CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	219155
PDUFA Goal Date	July 23, 2025
Nexus TTT #	2024-10223
Reviewer Name(s)	Carla Darling, PharmD, BCPS
Team Leader(s)	Jacqueline Sheppard, PharmD
Acting Division Director	Laura Zendel, PharmD
Review Completion Date	July 22, 2025
Subject	Evaluation of Need for a REMS
Established Name	delgocitinib
Trade Name	Anzupgo
Name of Applicant	Leo Pharma A/S
Therapeutic Class	Janus kinase (JAK) inhibitor
Dosage Form(s)	Cream 2%
Dosing Regimen	Apply twice daily to the affected areas only on the hands and wrists

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EXECUTIVE SUMMARY

This review documents the Division of Risk Management's (DRM) evaluation to determine if a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME), Anzupgo (delgocitinib), is necessary to ensure the benefits outweigh the risks. Leo Pharma A/S (Applicant) submitted New Drug Application (NDA) 219155 for delgocitinib on July 23, 2024, with the proposed indication for the topical treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable. The Applicant did not submit a proposed REMS or risk management plan with this application.

The efficacy and safety of delgocitinib was evaluated in two pivotal, 16-week, phase 3 clinical trials and a 36-week open label extension trial. The review team determined that the two pivotal trials showed statistically significant improvement in the Investigator's Global Assessment for the chronic hand eczema in subjects treated with delgocitinib compared to vehicle control therapy.

Delgocitinib is a Janus kinase (JAK) inhibitor. The serious adverse events associated with the JAK inhibitor class include serious infection, all-cause mortality (including sudden cardiovascular death), malignancies (including lymphoma and lung cancers), major adverse cardiovascular events (MACE, defined as cardiovascular death, myocardial infarction, and stroke) and thrombosis. While delgocitinib is a topical product and no new safety signals were identified, the review team determined that delgocitinib achieves measurable systemic exposure and may exhibit systemic pharmacological activity. Therefore, the use of topical delgocitinib carries the same potential risks associated with the class of JAK inhibitors used to treat other inflammatory conditions.

Based on the safety and efficacy information available, the Division of Dermatology and Dentistry (DDD) and DRM determined that a REMS is not needed to ensure the benefits outweigh the risks of delgocitinib. Prescribers are likely familiar with the potential risks of delgocitinib, which are the same as the known risks of other approved JAK inhibitors including the only currently approved topical JAK inhibitor, Opzelura (ruxolitinib). Additionally, no new safety signals requiring risk mitigation beyond labeling were identified by the review team. The potential risks associated with delgocitinib will be communicated in the Warnings and Precautions section of the Prescribing Information. At the time of this review, final labeling, and post-marketing requirements (PMRs) were still under negotiation. If new safety information becomes available, DRM can re-evaluate the need for a REMS.

1. Introduction

This review documents the Division of Risk Management's (DRM's) evaluation to determine if a REMS for the new molecular entity (NME), Anzupgo (delgocitinib) is necessary to ensure the benefits outweigh its risks. Leo Pharma A/S (Applicant) submitted new drug application (NDA) 219155 for delgocitinib with the proposed indication for the topical treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.[1] This application is under review in the Division Dermatology and Dentistry (DDD). The applicant did not

submit a proposed Risk Evaluation and Mitigation Strategy (REMS) or risk management plan with this application.

2. Background

2.1. Product Information

Delgocitinib, a NME,[a] is a Janus kinase (JAK) inhibitor that inhibits the activity of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2).[2] Delgocitinib is proposed for the topical treatment of moderate to severe CHE in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.[1,b] The exact mechanism of action of delgocitinib in the treatment of moderate to severe CHE is currently not known.[2] Delgocitinib is proposed as a topical 2% cream (20 mg of delgocitinib per gram) applied twice daily to the affected areas only on the hands and wrists. Delgocitinib is intended for administration by patients or caregivers in the outpatient setting.

