SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Anzupgo 20 mg/g cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of cream contains 20 mg of delgocitinib.

Excipients with known effect

Each gram of cream contains 10 mg of benzyl alcohol (E 1519), 0.2 mg of butylhydroxyanisole (E 320), and 72 mg of cetostearyl alcohol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream

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 (see section 5.1).

4.2 Posology and method of administration

Anzupgo should be initiated and supervised by physicians with experience in the diagnosis and treatment of chronic hand eczema.

Posology

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 (see section 5.1). 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, the cream should be applied as soon as possible. Thereafter, applications should be resumed at the regular scheduled time.

Special populations

Elderly patients

No dose adjustment is recommended for elderly patients.

Hepatic and renal 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).

Paediatric population

The safety and efficacy of Anzupgo in children and adolescents below 18 years of age has not been established. No data are available.

Method of administration

Anzupgo is for cutaneous use only. A thin layer of Anzupgo should be applied 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). 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.

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.

Excipients with known effect

Benzyl alcohol

This medicinal product contains 10 mg benzyl alcohol (E 1519) in each gram of cream.

Benzyl alcohol may cause allergic reactions or mild local irritation.

Butylhydroxyanisole

Butylhydroxyanisole (E 320) may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

Cetostearyl alcohol

Cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis).

Fire hazard

Instruct patients not to smoke or go near naked flames – risk of severe burns. Fabric (clothing, bedding, dressings etc) that has been in contact with this product burns more easily and is a serious fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical interaction studies have been performed with topically or systemically administered delgocitinib (see section 5.2 for *in vitro* interaction studies). 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 treatments.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or a limited amount of data (less than 300 pregnancy outcomes) from the use of delgocitinib in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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

Breast-feeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to delgocitinib is negligible (see section 5.3).

Anzupgo can be used during breast-feeding.

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.

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 (see section 5.3).

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

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 Undesirable effects

Summary of the safety profile

The most common adverse reactions were application site reactions (1.0%).

Tabulated list of adverse reactions

Table 1 lists the adverse reactions that were observed in clinical studies. The adverse reactions are 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 1Adverse reactions

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

*see Description of selected adverse reactions

Description of selected adverse reactions

Application site reactions

In the pool of three vehicle-controlled clinical studies through 16 weeks, 9 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. 8 application site reactions were mild in severity and 1 was moderate. 7 of 9 occurred within the first week of treatment. No application site reactions 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

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 cells, 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 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 efficacy and safety

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 2) 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 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, 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. In DELTA 1 and DELTA 2, 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 most relevant multiplicity-controlled secondary endpoints are presented in Table 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 3 Efficacy results of delgocitinib cream at Week 16 in DELTA 1 and DELTA 2

