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Reimbursement Recommendation

Delgocitinib (Anzupgo)

Indication: For the treatment of moderate to severe chronic hand eczema in adults for whom topical corticosteroids are inadequate or are not advisable

Sponsor: Leo Pharma Inc.

Final Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Anzupgo?

Canada's Drug Agency (CDA-AMC) recommends that Anzupgo be reimbursed by public drug plans for the treatment of moderate to severe chronic hand eczema (CHE), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Anzupgo should only be covered to treat adults (aged ≥ 18 years) with moderate to severe CHE who have had an inadequate response to, or cannot use, topical corticosteroids (TCSs). Patients must have tried appropriate topical therapy (emollients with or without TCSs) before starting Anzupgo.

What Are the Conditions for Reimbursement?

Anzupgo should only be reimbursed for patients who have received an adequate trial of appropriate topical therapy, when prescribed by — or in consultation with — a dermatologist or clinician experienced in the management of CHE, and the cost of Anzupgo should not exceed the total drug cost of alitretinoin.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 3 phase III clinical trials (the DELTA 1, DELTA 2, and DELTA FORCE trials) demonstrated that Anzupgo significantly reduced eczema severity and improved symptoms and health-related quality of life (HRQoL) compared with an inactive cream, and also showed comparable or greater efficacy than alitretinoin, the only approved therapy for CHE in Canada. Anzupgo was generally well tolerated, with mostly mild local reactions and no systemic safety concerns.
- Based on the CDA-AMC assessment of the health economic evidence, Anzupgo does not represent good value to the health care system at the public list price. The Canadian Drug Expert Committee (CDEC) determined that there is not enough evidence to justify a greater annual cost for Anzupgo compared with alitretinoin.
- Clinical experts and patient groups confirmed a substantial unmet need for an effective nonsteroidal topical option that improves symptoms such as itch and pain, and preserves hand function.
- The sponsor-submitted budget-impact analysis (BIA) was associated with major limitations that precluded an accurate estimation of the budget impact.

Summary

Additional Information

What Is CHE?

CHE is a long-lasting, inflammatory skin condition that causes redness, itching, cracking, and pain in the hands, which can interfere with daily activities and work. It affects about 6% of adults in Canada, occurring more often in females and people whose jobs involve frequent handwashing or exposure to irritants.

Unmet Needs in CHE

Many patients with CHE do not experience adequate relief with high-potency TCSs or cannot use them safely for long periods, leaving no other topical options and few effective and well-tolerated treatments for persistent or severe disease.

How Much Does Anzupgo Cost?

Treatment costs with Anzupgo are expected to range from $637 to $5,096 per patient per year (minimum to maximum usage based on the sponsor's suggested discontinuation criteria).

Recommendation

CDEC recommends that delgocitinib be reimbursed for the treatment of moderate to severe CHE in adults for whom TCSs are inadequate or are not advisable, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 2 pivotal, phase III randomized controlled trials (RCTs) (the DELTA 1 [N = 487] and DELTA 2 [N = 473] trials) demonstrated that delgocitinib provides clinically meaningful improvements compared with vehicle in adults with moderate to severe CHE. At week 16, Investigator Global Assessment of Chronic Hand Eczema (IGA-CHE) treatment success was experienced by 19.7% of individuals receiving delgocitinib versus 9.9% of those receiving vehicle (inactive cream) in the DELTA 1 trial (absolute difference = 9.8%; 95% confidence interval [CI], 3.6% to 16.1%) and 29.1% versus 6.9% in the DELTA 2 trial (absolute difference = 22.2%; 95% CI, 15.8% to 28.5%). Secondary end points also favoured delgocitinib: Hand Eczema Severity Index (HECSI)-90 responses (corresponding to a 90% reduction in HECSI score from baseline) were 29.5% with delgocitinib versus 12.3% with vehicle in the DELTA 1 study and 31.0% versus 8.8% in the DELTA 2 study, while approximately half of patients receiving delgocitinib achieved HECSI-75 responses (corresponding to a 75% reduction in HECSI score from baseline) compared with less than one-quarter of those receiving vehicle. Patient-reported outcomes were consistent, with 47% of patients who received delgocitinib experiencing a clinically meaningful reduction in itch, compared with 20% to 23% of patients who received vehicle, alongside improvements in pain, sleep, and quality of life (QoL). Benefits were evident as early as week 4, increased through week 16, and were sustained in the DELTA 3 extension trial, although this study only enrolled individuals who were categorized as prior responders.

