▼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 - ANZUPGO® (DELGOCITINIB) CREAM

1 NAME OF THE MEDICINE

Delgocitinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of ANZUPGO cream contains 20 mg of delgocitinib.

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

3 PHARMACEUTICAL FORM

Cream

Delgocitinib is a white to slightly brown cream.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ANZUPGO is indicated for the treatment of moderate to severe chronic hand eczema (CHE) in adults for whom topical corticosteroids are inadequate or inappropriate.

4.2 DOSE AND METHOD OF ADMINISTRATION

ANZUPGO should be initiated and supervised by physicians with experience in the diagnosis and treatment of CHE.

Dosage

A thin layer of ANZUPGO should be applied twice daily to the affected skin of the hands and wrists until the skin is clear or almost clear. It is recommended to apply the cream at regular intervals, approximately 12 hours apart.

In the event of recurrence of the signs and symptoms of CHE (flares), twice daily treatment of the affected areas should be re-initiated as needed.

Treatment should be discontinued if no improvement is seen after 12 weeks of continuous treatment.

Missed dose

If an application is missed, ANZUPGO should be applied as soon as possible. Thereafter, applications should be resumed at the regular scheduled time.

Method of administration

ANZUPGO is for topical use only. A thin layer of ANZUPGO should be applied twice daily to clean and dry skin of the affected areas of the hands and wrists.

Patients should avoid applying other topical products immediately before and after application of ANZUPGO (see Section 4.5 Interactions with other medicines and other forms of interactions). Co-application with emollients within 2 hours before and after application of delgocitinib has not been studied.

If someone else applies the cream to the patient, they should be instructed to wash their hands after application.

Contact with eyes, mouth, or other mucous membranes should be avoided. If contact with mucous membranes occurs, rinse thoroughly with water.

Dosage Adjustment

Renal and Hepatic impairment

No studies with ANZUPGO have been performed in patients with severe hepatic or renal impairment. However, dose adjustment is not recommended due to the minimal systemic exposure of topically applied delgocitinib (see Section 5.2 Pharmacokinetic Parameters).

Elderly patients

No dose adjustment is recommended for elderly patients (see Section 4.4 Special Warnings and Precautions For Use).

Paediatric population

No safety and efficacy data are available in children and adolescents below 18 years of age (see Section 4.4 Special Warnings and Precautions For Use).

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

Non-melanoma skin cancer

Non-melanoma skin cancer (NMSC), predominantly basal cell carcinoma, has been reported in patients treated with topical JAK inhibitors. Periodic skin examination of the application site is recommended for all patients, particularly those with risk factors for skin cancer.

Use in the elderly

See Section 4.2 Dose and Method of Administration

Paediatric use

See Section 4.2 Dose and Method of Administration

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinical interaction studies have been performed. Given the limited metabolism of delgocitinib, application to a limited body surface area (hands and wrists), and minimal systemic exposure of topically applied delgocitinib, there is a low potential for interaction with systemic medications.

ANZUPGO has not been evaluated in combination with other topical medications and co-application on the same skin area is not recommended.

The limited metabolism of delgocitinib occurs primarily through CYP3A4/5 and to a lesser extent by CYP2C9, CYP2C19, and CYP2D6.

Based on *in vitro* data, delgocitinib does not inhibit cytochrome P450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 or induce cytochrome P450 enzymes 1A2, 2B6 or 3A4. Delgocitinib does not inhibit transporter systems such as organic anion transporters (OAT), organic anion transporting proteins (OATP), organic cation transporters (OCT), P- glycoprotein (P-gp), breast cancer resistance protein (BCRP), or multi-antimicrobial extrusion protein (MATE) at clinically relevant concentrations.

Delgocitinib is a substrate of P- glycoprotein (P-gp) and a weak substrate of human organic cation transporter 2 (OTC2) and human organic anion transporter 3 (OAT3). Delgocitinib is not a substrate of BCRP.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No human data on the effect of delgocitinib on fertility are available.

In male rats, orally administered delgocitinib did not result in effects on fertility at dose levels up to 30 mg/kg/day (1731 times the maximum recommended human dose (MRHD) based on AUC comparison). In female rats, orally administered delgocitinib resulted in effects on female fertility (lower fertility index, decreased corpora lutea, and decreased implantations) at 100 mg/kg/day (5897 times the MRHD based on AUC comparison). No effect on female fertility was observed at 30 mg/kg/day (1088 times the MRHD based on AUC comparison). Post-implantation losses and a decrease in the number of live embryos were observed at >10 and >30 mg/kg/day (435 and 1088 times the MRHD based on AUC comparison, respectively).