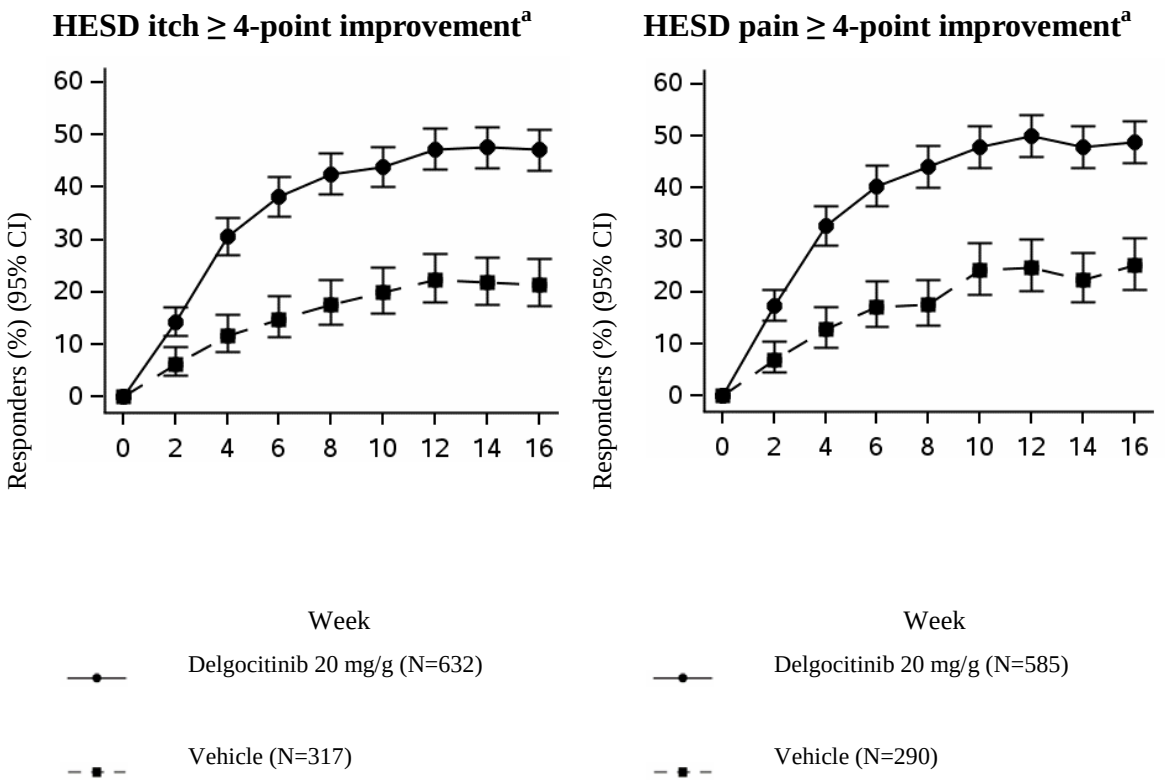
	DELTA 1		DELTA 2	
	Delgocitinib (N=325)	**Vehicle (N=162)**	**Delgocitinib (N=313)**	**Vehicle (N=159)**
IGA-CHE TS, % responders[a]	19.7[#]	9.9	29.1[§]	6.9
HECSI-90, % responders[a, b]	29.5[§]	12.3	31.0[§]	8.8
HECSI-75, % responders[a, c]	49.2[§]	23.5	49.5[§]	18.2
HECSI, LS mean % change from baseline (± 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 treatment, 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 statistically significantly greater proportion of patients treated with delgocitinib cream 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 delgocitinib cream 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



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 delgocitinib cream showed a statistically significantly greater improvement from baseline to Week 16 compared to vehicle in the Hand Eczema Impact Scale (HEIS) (see Table 4). 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). 9 items are scored on a 5-point scale where 0='not at all' and 4='extremely', and the HEIS score is then calculated as the average of the 9 items.

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 4).

Table 4 Quality of life/patient-reported outcomes results of delgocitinib cream 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]	-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 treatment, 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.

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.

Phase 3 active comparator study versus alitretinoin (DELTA FORCE)

The efficacy and safety of delgocitinib cream compared to alitretinoin was evaluated in a randomised, assessor-blinded, 24-week study with 513 patients 18 years of age and older with

severe CHE as defined by an IGA-CHE score of 4. Eligible patients had a previous inadequate response to topical corticosteroids or were those in which topical corticosteroids are not advisable. The patients were randomised to either delgocitinib 20 mg/g cream twice-daily treatment for 16 weeks or alitretinoin 30 mg capsules once-daily treatment (with an option to reduce to 10 mg once daily) for 12 weeks. Treatment could continue up to 24 weeks. Permanent discontinuation of treatment (35.9% for alitretinoin vs. 13.4% for delgocitinib) and use of rescue medications (8.1% for alitretinoin vs. 4.7% for delgocitinib) were more frequent for patients treated with alitretinoin compared to delgocitinib.

Statistically significantly greater improvements for the primary endpoint, change in HECSI score from baseline to Week 12, was achieved for delgocitinib cream compared to alitretinoin. Statistically significantly greater improvements were also achieved for delgocitinib cream for HECSI-90 and IGA-CHE TS. The results for the primary and the most relevant secondary endpoints are presented in Table 5.