The body of evidence also consisted of the open-label, randomized DELTA FORCE study (N = 513), in which delgocitinib was directly compared with alitretinoin in patients with severe CHE. At week 12, IGA-CHE treatment success was experienced by 27.2% of patients receiving delgocitinib versus 16.6% receiving alitretinoin (difference = 10.6%; 95% CI, 3.3% to 17.9%). Mean change from baseline in HECSI scores also favoured delgocitinib at both week 12 (–67.6 versus –51.5; difference = –16.1; 95% CI, –23.3 to –8.9) and week 24 (–69.6 versus –45.1; difference = –24.5; 95% CI, –32.6 to –16.4). HECSI-90 responses were 38.6% with delgocitinib versus 26.0% with alitretinoin (difference = 12.6%; 95% CI, 4.3% to 20.8%). Differences in itch, Dermatology Life Quality Index (DLQI), and Hand Eczema Impact Scale (HEIS) scores also favoured delgocitinib, although these were not considered clinically meaningful. Safety data across clinical trials indicate that delgocitinib was generally well tolerated, with most adverse events (AEs) being mild to moderate local application site reactions. No systemic safety concerns were observed during long-term use.

Indirect evidence from a network meta-analysis (NMA) and a matching-adjusted indirect comparison (MAIC) suggests that delgocitinib provides comparable or favourable outcomes relative to available systemic therapy (alitretinoin), particularly for physician-assessed treatment success and patient-reported symptom relief, although limitations in methodology and data availability introduce some uncertainty. No direct or indirect evidence was submitted on the effectiveness and safety of delgocitinib compared with other topical therapies, or systemic therapies (namely oral immunosuppressants), which are typically prescribed after TCSs in patients with limited access to alitretinoin or phototherapy.

Input from patients emphasized the burden of CHE, including pain, itching, impaired hand function, and social stigma, and the need for effective topical options with fewer systemic adverse effects. Patients highlighted the benefits of delgocitinib in improving symptoms and daily functioning. Input from clinical specialists confirmed an unmet need for new topical therapies, noting that many patients cannot tolerate, or have disease that does not respond adequately to, TCSs or systemic therapies such as alitretinoin. Overall, CDEC concluded that delgocitinib addresses some important unmet needs in CHE by offering a topical option that affords a clinically meaningful reduction of symptoms and represents a valuable addition to the current treatment landscape.

CDEC considered an analysis conducted by CDA-AMC, using the sponsor's economic model in the indicated population (i.e., adult patients with moderate to severe CHE for whom TCSs are inadequate or not advisable), which considered the cost-effectiveness of delgocitinib relative to alitretinoin, phototherapy, and dupilumab. CDEC noted that, based on the expected place in therapy, delgocitinib is most likely to be prescribed immediately after a topical calcineurin inhibitor (TCI) or high-potency TCS, meaning that the most appropriate comparators may include alitretinoin or phototherapy, and when those are not available or not indicated, conventional oral immunosuppressants (methotrexate, cyclosporine, azathioprine, and mycophenolate mofetil). CDEC noted that there is considerable uncertainty arising from limitations in the modelling approach, drug dispensing required for maintenance therapy, variability across jurisdictions in the access to alitretinoin and phototherapy, and lack of evidence against conventional oral immunosuppressants. Compared to alitretinoin, delgocitinib provides at least a comparable response; however, improvements in symptom scores and QoL were not deemed to be clinically meaningful. No definitive conclusions can be drawn regarding the overall relative efficacy or cost-effectiveness of delgocitinib when considering other appropriate comparators. Therefore, the total drug cost of delgocitinib should not exceed the total drug cost of alitretinoin.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with delgocitinib should be initiated in adults (≥ 18 years): 1.1. with moderate to severe CHE, as defined by a PGA or IGA-CHE score of 3 to 4 1.2. who have had an adequate trial of (with documented refractory disease), or are intolerant to (with documented intolerance), or are ineligible for high-potency TCSs.	In pivotal DELTA 1 and DELTA 2 trials, delgocitinib improved clinical outcomes in adults with moderate to severe CHE who had inadequate response or contraindications to corticosteroids. Clinical experts confirmed that this population represents the key unmet need in Canada and that high-potency TCSs should be considered before initiation.	Documentation of CHE diagnosis and baseline severity (e.g., IGA-CHE) is needed. A minimum 8-week duration of high-potency TCS use is required before initiation, except in cases of intolerance or contraindication.
Renewal		
2. Response should be assessed at 12 weeks for renewal of reimbursement.	Experts advised that response should be evident by 12 weeks, consistent with the	The DELTA 3 trial results suggest that treatment response is sustained if the drug is used