Use in pregnancy – Pregnancy Category B1

There are limited data (less than 300 pregnancy outcomes) from the use of delgocitinib in pregnant women. When administered orally in animals, studies have shown reproductive toxicity at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use. As a precautionary measure, it is preferable to avoid the use of ANZUPGO during pregnancy.

In embryofetal development studies in rats or rabbits, oral administration of delgocitinib did not result in adverse effects to the fetus at 3 mg/kg/day (120 and 193 times the MRHD based on AUC comparison, respectively). Teratogenic effects were not observed at any dose studied in rats or rabbits up to dose levels of 30 and 10 mg/kg/day (1441 and 992 times the MRHD based on AUC comparison, respectively).

In rats, decreases in fetal weight and skeletal variations (wavy ribs) were observed at >10 mg/kg (512 times the MRHD based on AUC comparison). An increase in post-implantation loss, skeletal variations (asymmetry and splitting of the sternebra, splitting of the thoracic vertebral body and delayed sternum ossification) and visceral variations (thymic remnants in the neck) was observed at 30 mg/kg (1441 times the MRHD based on AUC comparison). In rabbits, an increase in post-implantation loss, a reduced number of live fetuses, and a decrease in fetal weights were observed at 10 mg/kg (992 times MRHD based on AUC comparison). No adverse effect on embryo-fetal development was observed at 3 mg/kg/day (193 times the MRHD based on AUC comparison).

In a pre- and postnatal development study in rats, oral administration of delgocitinib resulted in decreased fetal viability and reduced pup weights during the early postnatal period at 30 mg/kg (2058 times the MRHD based on AUC comparison).

Use in lactation

It is unknown whether delgocitinib is excreted in human milk.

After oral administration, delgocitinib was present in the milk of lactating rats at concentrations approximately 3-fold those in plasma. Based on the minimal systemic exposure after topical application of delgocitinib, no effects on the breastfed newborns/infants are anticipated.

ANZUPGO can be used during breastfeeding.

When ANZUPGO is used during breast-feeding, care should be taken to avoid direct contact with the nipple or surrounding area after applying the cream to the hands and/or wrists.

As a precautionary measure, care should be taken to avoid direct skin contact when taking care of an infant immediately after applying ANZUPGO to the hands and/or wrists.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ANZUPGO has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse events reported in clinical studies

The safety data described below is based on a pool of three vehicle-controlled clinical studies in 1062 patients with CHE, of which 691 were treated with delgocitinib 20 mg/g cream. Patients applied delgocitinib 20 mg/g cream to affected areas of the hands and wrists twice daily for up to 16 weeks. A total of 466 patients continued with an additional 36 weeks of as-needed treatment with delgocitinib cream in an open-label, long-term extension study. The long-term safety profile up to 52 weeks was consistent with the safety profiles observed at 16-weeks. Treatment-emergent adverse events reported by ≥ 2% of subjects from either treatment group, based on the pool of the 3 vehicle-controlled studies, are listed in Table 1.

Table 1: Treatment-Emergent Adverse Events Reported in ≥ 2% of subjects in the pool of three vehicle-controlled clinical studies through 16 weeks treatment – Safety population

Adverse Events	Delgocitinib 20 mg/g Twice daily (N=691)	Vehicle Twice daily (N=371)
	n (adj. %)	n (adj. %)
COVID-19	71 (9.9)	34 (9.4)
Nasopharyngitis	58 (9.0)	44 (11.0)
Headache	32 (4.7)	15 (4.0)
Eczema	12 (2.1)	11 (2.6)
Hand dermatitis	4 (0.6)	13 (3.6)

Abbreviations: adj. = adjusted

Notes: None of these events were considered treatment-related adverse events. For the trials there was 16 weeks of treatment and 2 weeks of safety follow-up period (resulting in up to 18 weeks).

Adverse reactions in clinical studies

Table 2 lists the adverse reactions that were observed in clinical studies presented by MedDRA system organ class and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 2: Adverse reactions

System Organ Class	Frequency	Adverse Reaction
General disorders and administration site conditions	Common	Application site reactions *

*see Description of selected adverse reactions.

The only related adverse events were application site reactions (1%).