As of the time of this review, there are several FDA approved JAK inhibitors for oral use and one for topical use, Opzelura (ruxolitinib). None of the JAK inhibitors are approved with a REMS. All JAK inhibitors include class labeling that consists of a Boxed Warning and Warning and Precautions about the risk of serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis.

Delgocitinib cream, 2% under the brand name Anzupgo is currently approved for use in adults for the treatment of moderate to severe CHE in the European Union (September 2024), United Kingdom, Switzerland, and the United Arab Emirates.[3] Delgocitinib was also approved in Japan on January 2020 under the name Corectim as an ointment for the treatment of atopic dermatitis.[3] If approved, delgocitinib would be the first therapy specifically indicated for moderate to severe CHE in the United States.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 219155 relevant to this review:

- 06/12/2020: Fast track designation granted for IND 135351.[4]
- 07/23/2024: NDA 219155 submission received for the proposed topical treatment of moderate to severe CHE in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.[5]
- 02/25/2025: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that there were no major safety issues identified that require a REMS for delgocitinib.[6]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

CHE is a heterogenous, fluctuating, pruritic and painful inflammatory skin disease that refers to hand eczema (HE) lasting more than 3 months or recurs twice or more often per year.[7,8] Key clinical manifestations of CHE include dry, scaly, erythematous and pruritic hand macules or papules that may be accompanied by vesicles, pustules, edema, linear fissures or erosions, and hyperkeratosis.[8] Pruritus is the most common symptom and skin pain, burning, and stinging are also important symptoms.[7] Secondary chronic lesions include lichenification, hyperkeratosis, scaling, and fissures.[7] CHE is a cause of significant morbidity, can be intensely pruritic and painful, and can negatively impact work productivity and quality of life.[8-10,c] Hand eczema has a substantial health economic and socio-medical impact due to considerable occupational, domestic, social, and psychological consequences.[7,11]

The prevalence and incidence of HE or CHE in the United States are largely unknown. There are no general population studies focused on CHE and information available in general population studies for HE is limited due to the lack of clear definitions for CHE in these studies.[12] CHE has an estimated 1-year prevalence of 9 to 10% and a lifetime prevalence of 15% in the general population with a similar prevalence among adolescents and adults.[8,d] While the prevalence of CHE in the United States is largely unknown, a study of a managed care organization in Massachusetts estimated the prevalence of CHE in the United Sates to be more than 16%.[13]

3.2. Description of Current Treatment Options

There are no FDA approved products indicated for the treatment of CHE.[8] Pharmacological treatment options for CHE that are used off-label in clinical practice include topical and systemic treatments. Topical corticosteroids (TCS) have been the mainstay of CHE treatment for all age groups.[7,8] Additional therapies used off-label include topical tacrolimus and alitretinoin. Systemic treatments include cyclosporin, methotrexate, azathioprine, acitretin, and dupilumab.[14]

TCS are first line pharmacological treatment for HE, which can be used for flare or maintenance treatment on an intermittent basis.[7,8] Moderate to severe CHE may require use of TCS that exceeds the recommended treatment duration; however, long term use of TCS can induce skin atrophy and impair barrier function.[7,8] Additional treatment options for CHE are limited to use of products and modalities indicated for other skin diseases.[7] Phototherapy is a nonpharmacological treatment option for CHE when treatment with TCS has failed or when TCS are contraindicated.[7,8] Adverse events of phototherapy are erythema and burning of the skin.[7] Long-term use of phototherapy can increase the risk of (non-

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

melanoma) skin cancer.[7] As there is no FDA approved treatment for CHE, there is an unmet medical need for an efficacious and well tolerated treatment option specifically for the long-term control of CHE.