Reimbursement condition	Reason	Implementation guidance
	product monograph and supported by clinical experience.	intermittently as needed. Hence, subsequent renewals are not required. On average, approximately 2 tubes of delgocitinib per patient would be used in the initial reimbursement period.
3. Reimbursement should be renewed if patients demonstrate either a ≥ 2-step improvement in IGA-CHE or PGA score, or a score of 0 to 1 (clear or almost clear).	The DELTA 1 and DELTA 2 trials considered at least a 2-step improvement in IGA-CHE score or an IGA-CHE score of 0 or 1 to be a treatment success.	Use of a consistent tool (e.g., IGA-CHE or PGA) for follow-up assessment is recommended.
Prescribing		
4. Delgocitinib should be prescribed by a practitioner experienced in the management of CHE.	This is to ensure appropriate diagnosis and to ensure that patients receive adequate treatment initiation and follow-up.	Clinical experts noted that some primary care clinicians manage CHE with appropriate specialist support. Patients should be adherent to standard nonmedicated skin care, including avoidance of known and relevant irritants and allergens.
Pricing		
5. The price of delgocitinib should be negotiated so that it does not exceed the annual drug program cost of alitretinoin.	The clinical evidence comparing delgocitinib to alitretinoin showed at least comparable treatment response, yet improvements in symptom scores and quality of life were not clinically meaningful. The clinical evidence for delgocitinib compared to phototherapy and dupilumab was associated with limitations, and comparative evidence against immunosuppressants is lacking. However, a change in treatment paradigm if delgocitinib is reimbursed is expected. Due to considerable uncertainty arising from limitations in the modelling approach, drug dispensing required for maintenance therapy, and variability to access to comparators across jurisdictions, the overall cost-effectiveness of delgocitinib is unknown when considering all potential treatment options. As such, there is insufficient evidence to justify a cost premium for delgocitinib over alitretinoin.	During jurisdictional price negotiations, the inclusion of potential wastage (12-month stability) and dispense quantity or size (per tube) should be considered. Depending on the jurisdiction, appropriate comparators may include alitretinoin, phototherapy, methotrexate, cyclosporine, azathioprine, and mycophenolate mofetil.
Feasibility of adoption		
6. The feasibility of adoption of delgocitinib must be addressed.	At the submitted price, the uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given that the submitted BIA was associated with	—

Reimbursement condition	Reason	Implementation guidance
	major limitations that precluded an accurate estimation of the budget impact.	

BIA = budget impact analysis; CHE = chronic hand eczema; IGA-CHE = Investigator Global Assessment of Chronic Hand Eczema; PGA = Physician Global Assessment; TCS = topical corticosteroid.

