SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

STAQUIS®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of STAQUIS contains 20 mg of crisaborole (2 % w/w).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ointment (for topical use).

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 adults and paediatric patients 3 months of age and older. Safety and efficacy beyond 12 months of treatment have not been established.

4.2 Posology and method of administration

Posology

Apply a thin layer of STAQUIS topically, twice daily to affected areas of the skin.

Special populations

Elderly (≥ 65 years of age)

Evidence from clinical studies of STAQUIS did not include sufficient numbers of patients 65 years of age and over to determine whether they respond differently from younger patients.

Paediatric population

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

Method of administration

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

STAQUIS should be applied topically twice daily to all affected areas of skin.

4.3 Contraindications

STAQUIS is contraindicated in patients who are hypersensitive to crisaborole or to any of the excipients of STAQUIS listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity

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.

4.5 Interaction with other medicines and other forms of interaction

In vitro studies using human liver microsomes indicated that under the conditions of clinical use, STAQUIS and metabolite 1 are not expected to inhibit cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4.

In vitro studies using human liver microsomes 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.

In vitro studies in human hepatocytes showed that under the conditions of clinical use, STAQUIS and metabolites 1 and 2 are not expected to induce CYP enzymes.

Interactions

The most sensitive enzyme, CYP2C9, was further investigated in a clinical trial with coadministration of STAQUIS with warfarin, a CYP2C9 substrate. The results of this study showed no medicine interaction potential.

Abnormal laboratory findings: Haematologic, clinical chemistry and other quantitative data

Results for clinical laboratory testing have not identified clinically important changes from baseline to the end of study in mean or median values for any haematology or biochemistry parameters in any of the clinical studies in patients with atopic dermatitis.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safe use during pregnancy has not been established.

There is no available data with STAQUIS in pregnant women to inform the medicine-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).

Breastfeeding

STAQUIS is systemically absorbed following topical application, however it is unknown if STAQUIS is excreted in human milk. Safe use during breastfeeding has not been established.

Fertility

Reproduction studies in male or female rats using oral administration of STAQUIS revelated 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

Summary of the safety profile

The most common medicine-related adverse events reported in clinical trials among patients with mild to moderate atopic dermatitis 2 years of age and older have been application site reactions.

Tabulated summary of adverse reactions

In two randomised, double-blind, parallel-group, vehicle-controlled Phase 3 clinical trials (studies AN2728-AD-301 and AN2728-AD-302), 1 012 patients 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 patients is listed in Table 1.

Table 1: Adverse reaction occurring in ≥ 1 % of patients in atopic dermatitis trials through week 4

Adverse Reaction	STAQUIS N=1 012 n (%)	Vehicle N=499 n (%)
Application site pain[a]	45 (4,45 %)	6 (1,20 %)

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

Summary of adverse reactions

Less common clinical trial adverse reactions

Less common (< 1 %) adverse reactions in patients treated with STAQUIS included application site reactions (including contact dermatitis and pruritus) and flare of atopic dermatitis.

In an open-label, single arm, long-term safety study, 517 patients 2 to 72 years of age (including 454 patients 2 to 17 years of age), who had completed one of the Phase 3 studies without safety issues that precluded further

treatment, were treated with STAQUIS twice daily intermittently for up to 48 weeks in 28 day on-treatment or off-treatment cycles. A total of 9 (2 %) patients discontinued the therapy due to adverse events. The most frequently reported adverse events included atopic dermatitis, application site pain, and application site infection.

Paediatric population

See clinical trial adverse reactions.

In a multi-centre, open-label, uncontrolled trial, 137 paediatric patients 3 months to < 2 years of age were treated with STAQUIS twice daily for 4 weeks. Overall, the safety profile of STAQUIS in this age group was consistent with that of studies AN2728-AD-301 and AN2728-AD-302 in patients 2 years of age and older.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse medicine reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Report any suspected adverse drug reactions associated with the use of the medicine directly to Pfizer via ZAF.AEReporting@pfizer.com

4.9 Overdose

There are no data from clinical trials regarding signs and symptoms of overdose of STAQUIS. If surplus STAQUIS has been applied, the excess should be thoroughly wiped off.

In cases of accidental oral mucosal, ophthalmic, intranasal or intravaginal exposure, the ointment should be thoroughly washed off and the area cleansed with water.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicines for dermatitis, excluding corticosteroids. ATC code: D11AH06

Mechanism of action

Crisaborole is a phosphodiesterase 4 (PDE-4) inhibitor. PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate (cAMP) levels. While the specific mechanism(s) by which crisaborole exerts its therapeutic action is not well defined, crisaborole reduces the production of some inflammatory cytokines implicated in the pathophysiology of atopic dermatitis.

Pharmacodynamic effects

At therapeutic doses, crisaborole ointment is not expected to prolong QTc to any clinically relevant extent. In a thorough QT/QTc study of healthy volunteers, there was no clinically important prolongation of QT/QTc interval induced by either crisaborole or its metabolites and there were no clinically significant effects on heart rate or PR or QRS intervals.

A randomised clinical study was carried out to determine the potential of crisaborole ointment, 2 %, to induce sensitisation and to cause irritation by repeated topical application to normal skin of healthy volunteers (18 years of age or older) under controlled conditions. In this study, crisaborole showed no evidence of skin sensitisation potential. Some skin irritations (e.g. erythema, oedema and papules) were reported.