4. Benefit Assessment

The efficacy and safety of delgocitinib for the treatment of moderate to severe CHE was evaluated in three phase 3 clinical trials: 1) trial 1401, LP0133-1401, DELTA 1 (NCT04871711); 2) trial 1402, LP0133-1402, DELTA 2 (NCT04872101); and 3) trial 1403, LP0133-1403, DELTA 3 (NCT04949841). Trials 1401 and 1402 are the pivotal trials supporting the effectiveness of delgocitinib. Trials 1401 (n=487) and 1402 (n=473) are similar in design: randomized, double-blind, vehicle-controlled, parallel-group, multicenter trials with a 16-week duration followed by a 2-week safety follow up period. Both trials were designed to evaluate delgocitinib compared with vehicle cream in adult subjects, 18 years of age and older, with moderate to severe CHE. Trial 1403 (n=801) is a 36-week, long-term, open label, non-controlled, extension trial, with subjects from trials 1401 and 1402 who applied twice-daily delgocitinib as-needed.

Both pivotal trials (trials 1401 and 1402) had the same primary endpoint: proportion of subjects with Investigator's Global Assessment for the chronic hand eczema (IGA-CHE) treatment success, defined as score of 0 or 1 at Week 16 with at least a 2-step improvement from baseline. The IGA-CHE scale is an investigator-rated instrument that assesses the global disease severity of a subject's CHE that considers both sides of hands and wrists. The IGA-CHE consists of a 5-point scale ranging from 0 (clear) to 4 (severe), and scoring is based on the intensity of erythema, scaling, hyperkeratosis/lichenification, vesiculation, edema, or fissures.

Both pivotal trials (trials 1401 and 1402) had the same 23 secondary endpoints, which were controlled for multiplicity. Secondary endpoints cover a broad range of aspects of CHE. These include instruments to rate the severity and extent of CHE (IGA-CHE and Hand Eczema Severity Index [HECSI]), severity of CHE signs and symptoms (Hand Eczema Symptom Diary [HESD]), and the impact of CHE on the subjects' quality of life (Dermatology Life Quality Index [DLQI]), daily life (Hand Eczema Impact Scale [HEIS]), and work productivity (Work Productivity And Activity Impairment: Chronic Hand Eczema [WPAI:CHE]).

Adults from Canada and Europe with moderate to severe CHE in both pivotal trials were randomized to vehicle control or delgocitinib 20 mg/g applied topically twice daily over a 16-week treatment period. All primary and key secondary efficacy endpoints (i.e., endpoints controlled for multiplicity) were statistically significant. In both trials, delgocitinib was statistically superior to vehicle on the primary efficacy endpoint (p-values ≤ 0.025). Table 1 below represents the pivotal trial primary endpoint results.

Table 1: Results of the Primary Efficacy Endpoints in Pivotal Trials 1401 and 1402

Primary Endpoint	Trial 1401		Trial 1402	
	Delgocitinib (N =325)	Vehicle (N=162)	Delgocitinib (N =313)	Vehicle (N=159)
Proportion of subjects with IGA-CHE treatment success at Week 16	19.7% (64/325)	9.9% (16/162)	29.1% (91/313)	6.9% (11/159)
Difference (95% CI)	9.8% (3.6%, 16.1%)		22.2% (15.8%, 28.5%)	
P-value	0.006		<0.001	

Source: Adapted from the draft Integrated Review, section 6.2.6, accessed June 24, 2025.

The review team concluded that Applicant provided reliable and statistically significant evidence that delgocitinib can help patients achieve clinically meaningful improvements with their CHE.[8,e] The DDD determined that the Applicant provided substantial evidence of effectiveness based on two adequate and well-controlled clinical trials (trials 1401 and 1402).[8]

5. Risk Assessment & Safe-Use Conditions

The safety analysis for delgocitinib consists of 638 randomized subjects who received at least 1 delgocitinib application and 321 subjects who received the vehicle control from the two phase 3 trials, trials 1401 and 1402.[8] For subjects who rolled over into the open-label trial, 1403, a total of 198 subjects were continuously exposed to delgocitinib BID for 52 weeks with no treatment breaks. Notably, the safety database for delgocitinib included fewer than 700 subjects for 16 weeks and fewer than 200 subjects for 52 weeks, which limits characterization of rare, long-latency of adverse events.