Description of selected adverse reactions

Application site reactions

In the pool of three vehicle-controlled clinical studies through 16 weeks, application site reactions (including application site pain, application site paraesthesia, application site pruritus, and application site erythema) were reported in 1.0 % of patients treated with delgocitinib cream compared with 2.5 % of patients treated with vehicle cream. The majority of application site reactions were mild in severity with no serious or severe events being reported. Of the application site reactions observed in patients receiving delgocitinib cream treatment, over 75 % occurred within the first week of treatment, none resulted in treatment interruption, and the median time to resolution was 3 days.

The event rate of application site reactions in the long-term extension study (0.56 events per 100 patient years of observation) was lower than in the 16-week vehicle-controlled clinical studies (4.11 events per 100 patient years of observation).

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 www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No systemic signs of overdose are expected following topical application of ANZUPGO due to the minimal systemic absorption of delgocitinib. If too much cream has been applied, the excess can be wiped off.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other dermatological preparations, agents for dermatitis, excluding corticosteroids, ATC code: D11AH11

Mechanism of action

Delgocitinib is a pan Janus kinase (JAK) inhibitor that targets the activity of all four members of the JAK family of enzymes consisting of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) in a concentration dependent manner.

In human cellular studies, inhibition of the JAK-STAT pathway by delgocitinib attenuates the signalling of several pro-inflammatory cytokines (including interleukin (IL)-2, IL-4, IL-6, IL-13, IL-21, IL-23, Granulocyte-Macrophage-Colony-Stimulating Factor (GM-CSF), and Interferon (IFN)-α) downregulating the immune and inflammatory responses in cells of relevance to CHE pathology.

Pharmacodynamic effects

In patients with CHE, treatment with topically applied delgocitinib resulted in reduced levels of pro-inflammatory markers of CHE such as S100 calcium binding protein A9/12 (S100A9/12), peptidase inhibitor 3 (PI3), kallikrein related peptidase 6 (KLK6), and serpin family B member 3 (SERPINB3).

Treatment with delgocitinib cream resulted in reductions of epidermal hyperplasia in lesional skin, which was observed together with a down-regulation of the keratinocyte differentiation marker keratin 16 (K16) and reduced T-cell infiltration of the skin compartment. Treatment with topically applied delgocitinib also resulted in the increased expression of genes involved in skin barrier function (e.g., filaggrin, loricrin, and claudins) in lesional skin. Skin colonisation with *Staphylococcus aureus* was reduced more than 70-fold compared to vehicle.

In a thorough QT study in healthy subjects, there was no indication of a QTc prolonging effect of orally administered delgocitinib at single doses up to 12 mg (approximately 200 times the human exposure following topical application, based on C_{max}). Therefore, ANZUPGO is not expected to affect cardiac repolarisation under conditions of clinical use.

Dermal safety studies

Clinical studies in healthy subjects demonstrated that delgocitinib cream did not cause phototoxic skin reactions or photoallergic skin reactions.

Clinical trials

The safety and efficacy of delgocitinib cream were evaluated in two pivotal randomised, double-blind, vehicle-controlled studies of similar design (DELTA 1 and DELTA 2). CHE was defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months. The studies included 960 patients 18 years of age and older with moderate to severe CHE as defined by an Investigator's Global Assessment for chronic hand eczema (IGA-CHE) score of 3 or 4 (moderate or severe) (see Table 3) and required a Hand Eczema Symptom Diary (HESD) itch score of ≥ 4 points at baseline. Eligible patients had a previous inadequate response to topical corticosteroids or were those in which topical corticosteroids are not advisable (e.g. due to important side effects or safety risks).

Table 3: Investigator's Global Assessment for chronic hand eczema (IGA-CHE)

IGA-CHE severity	IGA-CHE score	Sign and intensity
Clear	0	No signs of erythema, scaling, hyperkeratosis/lichenification, vesiculation, oedema or fissures
Almost clear	1	Barely perceptible erythema No signs of scaling, hyperkeratosis/lichenification, vesiculation, oedema or fissures
Mild	2	At least one: • Slight but definite erythema (pink) • Slight but definite scaling (mostly fine scales) • Slight but definite hyperkeratosis/lichenification and at least one: • Scattered vesicles, without erosion • Barely palpable oedema • Superficial fissures
Moderate	3	At least one: • Clearly perceptible erythema (dull red) • Clearly perceptible scaling (coarse scales) • Clearly perceptible hyperkeratosis/lichenification and at least one: • Clustered vesicles, without visible erosions • Definite oedema • Definite fissures
Severe	4	At least one: • Marked erythema (deep or bright red) • Marked and thick scaling • Marked hyperkeratosis/lichenification and at least one: • High density of vesicles with erosions • Marked oedema • One or more deep fissures

In DELTA 1 and DELTA 2, patients applied either delgocitinib 20 mg/g cream or vehicle cream twice daily to affected areas on the hands and wrists for 16 weeks. All patients who completed the two pivotal studies were eligible to enrol into the long-term extension study DELTA 3.

