Product Monograph

Including Patient Medication Information

PrANZUPGO®

Delgocitinib cream

For topical use

20 mg/g

Janus Kinase (JAK) Inhibitor

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Part 1: Healthcare Professional Information

1. Indications

ANZUPGO (delgocitinib cream) is indicated for the treatment of moderate to severe chronic hand eczema (CHE) in adults for whom topical corticosteroids are inadequate or are not advisable.

1.1. Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (≥ 65 years): Evidence from clinical studies suggests there are no clinically relevant differences in safety and efficacy between geriatric patients and adult patients less than 65 years of age.

2. Contraindications

ANZUPGO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.

4. Dosage and Administration

4.1. Dosing Considerations

- Health Canada has not authorized an indication for pediatric use, as no data are available in patients < 18 years of age [see 1.1 Indications, Pediatrics].

4.2. Recommended Dose and Dosage Adjustment

- The recommended dose is a thin layer of ANZUPGO applied twice daily, approximately 12 hours apart, to the affected skin of the hands and wrists until the skin is clear or almost clear.

- ANZUPGO should be discontinued when signs and symptoms of CHE resolve.

- 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.

- If signs and symptoms of CHE do not improve within 12 weeks of treatment, continued therapy should be re-evaluated by a healthcare professional.

Geriatric patients (≥ 65 years)
No dose adjustment is required for geriatric patients.

Hepatic and renal impairment
No dose adjustment is required in patients with hepatic or renal impairment due to the low systemic exposure of topically applied delgocitinib to the hands and wrists [see 10.3 Pharmacokinetics].

4.4. Administration

ANZUPGO is for topical use only. It is not for ophthalmic, oral or intravaginal use. Contact with eyes, mouth, or other mucous membranes should be avoided. If contact with mucous membranes occurs, rinse thoroughly with water.

A thin layer of ANZUPGO should be applied, approximately 12 hours apart, to clean and dry skin of the affected areas of the hands and wrists.

Patients should avoid applying other topical products within 2 hours before and after application of ANZUPGO. Co-application with emollients within 2 hours before and after application of delgocitinib has not been studied.

Patients should be advised to not use more than one 60 g tube per month.

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

4.5. 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.

5. Overdose

There are no data from clinical trials regarding overdose with ANZUPGO. No systemic signs of overdose are expected following topical application of ANZUPGO to the hands and wrists due to the low systemic absorption of delgocitinib. If too much cream has been applied, the excess should be wiped off.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1-1: Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Topical	Cream; 20 mg/g	Benzyl alcohol, butylhydroxyanisole, cetostearyl alcohol, citric acid monohydrate, disodium edetate, hydrochloric acid, liquid paraffin, macrogol cetostearyl ether, purified water.

Description

ANZUPGO is a white to slightly brown cream. Each gram of cream contains 20 mg of delgocitinib.

ANZUPGO is supplied in 5 g and 15 g (sample sizes) and 60 g laminate tubes. The laminate tubes are comprised of an inner layer of low-density polyethylene fitted with a polypropylene cap.

7. Warnings and Precautions

General

ANZUPGO is not for ophthalmic, oral, or intravaginal use.

Use of ANZUPGO in combination with other treatments for CHE, such as alitretinoin, has not been studied. Use of ANZUPGO in combination with other JAK inhibitors, immunomodulators or potent immunosuppressants has not been studied, and therefore, should be used with caution.

Carcinogenesis and Genotoxicity

Non-melanoma skin cancer

Non-melanoma skin cancer (NMSC), including basal cell carcinoma and squamous cell carcinoma, has been reported in patients treated with topical JAK inhibitors. A skin examination prior to initiation and periodically during treatment of the application site should be considered for patients with a history of skin cancer, or who have risk factors for skin cancer.

Reproductive Health

- **Fertility**

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

Based on findings in female rats, oral administration of delgocitinib resulted in reduced fertility at exposures considered sufficiently in excess of the human exposure with topical administration to affected areas of the hands and/or wrists [see 16 Non-Clinical Toxicology].

Animal studies did not indicate effects with respect to fertility in males.

