AUC comparison basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

STAQUIS ointment also contains white soft paraffin, propylene glycol, glyceryl monostearate, synthetic paraffin, butylated hydroxytoluene, and sodium calcium edetate.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

STAQUIS is supplied in 2.5 g x 6 «, 30 g «, 60 g and 100 g « multi-layered laminate tubes with a high density polyethylene tube head with a peel seal, and a white polypropylene cap closure.

« *Not all pack sizes available*.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

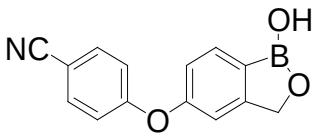
6.7 Physicochemical properties

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.

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

Chemical structure

The structural formula is represented below:



CAS number

906673-24-3

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street

Sydney NSW 2000

Toll Free Number: 1800 675 229

www.pfizer.com.au

9. DATE OF FIRST APPROVAL

20 February 2019.

10. DATE OF REVISION

Not applicable.

TM Trade Mark