Endpoints

In DELTA 1 and DELTA 2, the primary endpoint was the proportion of patients achieving IGA-CHE treatment success (IGA-CHE TS), defined as an IGA-CHE score of 0 (clear) or 1 (almost clear: barely perceptible erythema only) with at least a 2-step improvement from baseline to Week 16. The IGA-CHE instrument rates the severity of the subject's global disease and is based on a 5-point scale ranging from 0 (clear) to 4 (severe).

Additional efficacy outcomes included the Hand Eczema Severity Index (HECSI) and the HESD at various timepoints. The HECSI rates the severity of six clinical signs (erythema, infiltration/papulation, vesicles, fissures, scaling, and oedema) and the extent of the lesions on each of the five hand regions (fingertips, fingers, palm of hands, back of hands, and wrists). The HESD is a daily 6-item patient-reported outcome (PRO) instrument designed to assess the worst severity of signs and symptoms of CHE (itch, pain, cracking, redness, dryness, and flaking) using an 11-point numeric rating scale.

Baseline characteristics

Across all treatment groups in DELTA 1 and DELTA 2, the mean age was 44.1 years, 7.6 % of patients were 65 years of age or older, 64.4 % were female, 90.4 % were White, 3.5 % were Asian, and 0.7 % were Black. The frequency of CHE by main subtype was 35.9% atopic hand eczema, 21.5% hyperkeratotic eczema, 19.6% irritant contact dermatitis, 13.9% allergic contact dermatitis, 9.1% vesicular hand eczema (pompholyx), and 0.1% contact urticaria/protein contact dermatitis. Across all trial arms, 27.7% of subjects were diagnosed with two or more overlapping CHE subtypes. In these studies, 71.6 % of patients had a baseline IGA-CHE score of 3 (moderate CHE), and 28.4 % of patients had a baseline IGA-CHE score of 4 (severe CHE). The mean baseline Dermatology Life Quality Index (DLQI) score was 12.5, HECSI score was 71.6, and HESD score was 7.1. The mean HESD itch and pain scores were 7.1 and 6.7, respectively.

Clinical response

DELTA 1 and DELTA 2

In DELTA 1 and DELTA 2, a statistically significantly greater proportion of patients randomised to delgocitinib cream achieved the primary endpoint of IGA-CHE TS compared to vehicle at Week 16. The results for the primary and selected multiplicity-controlled secondary endpoints are presented in Table 4. Figure 1 shows the proportion of patients who achieved HECSI-75, HESD itch ≥ 4-point improvement, and HESD pain ≥ 4-point improvement over time in DELTA 1 and DELTA 2.