7.1. Special Populations

7.1.1. Pregnancy

The limited data from the use of ANZUPGO in pregnant women is insufficient to evaluate a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

When administered orally in animals, studies have shown reproductive toxicity at exposures considered sufficiently in excess of the human exposure with topical administration to affected areas of the hands and/or wrists [see 16 Non-Clinical Toxicology].

As a precautionary measure, it is preferable to avoid the use of ANZUPGO during pregnancy.

7.1.2. Breastfeeding

It is unknown whether delgocitinib is excreted in human milk. ANZUPGO should only be used during breast feeding if the benefit justifies the potential risk to the newborn/infant.

After oral administration, delgocitinib was present in the milk of lactating rats [see 16 Non-Clinical Toxicology].

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

7.1.3. Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use [see 1.1 Indications, Pediatrics].

7.1.4. Geriatrics

Evidence from clinical studies suggests there are no clinically relevant differences in safety and efficacy between geriatric patients and adult patients less than 65 years of age.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The most common adverse reactions reported in Phase 3 clinical studies in adult patients with moderate or severe CHE were application site reactions (1.1%).

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

The safety data described below is based on a pool of two vehicle-controlled clinical studies in 959 patients with CHE, of which 638 were treated with ANZUPGO. Patients applied ANZUPGO 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 ANZUPGO in an open-label, long-term extension study.

Table 1-2: Adverse Reactions Reported in ≥1% of Patients in CHE Trials through Week 16

Adverse Reaction	ANZUPGO N=638		Vehicle N=321	
	n	%	n	%
General disorders and administration site conditions				
Application site reactions*	7	1.1	9	2.8

* Includes: application site pain, application site paraesthesia, application site pruritus, and application site erythema.
N=number of subjects; n=number of subjects with events; %=proportion of subjects

The long-term safety of as-needed treatment with ANZUPGO through Week 52 was consistent with the safety profile observed up to Week 16.

8.2.1. Clinical Trial Adverse Reactions – Pediatrics

Not applicable. No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Clinical Trial Findings

No clinically meaningful trends in hematologic, chemistry parameters or vital signs were observed in clinical trials.

8.5. Post-Market Adverse Reactions

Not applicable, as post-market adverse reactions have yet to be reported.

9. Drug Interactions

9.2. Drug Interactions Overview

No drug interaction studies have been performed with topical or oral delgocitinib.

Given the limited metabolism of delgocitinib, application to a limited body surface area (hands and wrists), and low 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.

9.3. Drug-Behaviour Interactions

Drug-behavioural interactions have not been evaluated.

9.4. Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5. Drug-Food Interactions

Interactions with food have not been evaluated.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been evaluated.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been evaluated.

10. Clinical Pharmacology

10.1. 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. Upon activation by cytokines, JAK signaling involves activation of signal transducers and activators of transcription (STATs). Activated STATs, in turn, activate the expression of cytokine-responsive genes to induce specific biological responses in target cells. Inhibition of JAK activity with delgocitinib prevents the activation of STATs.

In *in vitro* studies in human cells, inhibition of the JAK-STAT pathway by delgocitinib attenuated the signaling 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.

10.2. Pharmacodynamics

Cardiac Electrophysiology

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 effect cardiac repolarization under conditions of clinical use.

Dermal Safety Studies

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

10.3. Pharmacokinetics

The pharmacokinetics of delgocitinib was investigated in 15 adult subjects with moderate (n=13) or severe (n=2) CHE that were administered ANZUPGO twice daily for 8 days (Table 1-3).

Table 1-3: Mean SD Pharmacokinetic Parameters for Systemic Concentrations of delgocitinib in Moderate and Severe CHE

*C_{max} (ng/mL) (N=15)	*AUC_{0-12} (ng*h/mL) (N=15)	T_{max} (h) (N=15)	*$t_{½}$ (h) (N=6)
0.46 (1.74)	3.7 (1.74)	6.4 (4.36)	20.3 (1.3)

C_{max}=maximum observed concentration (0-12 hours post dose) at Day 8
AUC_{0-12}=area under the concentration-time curve (0-12 hours post dose) at Day 8
T_{max}=time to reach maximum observed concentration at Day 8
$t_{1/2}$=terminal elimination half-life
* Geometric mean (Geometric standard deviation)

Absorption

The pharmacokinetics of delgocitinib cream were evaluated in a study involving 15 adult patients 22 to 69 years of age with moderate (n=13) to severe (n=2) CHE. Patients applied delgocitinib 20 mg/g cream to the affected areas of the hands and wrists twice a day for 8 days. Subjects applied a mean 0.87 g (range 0.3 g to 1.9 g) per application, twice a day.