A total of 17 serious adverse reactions (SAR)[f] were reported including 11 (1.7%) subjects treated with delgocitinib and 6 (1.9%) subjects treated with vehicle control. None of the SARs occurred in >1% of subjects treated with delgocitinib or in subjects treated with vehicle control. The highest risk difference was reported with infections and infestations with a 0.6% difference between the delgocitinib group compared to the vehicle control. Four (4) subjects in the delgocitinib group reported infections and infestations events that include COVID-19 pneumonia, keratitis bacterial, peritonsillar abscess, and tonsillitis compared to zero events in the vehicle control group. The review team concluded that none of

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

the events were related to treatment and there was no clustering of events over time.[8,g] Overall, the review team determined that no new safety signals were identified.[8]

No deaths were reported during the double-blind period of the pivotal trials (trials 1401 and 1402). Three deaths were reported in subjects treated with delgocitinib during trial 1403, which are related to metastatic esophageal cancer, myocardial infarction, and death (unknown cause). The Applicant states that these deaths are unlikely related to delgocitinib use as these subjects had other predisposing medical factors. The review team concluded that the deaths were unlikely related to delgocitinib; however, there was insufficient information to entirely exclude the role of delgocitinib in 2 of the 3 deaths.[8]

It is also important that the review team identified other key safety findings including measurable systemic exposure, possible systemic pharmacological effects, and a limited safety database. Delgocitinib demonstrated systemic absorption with median Cmax of 0.61 ng/mL (1.96nM) in maximal use trials, with individual subjects reaching concentrations up to 29.2 ng/mL (94.09nM). Additionally, clinical trials demonstrated hematologic imbalances (13.6% versus 6.2% vehicle experiencing worsening leukocyte shifts) and possible immune-related adverse events, including herpes zoster in healthy subjects under 50 years of age and a report of eczema herpeticum.

5.1. JAK Inhibitor Class Safety Risks

The class labeling for JAK inhibitors include a Boxed Warning with the following risks: serious infections, mortality, malignancy, MACE, and thrombosis.

Given the class effects of JAK inhibitors for inflammatory conditions, the review team analyzed the delgocitinib safety database to assess for potential JAK inhibitor class related adverse reactions. A summary of the review teams findings and labeling recommendations are as follows:

Serious Infections: In the two pivotal trials, trials 1401 and 1402, no serious infections were reported in the 16-week treatment period. In the open-label extension trial, 1403, eczema herpeticum (1 subject delgocitinib, 0 vehicle) and herpes zoster (2 subjects delgocitinib, 0 vehicle) were reported. No cases of tuberculosis were reported in the trials; however, monitoring for tuberculosis was not included in the trials. The review team concluded that delgocitinib may have contributed to the eczema herpeticum event; however, a causal role for delgocitinib could not be ruled out for the two cases of herpes zoster.[8]

Mortality: There were three deaths in the development program for subjects treated with delgocitinib. The review team concluded that delgocitinib did not appear to increase the risk of all-cause mortality compared to vehicle control.[8]

Malignancy: There were no reports of lymphomas nor lung cancers in the delgocitinib program. In trials 1401, 1402, and 1403, the following malignancies were reported in subjects who received delgocitinib: gallbladder adenocarcinoma (1 in delgocitinib, 0 in vehicle), metastatic esophageal cancer (1 in

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

delgocitinib, 0 in vehicle), basal cell carcinoma (1 in delgocitinib, 0 in vehicle), and intraductal proliferative breast lesion (1 in delgocitinib, 0 in vehicle). The review team concluded that there were no imbalances between treatment groups in the development of malignancies.[8]

MACE: In the phase 3 trials, one case myocardial infarction was reported in a 71-year-old male subject who had been off-delgocitinib treatment for 6 months prior to the event. The subject died 2 weeks later, which corresponded to approximately 7 months after last dose of delgocitinib 20 mg/g. The subject had been on antihypertensive medication for 3 months prior to the event. The review team concluded that this event was not considered related to delgocitinib. The review team concluded that delgocitinib does not appear to have cardiovascular effects in the studied population.[8]