Discussion Points

- **Unmet need and patient perspectives:** The committee recognized that moderate to severe CHE causes substantial morbidity, including pain, itching, fissures, impaired hand function, and reduced QoL. TCSs are often inadequate or inadvisable, and systemic options such as alitretinoin have restricted use — due to safety concerns and teratogenicity — and may not be available for all patients. Phototherapy also presents barriers to access in many provinces. Patients and clinicians emphasized the importance of a safe, effective, nonsteroidal topical treatment. The committee concluded that delgocitinib addresses an important unmet need in this population.
- **Place in therapy:** CDEC noted that delgocitinib is positioned as a second-line topical treatment for adults with moderate to severe CHE who have not had an adequate response to high-potency TCSs or for whom TCSs are contraindicated. In Canadian clinical practice, treatment escalation typically progresses from a low-potency or medium-potency TCS to a high-potency TCS, sometimes with the addition of TCIs, followed by phototherapy or systemic therapies such as alitretinoin and oral immunosuppressants (e.g., methotrexate, cyclosporine). In most jurisdictions, dupilumab and oral Janus kinase (JAK) inhibitors may be accessed after failure of oral immunosuppressants. CDEC acknowledged that the Non-Insured Health Benefits (NIHB) program allows reimbursement of dupilumab for atopic dermatitis without prior exposure to oral immunosuppressants, but the committee considered that this exception did not position dupilumab as a direct alternative to delgocitinib for the vast majority of the population of Canada. While delgocitinib has been directly compared with vehicle and alitretinoin, there is no direct evidence available for its effectiveness and safety relative to other key comparators, creating uncertainty about its place in therapy. Furthermore, alitretinoin is not indicated for patients with moderate CHE, and the availability of alitretinoin or phototherapy may be limited in some jurisdictions. For such patients, the next available therapy would be conventional oral immunosuppressants such as methotrexate, azathioprine, or calcineurin inhibitors. CDEC emphasized that the definition of an “inadequate response” to a TCS remains unclear and may rely on clinical judgment. Although TCIs may precede delgocitinib use, they should not be mandatory due to their lower efficacy compared to high-potency TCSs. Delgocitinib’s topical formulation and favourable safety profile make it an option for patients seeking disease control before systemic treatments. However, uncertainties persist regarding its long-term safety and efficacy beyond 36 weeks, and its role versus systemic agents (e.g., immunosuppressants, JAK inhibitors, dupilumab). CDEC considered delgocitinib as a complement to other therapies for CHE. It was noted that the Health Canada monograph indicates that delgocitinib cream interactions with other drugs

have not been evaluated and that no evidence on combination use was submitted. Delgocitinib's therapeutic positioning may evolve with emerging evidence.

- **Clinical evidence and certainty:** Two pivotal, phase III RCTs (the DELTA 1 and DELTA 2 trials) provided high-certainty evidence that delgocitinib improves physician-assessed outcomes (IGA-CHE treatment success, HECSI-75, HECSI-90) and patient-reported outcomes (itch, pain, function, DLQI) compared with vehicle. Benefits were observed as early as week 4, increased through week 16, and were sustained in the long-term extension study (the DELTA 3 study). An additional phase III trial (the DELTA FORCE trial) also demonstrated clinically meaningful improvements in IGA-CHE treatment success and patient-reported symptoms of delgocitinib when compared to alitretinoin. The committee noted limitations in the evidence from indirect treatment comparisons (ITCs) against other therapies for advanced CHE or atopic dermatitis — such as psoralen and UVA (PUVA) and dupilumab — due to network sparsity, heterogeneity, and reduced effective sample size in the MAIC. Other limitations include the exclusion of patients with major comorbidities and responder enrichment in the long-term extension study, which reduced generalizability. Nevertheless, the consistency of findings across multiple outcomes, the alignment with patient-reported priorities, and the biological rationale increased confidence in a clinically meaningful effect.
- **Implementation considerations:** The committee highlighted the need for clear and consistent outcome measures (e.g., IGA-CHE, Physician Global Assessment [PGA]) to support renewal and discontinuation decisions. Renewal at 12 weeks aligns with both clinical trial evidence and the product monograph and is supported by the clinical experts consulted by CDA-AMC. Discontinuation at remission, with reinitiation at flare, supports intermittent use and aligns with clinical practice. Patient education on safe topical use, avoidance of overuse, and reinitiation at flare is important for appropriate utilization.
- **Safety and tolerability:** CDEC noted that across studies, delgocitinib was generally well tolerated, with AEs limited primarily to mild, local, application site reactions. No systemic safety concerns were identified. Compared with oral drugs, delgocitinib may limit the risks of systemic toxicities. While systemic exposure relative to oral drugs is low, data on safety in pregnancy are not available. The committee rated the certainty of safety evidence as moderate, acknowledging that long-term, real-world data remain limited.
- **Budget impact:** CDEC noted that the sponsor-submitted BIA was associated with major limitations that precluded an accurate estimation of the budget impact. Costs associated with other comparators could not be reliably estimated given the submitted structure of the analysis that precludes accurate assessment of costs and impact of subsequent therapies.

Background

CHE is a painful, relapsing, inflammatory skin condition characterized by erythema, scaling, fissures, vesicles, and lichenification. Patients commonly experience itching, pain, dryness, and bleeding, which vary in severity and may result in impaired hand function, sleep disturbances, psychological distress, and reduced

work productivity. In Canada, the prevalence of CHE among adults is estimated at 6.2%, with a higher occurrence in women, and the disease represents a significant clinical and socioeconomic burden.