The geometric mean (geometric standard deviation) 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 (1.74) ng/mL and 3.7 (1.74) ng*h/mL, respectively (Table 1-3). 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 a Phase 3, 16 week clinical trial (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, each at <2% of the average unchanged delgocitinib plasma concentrations. The limited metabolism of delgocitinib occurs primarily though CYP3A4/5 and to a lesser extent by CYP1A1, CYP2C19, and CYP2D6.

Based on *in vitro* data, delgocitinib is a substrate of P-glycoprotein (P-gp) and a weak substrate of human organic cation transporter 2 (OCT2) and organic anion transporter 3 (OAT3). Delgocitinib inhibited OAT1 and OAT3. However, at clinically relevant concentrations from topical administration, delgocitinib is not expected to inhibit or induce cytochrome P450 enzymes or inhibit transporter systems such as organic anion transporters (OAT), organic anion transporting proteins (OATP), organic cation transporters (OCT), P-gp, breast cancer resistance protein (BCRP), or multi-antimicrobial extrusion protein (MATE).

Elimination

Delgocitinib is primarily eliminated by renal excretion as approximately 70% to 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 and conditions

- **Pediatrics:** The pharmacokinetics of delgocitinib in pediatric patients has not been studied.

- **Geriatrics:** No dose adjustment is required for patients aged ≥ 65 years [see 4.2 Recommended Dose and Dosage Adjustment]. Age ≥ 65 years does not have a clinically significant effect on exposures of delgocitinib.

- **Hepatic Insufficiency:** No formal studies of delgocitinib cream in patients with hepatic impairment have been conducted. Due to the low systemic exposure of topically applied delgocitinib to the hands and wrists 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 4.2 Recommended Dose and Dosage Adjustment].

- **Renal Insufficiency:** Pharmacokinetic parameters of delgocitinib were analyzed 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 low systemic exposure of topically applied delgocitinib to the hands and wrists, changes in renal function are unlikely to be of clinical importance. Therefore, no dose adjustments are needed in patients with renal impairment [see 4.2 Recommended Dose and Dosage Adjustment].

11. Storage, Stability, and Disposal

Store below 30°C. Do not freeze.

15 g and 60 g tubes	Use within 12 months of first opening the tube and not past the expiry date.
5 g tube	Use within 1 week of first opening the tube and not past the expiry date.

Keep out of reach and sight of children.

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

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

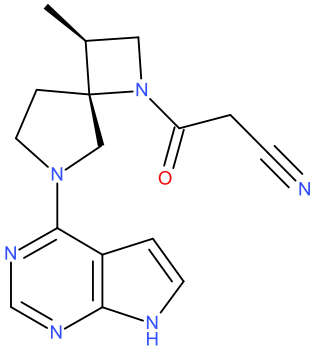
Non-proprietary name: Delgocitinib

Chemical name: 3-[(3*S*,4*R*)-3-Methyl-6-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1,6-diazaspiro[3.4]octan-1-yl]-3-oxopropanenitrile

Molecular formula: $C_{16}H_{18}N_6O$

Molecular mass: 310.35 g/mol

Structural formula:



Physicochemical properties:

Appearance: Delgocitinib is a white to almost white powder.

Polymorphism: Delgocitinib exists in different polymorphic forms. Five anhydrous crystal forms (6, 12, 15, 18 and 27) and one monohydrate crystal form (16) have been identified. The five anhydrous crystal forms have been assessed to be very similar in terms of solubility, hygroscopicity and stability.