Table 4: Efficacy results of delgocitinib at Week 16 in DELTA 1 and DELTA 2

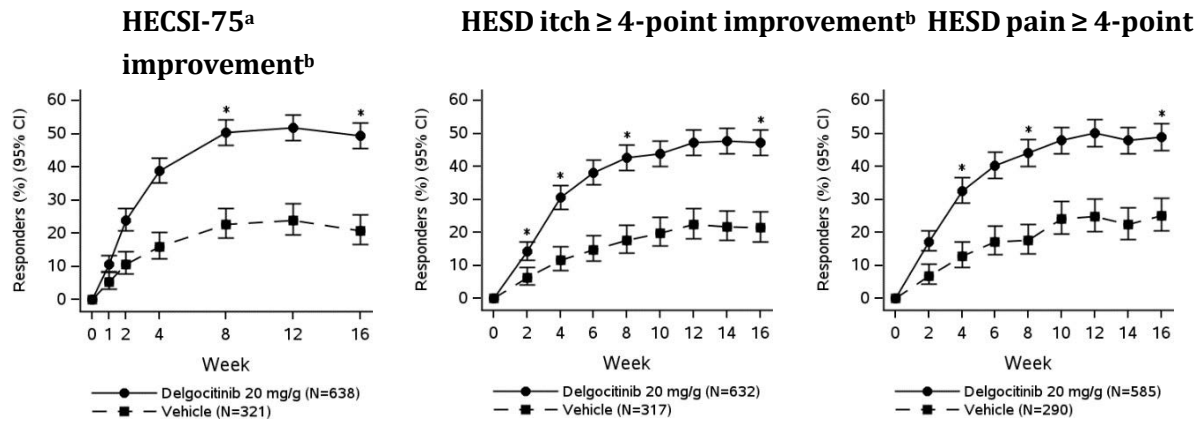
	DELTA 1		DELTA 2	
	Delgocitinib (N=325)	**Vehicle (N=162)**	**Delgocitinib (N=313)**	**Vehicle (N=159)**
IGA-CHE TS, % responders[a]	19.7[#]	9.9	29.1[§]	6.9
HECSI-90, % responders[a, b]	29.5[§]	12.3	31.0[§]	8.8
HECSI-75, % responders[a, c]	49.2[§]	23.5	49.5[§]	18.2
HECSI, LS mean % change from baseline (± SE)[d]	-56.5[§] (± 3.4)	-21.2 (± 4.8)	-58.9[§] (± 3.2)	-13.4 (± 4.5)
HESD itch ≥ 4-point improvement, % responders[a, e]	47.1[§] (152/323)	23.0 (37/161)	47.2[§] (146/309)	19.9 (31/156)
HESD pain ≥ 4-point improvement, % responders[a, e]	49.1[§] (143/291)	27.5 (41/149)	48.6[§] (143/294)	22.7 (32/141)
HESD ⩾ 4-point improvement, % responders[a, e]	47.2[§] (146/309)	24.4 (38/156)	44.5[§] (137/308)	20.9 (32/153)

[#]p<0.01, [§]p<0.001
All p-values were statistically significant versus vehicle with adjustment for multiplicity.
Abbreviations: LS=least squares; N=number of patients in the full analysis set (all patients randomised and dosed); SE = standard error
a. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered non-response.
b. HECSI-90 responders were patients with ≥ 90 % improvement in HECSI from baseline.
c. HECSI-75 responders were patients with ≥ 75 % improvement in HECSI from baseline.
d. Data after initiation of rescue medication, permanent discontinuation of treatment, or missing data were considered non-response by using worst observation carried forward.
e. Based on the number of patients whose baseline value was ≥ 4 (scale from 0-10).

In both DELTA 1 and DELTA 2, a greater proportion of patients treated with delgocitinib cream achieved improvements in the signs and extent of CHE, as measured by the percentage change from baseline in HECSI, as early as Week 1 compared to vehicle.

Greater improvements in itch and pain, as measured by the mean change in HESD itch and pain scores, were observed compared to vehicle 1 day and 3 days after starting delgocitinib cream treatment, respectively.

Figure 1: Proportion of patients who achieved HECSI-75, HESD itch ≥ 4-point improvement, and HESD pain ≥ 4-point improvement over time – pooled data from DELTA 1 and DELTA 2



CI = Confidence Interval
*Statistically significant versus vehicle with adjustment for multiplicity
a. HECSI-75 responders were patients with ≥ 75 % improvement in HECSI from baseline.
b. Based on the number of patients whose baseline value was ≥ 4 (scale from 0-10).

Across DELTA 1 and DELTA 2, treatment effects in subgroups (weight, age, gender, race, disease severity, duration of CHE, and previous treatment) were consistent with the results in the overall study population.

Additional quality of life/patient-reported outcomes

In both DELTA 1 and DELTA 2, patients treated with delgocitinib cream showed a statistically significantly greater improvement from baseline in the Hand Eczema Impact Scale (HEIS) compared to vehicle at Week 16 (see Table 5). Improvements versus vehicle were observed for all six domains of the HEIS (proximal daily activity limitations, embarrassment, frustration, sleep, work, and physical functioning [ability to hold or grip objects]) at Week 16.

Across DELTA 1 and DELTA 2, statistically significantly greater improvements in health-related quality of life, as measured by the DLQI were observed in delgocitinib patients compared to vehicle at Week 16 (see Table 5).