Management in Canada generally follows a stepwise approach, beginning with avoidance of irritants and protective hand care, followed by emollients and TCSs. TCIs may be used as steroid-sparing options, although their use is constrained by tolerability and cost. For patients with more severe or refractory disease, systemic therapy may be considered, most notably oral alitretinoin — the only systemic treatment approved by Health Canada for CHE — although its long-term use is limited by adverse effects and teratogenicity.

Delgocitinib has been approved by Health Canada for the treatment of moderate to severe CHE in adults for whom TCSs are inadequate or not advisable. Delgocitinib is a topical pan-JAK inhibitor, available as a cream (20 mg/g, in 60 g tubes). The recommended dose is a thin layer applied to affected areas twice daily.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 3 RCTs (the DELTA 1, DELTA 2, and DELTA FORCE trials) in adults with moderate to severe CHE, 1 long-term extension study (the DELTA 3 study), and 2 ITCs (an NMA and an MAIC)
- patients' perspectives gathered by 2 patient groups: the Eczema Society of Canada (ESC) and the Canadian Association of Neonatal Nurses (CANN)
- input from public drug plans that participate in the reimbursement review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with CHE
- input from 5 clinician groups: the Dermatology Association of Ontario (DAO), the Atlantic Dermatology Group, the Canadian Dermatology Association Pharmacy and Therapeutics Advisory Board, the Saskatchewan Dermatology Association, and a group of dermatologists in Canada with an interest in CHE
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to our call for input and from clinical experts consulted by for the purpose of this review.

Patient Input

Two patient groups, ESC and CANN, submitted input for this review. Another patient group, the Canadian Skin Patient Alliance, did not directly provide input for this submission but provided a letter of support for the patient submission developed and submitted by ESC. ESC obtained information through questionnaires and interviews with patients, caregivers, and health care professionals related to CHE, as well as survey data from more than 3,000 Canadians who live with eczema on various topics (e.g., QoL impact, experience

with treatments, patient journeys, and so on). CANN collected anonymous data through previous qualitative interviews with nurses in July 2024 and obtained their perspectives on living and working with CHE. The group also conducted an online quantitative survey of their nursing members between October 23, 2024, and November 10, 2024 (those living with CHE only, n = 27), which was distributed through CANN's email communication and established membership channels. All information was gathered in Canada.

Both patient groups highlighted a significant impairment to everyday living and QoL due to CHE. The groups reported that patients with CHE experienced negative impacts on sleep quality (due to pain), skin (burning, itching lesions, blisters, bleeding skin), work (loss of productivity, change in careers due to CHE), social interactions, fitness, intimacy, family life, and hygiene. CANN further noted that survey respondents reported itchy skin as the symptom that caused the greatest burden, followed by dry or chapped skin; dyshidrotic blisters; cracking skin or fissures; open wounds with bleeding; and painful, stinging, and throbbing hands. Both patient groups highlighted that current treatment regimens may not be sufficient and expressed concerns regarding long-term steroid use. In the survey conducted by CANN, 52% of the respondents reported that their current treatment and management could not control or only somewhat helped them manage their hand eczema.

Regarding outcomes, both patient groups highlighted a need for better disease management, including relief from itching, stinging, burning, and pain; improvement in skin disease; and reduction of flares. CANN further highlighted that patients with CHE want to function normally, return to work, have a reduced severity of flares, and have a decreased risk from blisters and open wounds. ESC also noted that patients were looking for treatments suitable for long-term use, which could allow them to regain their confidence and self-esteem, and improve their social life and QoL. Both patient groups noted positive experiences with delgocitinib by those who had the opportunity to be treated with it. ESC further highlighted that it offered patients relief and was well tolerated (without stinging or burning, and not greasy on the hands).

Clinician Input

Input From Clinical Experts Consulted for This Review

The experts identified a clear unmet need for effective, well-tolerated, nonsystemic therapies for adults with moderate to severe CHE, particularly for patients whose disease is unresponsive to TCSs or who cannot tolerate systemic therapies such as alitretinoin due to side effects or contraindications. According to the experts, delgocitinib may fill this gap by offering a topical, nonsteroidal option that can be used earlier in the treatment pathway and may delay or prevent the need for systemic treatment.