Solubility: There are no observed differences in solubility between the different anhydrous forms (6, 12, 15, 18 and 27) which are slightly soluble in ethyl acetate, ethanol, methanol, and isopropanol; sparingly soluble in acetone; insoluble in n-hexane; and freely soluble in DMSO. At aqueous pH solutions of 3.2, 5.0 and 7.5 the anhydrous forms are freely soluble, sparingly soluble, and slightly soluble, respectively, and are controlled solely by the solubility of the monohydrate form 16.

14. Clinical Trials

14.1. Clinical Trials by Indication

Chronic Hand Eczema

The safety and efficacy of ANZUPGO were evaluated in two pivotal randomized, 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 previous 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 (moderate) or 4 (severe) 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).

Patients in DELTA 1 and DELTA 2 applied either ANZUPGO cream (20 mg/g delgocitinib) or vehicle cream twice daily to affected areas on the hands and wrists for 16 weeks.

Table 2-1: Summary of patient demographics for clinical trials in moderate to severe Chronic Hand Eczema (CHE)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
DELTA 1	Phase 3, randomized, double-blind, vehicle-controlled, parallel-group, multi-site, efficacy and safety	20 mg/g delgocitinib cream, topical, twice-daily for 16 weeks	325	44.3 years (19-87)	Male: 123 Female: 202
		Vehicle cream, topical, twice-daily for 16 weeks	162	42.9 years (20-73)	Male: 58 Female: 104
DELTA 2	Phase 3, randomized, double-blind, vehicle-controlled, parallel-group, multi-site, efficacy and safety	20 mg/g delgocitinib cream, topical, twice-daily for 16 weeks	314	45.3 years (18-83)	Male: 110 Female: 204
		Vehicle cream, topical, twice-daily for 16 weeks	159	42.6 years (18-86)	Male: 51 Female: 108
DELTA 3	Phase 3, open-label, multi-site, long-term extension	20 mg/g delgocitinib cream, topical, twice-daily, as needed, for 36 weeks	801	45.0 years (18-86)	Male: 289 Female: 512

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 scoring scale (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease and 4 = severe disease).

Table 2-2: 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, edema or fissures
Almost clear	1	Barely perceptible erythema No signs of scaling, hyperkeratosis/lichenification, vesiculation, edema 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 edema • 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 edema • 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 edema • One or more deep fissures

Additional secondary 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 edema) 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.

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% were female, 90% were White, 3.5% were Asian, and 0.7% were Black. The frequency of CHE by main subtype was 36% atopic hand eczema, 21% hyperkeratotic eczema, 20% irritant contact dermatitis, 14% allergic contact dermatitis, 9% vesicular hand eczema (pompholyx), and 0.1% contact urticaria/protein contact dermatitis. Overall, 72% of patients had a baseline IGA-CHE score of 3 (moderate CHE) and 28% 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.

Patients who completed either DELTA 1 or DELTA 2 were eligible to enroll in a 36-week open-label extension study (DELTA 3). In DELTA 3, the long-term safety and efficacy of as-needed ANZUPGO treatment was evaluated in 801 patients. Patients started application of ANZUPGO 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).

Study Results

DELTA 1 and DELTA 2

In DELTA 1 and DELTA 2, a statistically significantly greater proportion of patients randomized to ANZUPGO 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 2-3. Figure 1 shows the proportion of patients who achieved HESD itch ≥ 4-point improvement and HESD pain ≥ 4-point improvement over time in DELTA 1 and DELTA 2.