Table 5: Quality of life/patient-reported outcomes results of delgocitinib at Week 16 in DELTA 1 and DELTA 2

	DELTA 1		DELTA 2	
	Delgocitinib (N=325)	**Vehicle (N=162)**	**Delgocitinib (N=313)**	**Vehicle (N=159)**
HEIS, LS mean change from baseline (± SE)[a, e]	-1.46§ (± 0.05)	-0.82 (± 0.08)	-1.45§ (± 0.06)	-0.64 (± 0.08)
HEIS PDAL, LS mean change from baseline (± SE)[a, b]	-1.46§ (± 0.06)	-0.86 (± 0.08)	-1.48§ (± 0.06)	-0.66 (± 0.08)
DLQI ⩾ 4-point improvement, % responders[c, d]	74.4§ (227/305)	50.0 (74/148)	72.2§ (216/299)	45.8 (70/153)

§p<0.001
All p-values were statistically significant versus vehicle with adjustment for multiplicity.
Abbreviations: LS=least squares; N=number of patients in the full analysis set (all patients randomised and dosed); PDAL=proximal daily activity limitations; SE=standard error
a. Data after initiation of rescue medication, permanent discontinuation of treatment, or missing data were considered non-response by using worst observation carried forward.
b. HEIS PDAL assesses the patient's ability to use soaps/cleaning products, to do housework, and to wash themselves. The HEIS PDAL score is calculated as the average of the 3 items.
c. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered non-response.
d. Based on the number of patients whose baseline value was ≥ 4.
e. HEIS is an instrument used for assessing the patient's perceived impact on their daily activities (use of soaps/cleaning products, housework involving hands getting wet, washing themselves, embarrassment, frustration, sleep, work, and the ability to hold or grip objects).

Extension study (DELTA 3)

Patients who completed either DELTA 1 or DELTA 2 were eligible to enrol in a 36-week open-label extension study (DELTA 3). In DELTA 3, the long-term safety and efficacy of as-needed delgocitinib treatment was evaluated in 801 patients. Patients started application of delgocitinib cream twice daily to affected areas whenever the IGA-CHE score was ≥ 2 (mild or worse) and stopped treatment when an IGA-CHE score of 0 or 1 (clear or almost clear) was achieved. Patients entering DELTA 3 with an IGA-CHE score of 0 or 1 remained off treatment until loss of response (IGA-CHE score ≥ 2).

The proportions of patients achieving IGA-CHE 0 or 1, HECSI-75, HECSI-90, HESD itch ≥ 4-point improvement, and HESD pain ≥ 4-point improvement after the initial 16-week treatment period of delgocitinib cream were maintained through Week 52 with as-needed treatment. Among the 560 patients randomised to delgocitinib cream treatment in the pivotal studies (DELTA 1 and DELTA 2) enrolled in DELTA 3, the mean number of treatment periods was 1.5 (range 0 to 6), the mean treatment period duration was 123 days, and the mean cumulative number of days in response (days with an IGA-CHE score of 0 or 1 within the 36-week treatment period) was 46. The mean cumulative number of days in response was 111 among those patients who achieved IGA-CHE TS at Week 16 in the pivotal studies.

Of the patients randomised to delgocitinib cream in the pivotal studies who achieved IGA-CHE TS at Week 16, the median duration of response while off treatment was 4 weeks with 28.3 % maintaining response for at least 8 weeks. The median time to regain an IGA-CHE score of 0 or 1 following re-initiation of treatment was 8 weeks. Among patients who did not achieve an IGA-CHE TS at Week 16 of delgocitinib treatment in the pivotal studies, 48.1 % achieved IGA-CHE 0 or 1 with continued delgocitinib treatment in DELTA 3.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The pharmacokinetics of delgocitinib cream were evaluated in a study involving 15 adult patients 22 to 69 years of age with moderate to severe CHE. Patients applied on average 0.87 g of delgocitinib 20 mg/g cream to the affected areas of the hands and wrists twice a day for 8 days.

The geometric mean (GSD) maximum plasma concentration (C_{max}) and area under the concentration-curve from time 0 to 12 hours (AUC_{0-12}) on Day 8 was 0.46 ng/mL (1.74) and 3.7 ng*h/mL (1.74), respectively. Steady state was reached by Day 8. The systemic exposure (AUC and C_{max}) between Day 1 and Day 8 were similar.

Following twice daily application of delgocitinib 20 mg/g cream in DELTA 2, the geometric mean plasma concentration observed 2-6 hours after application at Day 113 was 48 % lower than that at Day 8 (0.11 ng/mL and 0.21 ng/mL, respectively).