Thrombosis: No deep vein thrombosis (DVT), pulmonary embolism (PE), or arterial thrombosis events were reported with delgocitinib in the development program. Superficial thrombophlebitis was reported in two subjects treated with delgocitinib. Both events were non-serious, of moderate severity, did not lead to withdrawal from trial, and were not considered related to delgocitinib by the review team.[8]

During the course of the review, the DDD solicited input from the Medical Policy and Program Review Council (MPPRC) regarding whether delgocitinib should carry class labeling (e.g., Warnings and Precautions, Box Warning) for JAK inhibitors. The MPPRC considered delgocitinib's non-negligible systemic exposure and that there is no known threshold for the adverse reactions associated with other JAK inhibitors for the treatment of inflammatory conditions. Overall, the MPPRC found the following options proposed by the review team reasonable: Option 1) a Boxed Warning plus Warnings and Precautions sections or Option 2) Warnings and Precautions section addressing potential risks of oral and topical JAK inhibitors along with a PMR for an active-controlled trial. During labeling negotiations, both options were discussed with the Applicant.

Ultimately, the review team concluded that the risk for major toxicities is low; therefore, a Boxed Warning was not warranted for delgocitinib at this time. The review team's conclusions about low risk for major toxicities was based on: 1) delgocitinib application to the hands and wrists only (<5% body surface area); 2) low delgocitinib systemic exposure (based on data from the maximal use study); 3) no observed adverse reactions such as thrombosis, malignancy, and MACE observed during the delgocitinib development program; and 4) the risk of these major toxicities are dose-dependent.[8] The potential risks associated with JAK inhibition will be communicated in section 5, Warnings and Precautions of the Prescribing Information.

6. Expected Postmarket Use

The likely prescribers of delgocitinib include dermatologists and primary care providers. These prescribers are likely familiar with the potential risks of delgocitinib, which are the same as the known risks of other approved JAK inhibitors including the only currently approved topical JAK inhibitor, Opzelura (ruxolitinib). These potential risks include serious infection, all-cause mortality, including sudden cardiovascular death, malignancies (including lymphoma and lung cancers), major adverse cardiovascular events (MACE, defined as cardiovascular death, myocardial infarction, and stroke) and thrombosis. Delgocitinib is intended for self-administration by the patient or caregiver in the outpatient

setting. If approved, delgocitinib will be the first FDA approved drug product for the treatment of moderate to severe CHE.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for delgocitinib beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The review team recommends approval of delgocitinib based on the efficacy and safety information currently available.

If approved, delgocitinib would be the first treatment for moderate to severe CHE in the United States. Delgocitinib is a topical JAK inhibitor proposed for the topical treatment of a serious condition: moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable. As there is no cure and no FDA treatments approved for CHE, there is an unmet medical need for treatment options. Delgocitinib can meet this medical need as the use of delgocitinib in subjects with moderate to severe CHE resulted in clinically meaningful improvement with CHE in the two pivotal trials (trial 1401 and 1402).

No new safety signals were identified by the review team. However, given the known serious risks associated with JAK inhibitors for inflammatory conditions, delgocitinib's measurable systemic exposure, and the evidence of potential systemic immunosuppressive effects in the delgocitinib development program, the review team determined that the use of topical delgocitinib carries the same potential risks associated with the class of JAK inhibitors. Upon discussion with the MPPRC and the Applicant, these potential risks will be communicated in the Warnings and Precautions section of the Prescribing Information and the Applicant has committed to a PMR to study long-term effects. As prescribers are likely familiar with the potential risks of delgocitinib and other agents of its class, this reviewer concluded that based on available safety information, a REMS is not necessary to ensure the benefits outweigh the risks.

9. Conclusion & Recommendations

The review team determined that the benefit-risk assessment for delgocitinib supports approval. Based on the Integrated Review of Marketing Applications review, the benefit-risk profile is favorable and no additional safety issues requiring risk mitigation beyond labeling were identified, therefore, a REMS is not necessary for delgocitinib to ensure the benefits outweigh the risks. At the time of this review final labeling and PMRs were still under negotiation. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

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