Table 2-3: Efficacy results of ANZUPGO at week 16 in DELTA 1 and DELTA 2

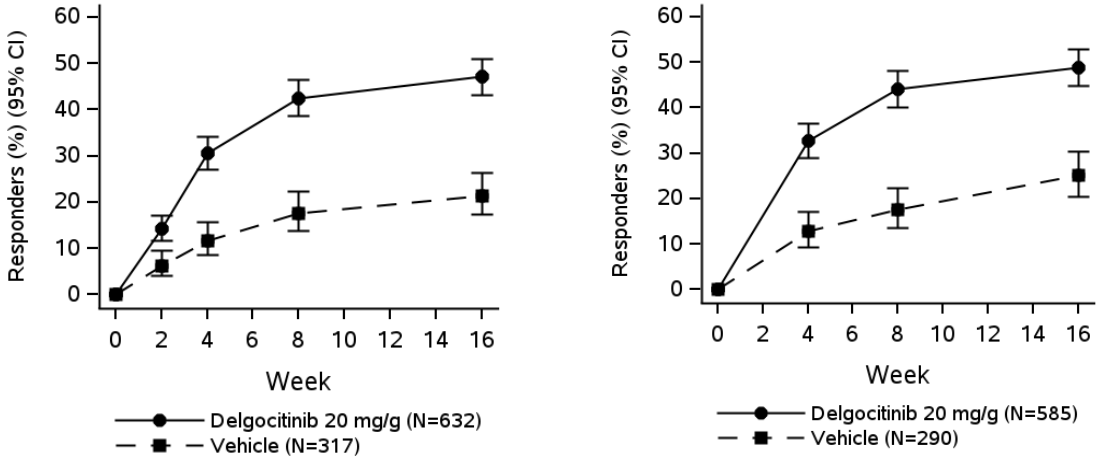
	DELTA 1		DELTA 2	
	ANZUPGO (N=325)	**Vehicle (N=162)**	**ANZUPGO (N=313)**	**Vehicle (N=159)**
IGA-CHE TS, % responders[a]	19.7[#]	9.9	29.1[§]	6.9
HECSI-90, % responders[a, b]	29.5[§]	12.3	31.0[§]	8.8
HECSI-75, % responders[a, c]	49.2[§]	23.5	49.5[§]	18.2
HESD itch ≥ 4-point improvement, % responders[a, d]	47.1[§] (152/323)	23.0 (37/161)	47.2[§] (146/309)	19.9 (31/156)
HESD pain ≥ 4-point improvement, % responders[a, d]	49.1[§] (143/291)	27.5 (41/149)	48.6[§] (143/294)	22.7 (32/141)
HESD ≥ 4-point improvement, % responders[a, d]	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: TS=treatment success; N=number of patients in the full analysis set (all patients randomized and dosed)
a. Patients who received rescue treatment, or permanently discontinued treatment, or with missing data were considered non-responders.
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. Based on the number of patients whose baseline value was ≥ 4 (scale from 0-10).

In both DELTA 1 and DELTA 2, a statistically significantly greater proportion of patients treated with ANZUPGO achieved IGA-CHE TS and a ≥ 4-point improvement in HESD as early as Week 4 compared to vehicle. A statistically significantly greater proportion of patients treated with ANZUPGO achieved HECSI-75 at Week 8 compared to vehicle.

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

HESD itch ≥ 4-point improvement[a] **HESD pain ≥ 4-point improvement[a]**



CI = Confidence Interval
a. Based on the number of patients whose baseline value was ≥ 4 (scale from 0-10).

Additional quality of life/patient-reported outcomes

In both DELTA 1 and DELTA 2, patients treated with ANZUPGO showed a statistically significant improvement [$p < 0.001$ with adjustment for multiplicity] from baseline compared to vehicle at Week 16 for the quality of life / patient reported outcomes Hand Eczema Impact Scale (HEIS) and the Dermatology Life Quality Index (DLQI).

Hand Eczema Impact Scale (HEIS):

The HEIS is a 9-item instrument designed to assess the patient's perceived impact of CHE on their daily activities (proximal daily activity limitations [use of soaps/cleaning products, housework involving hands getting wet, washing themselves], embarrassment, frustration, sleep, work, and physical functioning [ability to hold or grip objects] over the past 7 days). The 9 items are scored using a 5-point scale (0 = 'not at all', 1 = 'a little', 2 = 'moderately', 3 = 'a lot', 4 = 'extremely') and the HEIS score is the average of the 9 items. Improvements versus vehicle were observed and the HEIS least squares mean change from baseline in DELTA 1 was -1.46 for ANZUPGO vs -0.82 for vehicle, and for DELTA 2 was -1.45 for ANZUPGO vs -0.64 for vehicle.