Clinical efficacy and safety

The efficacy and safety of crisaborole ointment, 2 % was evaluated in two pivotal Phase 3, multi-centre, randomised, double-blind, parallel-group, vehicle-controlled trials (studies AN2728-AD-301 and AN2728-AD-302) that were identical in study design. Patients with mild to moderate atopic dermatitis were randomised 2:1 to receive crisaborole or vehicle applied twice daily for 28 days. A total of 1 522 patients 2 to 79 years of age were enrolled in these studies. About 62 % of patients in both treatment groups were 2 to 11 years of age, and 31 – 37 % of patients were 2 to 6 years of age.

In these Phase 3 trials, the primary efficacy endpoint was the proportion of patients 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. The secondary efficacy endpoints included the proportion of patients at Day 29 with ISGA grade of Clear (score of 0) or Almost Clear (score of 1), and the time to success in ISGA.

The results of the primary efficacy endpoint showed that patients treated with crisaborole ointment, 2 % had a statistically significant higher rate (32,8 % and 31,4 %) of success in ISGA at Day 29 in both pivotal trials, respectively.

Similarly, the results of the secondary efficacy endpoint showed that patients treated with crisaborole ointment, 2 % had a statistically significant higher rate (51,7 % and 48,5 %) of Clear or Almost Clear ISGA scores ratings at Day 29 in both pivotal trials, respectively. The time to success in ISGA was also statistically significantly earlier in the crisaborole group in both trials.

In a multi-centre, open-label, uncontrolled trial (study C3291002), 137 paediatric patients 3 months to < 2 years of age were treated with crisaborole twice daily for 4 weeks. The primary endpoint of safety was evaluated through 4 weeks, with support from pharmacokinetic analyses showing similar medicine exposure to older subjects.

The efficacy of crisaborole in children 3 months to < 2 years of age is extrapolated from efficacy in patients 2 years of age and older. The key exploratory efficacy endpoint in study C3291002 was the proportion of patients who achieved treatment success, defined as an ISGA grade of Clear or Almost Clear with a 2-grade or greater improvement from baseline. The results on ISGA were comparable to those observed among crisaborole-treated patients in studies AN2728-AD-301 and AN2728-AD-302.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics (PK) of crisaborole were investigated in 33 paediatric patients 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, patients applied approximately 3 mg/cm^2 of crisaborole ointment (dose range was approximately 6 g to 30 g per application) twice daily for 8 days. The lower limit of quantification for the PK assay used to detect presence of crisaborole in plasma was 0,2 ng/mL.

Plasma concentrations were quantifiable in all the patients. 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 ± 1 240 ng*h/mL, respectively (see Table 4). 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.

Table 4: Summary of crisaborole pharmacokinetic parameters in 2 – 17-year-old patients with mild to moderate atopic dermatitis and treated BSA range from 27 % - 92 %

	C_{max} (ng/mL)	T_{max} (hrs, median (range)	AUC_{0-12} (ng.hr/mL)
Steady state mean (SD)	127 (196)	3,00 (3,00 – 24,0)	949 (1 240)

The pharmacokinetics of crisaborole were investigated in 18 patients 3 months to < 24 months of age. Excluding outlier values from 5 patients, the mean ± SD C_{max} and AUC_{0-12} for crisaborole were 188 ± 100 ng/mL and 1 164 ± 550 ng.hr/mL, respectively.

Distribution

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

Metabolism

Crisaborole is substantially metabolised into inactive metabolites. The major metabolite 5-(4-cyanophenoxy)-2-hydroxyl benzyl alcohol (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.

Pharmacokinetics 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.

Elimination

Renal excretion of metabolites is the major route of elimination.

Special populations

Elderly population

PK profiles of crisaborole and its two metabolites have not been assessed in elderly subjects.

Renal impairment

PK profiles of crisaborole and its two metabolites have not been assessed in patients with renal impairment.

Hepatic impairment

PK profiles of crisaborole and its two metabolites have not been assessed in patients with hepatic impairment.

Paediatric population

A multi-centre, open-label maximal use, systemic exposure study with a PK Phase and a non-PK Safety Phase was conducted in children and adolescents with mild to moderate atopic dermatitis. Based on the PK exposures, no difference was seen in PK exposures in patients between the various age cohorts (2 to < 18 years old).

A separate PK study evaluated 18 patients 3 months to < 2 years of age. Following crisaborole 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.

5.3 Preclinical safety data

Carcinogenicity

In an oral carcinogenicity study in Sprague-Dawley rats, oral doses of 30, 100, and 300 mg/kg/day crisaborole were administered to rats once daily for 104 weeks. A medicine-related higher incidence of benign granular cell tumours in the uterus with cervix and vagina (combined) was noted in 300 mg/kg/day crisaborole treated female rats (1,5 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 % and 7 % crisaborole ointment were administered once daily for at least 99 (females) or 104 (males) weeks. No medicine-related neoplastic findings were noted at topical doses up to 7 % crisaborole ointment (1 time the MRHD on an AUC comparison basis).

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).

Reproductive and developmental toxicology

Rat and rabbit embryo-foetal development was assessed after oral administration of crisaborole. Crisaborole did not cause adverse effects to the foetus 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). Maternal toxicity was produced at the high dose of 600 mg/kg/day in pregnant rats and was associated with findings of decreased foetal body weight and delayed skeletal ossification. Crisaborole did not cause adverse effects to the foetus 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).

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylated hydroxytoluene

Edetate calcium disodium

Mono- and di-glycerides

Paraffin

White petrolatum

Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

STAQUIS is supplied in 30 g and 60 g multi-laminate tubes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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South Africa

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8. REGISTRATION NUMBER

55/13.12/0287

9. DATE OF FIRST AUTHORISATION

04 May 2021

10. DATE OF REVISION OF THE TEXT

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