The relative bioavailability of delgocitinib following topical application of ANZUPGO is approximately 0.6 % compared to administration via oral tablets.

Distribution

Based on an *in vitro* study, plasma protein binding of delgocitinib is 22 to 29 %.

Metabolism

As delgocitinib does not undergo extensive metabolism, the main plasma component is unchanged delgocitinib. Following oral administration, four metabolites (formed via oxidation and glucuronide conjugation) were detected at < 2 % of the average unchanged delgocitinib plasma concentrations. The limited metabolism of delgocitinib occurs primarily through CYP3A4/5 and to a lesser extent by CYP2C9, CYP2C19, and CYP2D6.

Excretion

Delgocitinib is primarily eliminated by renal excretion as approximately 70-80 % of the total dose after oral administration was found unchanged in the urine.

Following repeated topical application of delgocitinib cream, the average half-life of delgocitinib was estimated to be 20.3 hours.

Special populations

Hepatic impairment

No formal studies of delgocitinib cream in patients with hepatic impairment have been conducted.

Due to the minimal systemic exposure of topically applied delgocitinib and limited metabolism of delgocitinib, changes in hepatic function are unlikely to have any effect on the elimination of delgocitinib. Therefore, no dose adjustments are needed in patients with hepatic impairment (see Section 4.2 Dose and Method of Administration).

Renal impairment

Pharmacokinetic parameters of delgocitinib were analysed in 96 patients with mild or moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2) in DELTA 2. There were no clinically relevant differences in the pharmacokinetics observed in patients with mild or moderate renal impairment compared to the overall study population. Due to the minimal systemic exposure of topically applied delgocitinib, changes in renal function are unlikely to be of clinical importance. Therefore, no dose adjustments are needed in patients with renal impairment (see Section 4.2 Dose and Method of Administration).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Delgocitinib was not mutagenic or clastogenic in a bacterial reverse mutation test (Ames test) and did not demonstrate genotoxic potential in an in vivo chromosomal aberration test (rat bone marrow cells) or in a dermal skin micronucleus test (hairless mice). In an in vitro chromosomal aberration test (human peripheral blood lymphocytes), delgocitinib induced polyploidy but not chromosomal structural aberrations.

Carcinogenicity

In a 2-year dermal carcinogenicity study in mice, no local or systemic drug-related neoplastic findings were observed following dermal application of delgocitinib ointment (600 times MRHD based on AUC comparison).

Findings from a 2-year oral carcinogenicity study in rats included pancreatic acinar adenomas and subcutaneous lipoma (males only at ≥3 mg/kg), thymoma (females only at ≥10 mg/kg), and Leydig cell tumour (males at 30 mg/kg), respectively (160, 592, and 2072 times the MRHD based on AUC comparison, respectively). In addition, the incidence and severity of Leydig cell/hyperplasia were increased at 10 mg/kg and above (592 times the MRHD based on AUC comparison). The clinical relevance of tumour findings in rats is low given the tumour types in a single species, single sex, and the exposures at which the tumours occurred.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Benzyl alcohol
Butylated hydroxyanisole
Cetostearyl alcohol
Citric acid monohydrate
Disodium edetate
Hydrochloric acid
Liquid paraffin
Ceteareth – 20
Purified water

6.2 INCOMPATIBILITIES

Please refer to section 4.5 – Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

3 years

After first opening: 12 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

Laminate tube with an aluminium barrier layer and an inner layer of low-density polyethylene fitted with a polypropylene flip-top cap.

Package sizes: 15 g or 60 g.

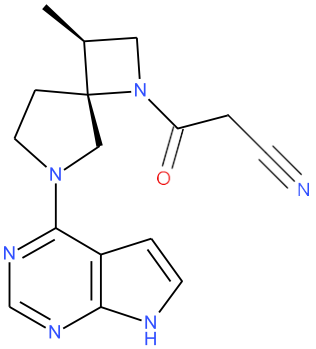
Not all pack sizes may be marketed.

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

Chemical structure



CAS number

1263774-59-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

LEO Pharma Pty Ltd
Suite 3, Level 1, 5 Lamington Street,
New Farm QLD 4005, Australia.
Australia Toll Free no.: 1800 991 778

9 DATE OF FIRST APPROVAL

XX-MMM-YYYY

10 DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	N/A