Dermatology Life Quality Index (DLQI):

For patients who had a baseline DLQI value ≥ 4, a larger proportion of patients treated with ANZUPGO had a ≥ 4-point improvement in DLQI. The proportion of responders in DELTA 1 was 74.4% for ANZUPGO vs 50.0% for vehicle, and for DELTA 2 was 72.2% for ANZUPGO vs 45.8% for vehicle.

Extension study (DELTA 3)

Patients who completed either DELTA 1 or DELTA 2 were eligible to enroll in a 36-week open-label extension study (DELTA 3). 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 ANZUPGO were maintained through Week 52 with as-needed treatment.

Of the patients randomized to ANZUPGO 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% 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.

16. Non-Clinical Toxicology

General Toxicology: Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, phototoxicity, local tolerability, skin sensitization, and juvenile toxicity.

Target organs such as peripheral blood, bone marrow and lymphoid tissues, in repeat dose oral toxicity studies, were associated with the pharmacological activity of delgocitinib. These effects had safety margins that were considered sufficiently in excess of the maximum human exposure.

Safety margins were calculated based on the clinical AUC with 20 mg/g delgocitinib cream applied topically to affected areas of the hand and/or wrists twice daily (see 10.3 Pharmacokinetics).

Carcinogenicity: In a 2-year dermal carcinogenicity study in mice, no local or systemic drug-related neoplastic findings were observed at strengths up to 50 mg/g delgocitinib ointment (exposures up to approximately 600 times the human exposure).

Findings from a 2-year oral carcinogenicity study in rats included pancreatic acinar adenomas and subcutaneous lipoma (males only), thymoma (females only), and Leydig cell tumour at exposures approximately 160, 580, and 1800 times the human exposure, respectively. The clinical relevance of tumour findings in rats is low given the tumour types in a single species and single sex, the exposures at which the tumours occurred, and the negative findings in the 2-year dermal carcinogenicity study in mice.

Reproductive and Developmental Toxicology:

Fertility and early embryonic development

Orally administered delgocitinib did not result in effects on fertility at any dose level evaluated in male rats (exposures approximately 1700 times the human exposure). In female rats, orally administered delgocitinib resulted in effects on female fertility (lower fertility index, fewer corpora lutea, and fewer implantations) at exposures approximately 5800 times the human exposure. Post-implantation losses and a decrease in the number of live embryos were observed at exposures approximately 432 and 1000 times the human exposure, respectively.

Embryo-fetal development

Orally administered delgocitinib did not result in adverse effects to the fetus in rats or rabbits at exposures approximately 120 and 194 times the human exposure, respectively. Teratogenic effects were not observed at any dose studied in rats or rabbits (exposures approximately 1400 and 992 times the human exposure, respectively).

In rats, decreases in fetal weight and increases in post-implantation loss were observed at 512 and 1400 times the human exposure, respectively. Increased incidence of skeletal variations such as wavy ribs, asymmetry of sternebra, splitting of the sternebra, splitting of the thoracic vertebral body and 7 lumbar vertebrae were observed at 512 times the human exposure.

In rabbits, an increase in post-implantation loss, a reduced number of live fetuses, and a tendency toward a decrease in fetal weights were observed at exposures approximately 992 times the human exposure.

Pre-and postnatal development

Orally administered delgocitinib in rats resulted in prolonged parturition and decreased fetal viability and reduced pup weights during the early postnatal period at exposures approximately 1800 times the human exposure. There was no effect on behavioral and learning assessments, sexual maturation, or reproductive performance of the offspring at any dose studied.

Following oral administration to lactating rats, delgocitinib was secreted in milk at concentrations approximately 3-fold those in serum.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrANZUPGO®
delgocitinib cream

This Patient Medication Information is written for the person who will be taking **ANZUPGO**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **ANZUPGO**, talk to a healthcare professional.

What ANZUPGO is used for:

ANZUPGO is used in adults to treat moderate to severe chronic hand eczema (CHE). It is used when other skin creams (corticosteroids) do not work well enough or cannot be used.