Table 5 Efficacy results at Week 12 from DELTA FORCE – delgocitinib cream versus alitretinoin

	DELTA FORCE	
	Delgocitinib (N=250)	**Alitretinoin (N=253)**
HECSI, LS mean change from baseline (± SE)[a]	-67.6[§] (± 3.37)	-51.5 (± 3.36)
HECSI-90, % responders[b, c]	38.6[#] (96/249)	26.0 (65/250)
HECSI-75, % responders[b, d, e]	55.4[*] (138/249)	46.0 (115/250)
IGA-CHE TS, % responders[b]	27.2[#]	16.6

*p < 0.05, #p < 0.01, §p < 0.001
All p-values were statistically significant versus alitretinoin with adjustment for multiplicity, except HECSI-75 % responders, which was not a multiplicity adjusted endpoint.
Abbreviations: LS=least squares; N=number of patients in the full analysis set; SE=standard error
a. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered non-response by using worst observation carried forward.
b. Data after initiation of rescue treatment, permanent discontinuation of treatment, or missing data were considered non-response.
c. HECSI-90 responders were patients with ≥ 90% improvement in HECSI from baseline.
d. HECSI-75 responders were patients with ≥ 75% improvement in HECSI from baseline.
e. HECSI-75 % responders were not a multiplicity adjusted endpoint.

Greater improvements for delgocitinib cream measured by the mean change in HECSI score compared to alitretinoin, were observed at Week 1 and maintained through to Week 24.

Paediatric population

The licensing authority has deferred the obligation to submit the results of studies with delgocitinib in one or more subset of the paediatric population for the treatment of chronic hand eczema (see section 4.2 for information on paediatric use).

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 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%.

Biotransformation

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 though CYP3A4/5 and to a lesser extent by CYP1A1, CYP2C19, and CYP2D6.

In vitro interaction studies

Based on *in vitro* data, delgocitinib does not inhibit or induce cytochrome P450 enzymes or inhibit transporter systems such as organic anion transporters (OAT), organic anion transporting polypeptides (OATP), organic cation transporters (OCT), P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), or multidrug and toxin extrusion proteins (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).

Elimination

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 (see section 4.2).

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 m2) 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. Renal function impairment is unlikely to result in clinically important changes in exposure to delgocitinib due to the minimal systemic exposure following topical administration (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, phototoxicity, local tolerability, skin sensitisation, and juvenile toxicity. Effects in repeat dose toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure following topical application.

Carcinogenicity

In a 2-year dermal carcinogenicity study in mice, no local or systemic drug-related neoplastic findings were observed (at exposures up to approximately 600 times the human exposure based on AUC).

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 1 700 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 5 800 times the human exposure. Post-implantation losses and a decrease in the number of live embryos were observed at exposures approximately 432 and 1 000 times the human exposure, respectively.

Embryo-foetal development

Orally administered delgocitinib did not result in adverse effects to the foetus 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 1 400 and 992 times the human exposure, respectively).

In rats, decreases in foetal weight and skeletal variations were observed at exposures 512 times the human exposure and a tendency toward an increase in post-implantation loss was observed at exposures approximately 1 400 times the human exposure. In rabbits, an increase in post-implantation loss, a reduced number of live foetuses, and a tendency toward a decrease in foetal weights were observed at exposures approximately 992 times the human exposure.

No effects during pregnancy are anticipated, since systemic exposure to delgocitinib is negligible. As a precautionary measure, it is preferable to avoid the use of delgocitinib during pregnancy (see section 4.6).

Pre-and postnatal development

Orally administered delgocitinib in rats resulted in decreased foetal viability and reduced pup weights during the early postnatal period at exposures > 2 000 times the human exposure. There was no effect on behavioural 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 the plasma.

No effects on the breastfed newborn/infant are anticipated since the systemic exposure in the breast-feeding woman to delgocitinib is negligible. Delgocitinib can therefore be used during breast-feeding (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol (E 1519)

Butylhydroxyanisole (E 320)

Cetostearyl alcohol

Citric acid monohydrate (E 330)

Disodium edetate

Hydrochloric acid (E 507) (for pH-adjustment)

Liquid paraffin

Macrogol cetostearyl ether

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

After first opening: 1 year

6.4 Special precautions for storage

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: 1 tube of 15 g or 60 g.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

LEO Pharma A/S

Industriparken 55

DK-2750 Ballerup

Denmark

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 05293/0191

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/11/2024

10 DATE OF REVISION OF THE TEXT

25/11/2025