How ANZUPGO works:

ANZUPGO belongs to a group of medicines called Janus kinase (JAK) inhibitors. It works by reducing the activity of enzymes in the body called 'Janus kinases'. This can help reduce skin inflammation, itching, and pain.

The ingredients in ANZUPGO are:

Medicinal ingredient(s): Delgocitinib.

Non-medicinal ingredients: Benzyl alcohol, butylhydroxyanisole, cetostearyl alcohol, citric acid monohydrate, disodium edetate, hydrochloric acid, liquid paraffin, macrogol cetostearyl ether, and purified water.

ANZUPGO comes in the following dosage form(s):

Cream (white to slightly brown): 20 mg/g of delgocitinib.

Do not use ANZUPGO if:

- you are allergic to delgocitinib or any of the other ingredients in ANZUPGO.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ANZUPGO. Talk about any health conditions or problems you may have, including if you:

- are taking other medicine for your hand eczema.
- are pregnant, think you may be pregnant, or are planning to have a baby. The effects of ANZUPGO are not known in pregnant women. ANZUPGO should be avoided if you are pregnant or think you may be pregnant.
- are breast-feeding or are planning to breast-feed. It is not known whether delgocitinib passes into human breast milk. If you are breast-feeding, ensure that the ANZUPGO

cream does not come into contact with your nipple or any other surrounding areas where your baby may ingest it during feeding.
- have a history of skin cancer or are at a higher risk for skin cancer. Patients taking JAK inhibitors, the class of medicines to which ANZUPGO belongs, have reported cases of a type of skin cancer called 'non-melanoma skin cancer'. Your healthcare professional may recommend regular skin examinations before and while using ANZUPGO.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ANZUPGO:

- Other topical medicines that are used on the same area of the skin as ANZUPGO.

How to take ANZUPGO:

- Always use this medicine exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- ANZUPGO is for use on the skin only. Avoid contact with your eyes, mouth, nose, or vagina. If the cream gets on any of these areas, thoroughly wipe off and/or rinse off the cream with water.
- Avoid applying other topical products, such as creams, ointments, or other medications, to the same area of the skin within 2 hours before and after applying ANZUPGO.
- If someone else applies this medicine to your skin, they should wash their hands after application.
- If your skin does not improve after 12 weeks of treatment with ANZUPGO, talk to your healthcare professional.
- Do not use more than one tube of ANZUPGO (60 g) per month.
- The tube has a seal at the top end of the tube. Peel off this seal before you first use the ANZUPGO cream.

Usual dose:

- A thin layer of ANZUPGO should be applied two times a day (about 12 hours apart) to the affected skin of the hands and wrists. Before you apply the cream, make sure the affected areas of your skin are clean and dry.
- You should use ANZUPGO until your skin has become clear or almost clear, or as directed by your healthcare professional.
- If signs or symptoms of chronic hand eczema reappear, your healthcare professional may restart your treatment with ANZUPGO.

Overdose:

If too much ANZUPGO has been applied, the excess should be wiped off.

If you think you, or a person you are caring for, have ingested ANZUPGO or applied too much on the skin, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you miss or forget to apply the cream, do it as soon as possible. Then apply your next dose at the regularly scheduled time. If you have any questions, ask your healthcare professional.

Possible side effects from using ANZUPGO:

These are not all the possible side effects you may have when taking ANZUPGO. If you experience any side effects not listed here, tell your healthcare professional.

The following side effects have been reported with ANZUPGO:

Common (may affect up to 1 in 10 people):

- application site reactions (i.e., pain, itching, redness, and tingling).

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store below 30°C. Do not freeze.
- **15 g (sample) and 60 g tube sizes:** Use within 12 months of first opening the tube and not past the expiry date, which is stated on the tube and carton. The expiry date refers to the last day of that month.
- **5 g (sample) tube size:** Use within 1 week of first opening the tube and not past the expiry date, which is stated on the tube and carton. The expiry date refers to the last day of that month.
- Keep out of reach and sight of children.

If you want more information about ANZUPGO:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.leo-pharma.ca); or by calling 1-800-263-4218.

This leaflet was prepared by LEO Pharma Inc.

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