The experts considered patients with moderate to severe CHE who have experienced treatment failure with first-line TCSs as the population most likely to benefit from delgocitinib. Those least likely to benefit may include individuals with primarily irritant-driven eczema, those with significant adherence issues, or patients with very limited disease extent that can be managed with intermittent topical steroids. The experts emphasized that treatment should begin once TCSs have proven insufficient to achieve control, especially in patients with persistent symptoms affecting function or QoL.

Response to treatment should be assessed based on improvements in visible skin signs, reduction in itching and pain, and enhanced ability to perform daily tasks, including work. Clinical tools such as the IGA-CHE and HECSI, along with patient-reported outcomes like DLQI and symptom diaries, were viewed as useful for monitoring treatment response. Experts recommended discontinuing delgocitinib if no meaningful clinical improvement is observed within 8 to 12 weeks, or sooner if disease worsens or adverse reactions occur.

Additional considerations raised by the experts included the importance of patient education on appropriate application and expectations for treatment response. They also highlighted the potential role of delgocitinib in reducing the need for systemic immunosuppressants or biologics, and its practical advantages for long-term management, especially for patients requiring maintenance therapy with a lower side effect burden.

Clinician Group Input

Five clinician groups (the DAO, the Atlantic Dermatology Group, the Canadian Dermatology Association Pharmacy and Therapeutics Advisory Board, the Saskatchewan Dermatology Association, and a group of dermatologists in Canada with an interest in CHE) provided input for this review. Information for this submission included input from 21 clinicians and was gathered through reviews of published literature, research and trial experience, clinical practice experience, and national and international meetings.

The input from the clinician groups was generally consistent with the input from the clinical experts consulted for this review, emphasizing the ongoing unmet need for new topical prescription therapy options for CHE that would control signs and symptoms of CHE, normalize QoL, and reduce or abolish occupational impacts. The DAO further emphasized the need to include therapies for long-term control of CHE that are safe, effective, and accessible. The clinician groups highlighted the limitations of current therapies, including AEs related to TCS use (e.g., skin atrophy, skin infections, pain, burning, fissures, reduced hand dexterity, and bleeding), limited efficacy and poor access to phototherapy, and contraindications to alitretinoin use (e.g., pregnancy and breastfeeding). The DAO noted that while TCIs like tacrolimus are sometimes used in mild cases of CHE when a steroid-sparing therapy is required due to AEs related to steroid use, they are not effective treatment alternatives for moderate and severe forms of CHE. The DAO also highlighted several off-label systemic options for patients with CHE in cases when phototherapy and alitretinoin are not suitable or accessible, or fail to control the condition, including traditional immunosuppressants (e.g., methotrexate and cyclosporine), biologics (particularly ones used in atopic dermatitis, such as dupilumab), and oral JAK inhibitors (e.g., upadacitinib). However, the group noted the limitations related to these off-label options as well, including accessibility and cost (i.e., the coverage criteria may make a biologic therapy inaccessible, or the copay cost to the patient may be a barrier), safety considerations (e.g., black box warnings and contraindications across the oral systemic therapies), and expected effectiveness (where traditional immunosuppressants are not as effective in managing CHE as biologics or oral JAK inhibitors). The groups indicated that people involved in certain professions with frequent exposure to irritants and allergens — such as health care, cleaning, and hairdressing — report particularly higher incidence rates of CHE.

The DAO and the Canadian Dermatology Association Pharmacy and Therapeutics Advisory Board considered topical delgocitinib to be a second-line treatment for patients with moderate to severe CHE (i.e., those with PGA scores of 3 to 4) who have disease that is refractory to TCSs or who have intolerances

or contraindications to TCSs, whereas the Atlantic Dermatology Group considered it to be a first-line or second-line treatment for adult patients with moderate to severe CHE for whom TCSs are inadequate or inappropriate. The groups noted that delgocitinib is expected to cause a shift in the current treatment paradigm as a new targeted topical prescription therapy for CHE. The DAO highlighted the ease of access and treatment administration of delgocitinib versus phototherapy, without the requirement for lab monitoring and the contraindications (e.g., pregnancy, breastfeeding, renal or hepatic insufficiency, and so on) that exist for alitretinoin. Referring to the clinical trials, the groups also noted the efficacy and favourable safety profile of delgocitinib in patients with moderate to severe CHE. The clinician groups provided additional details on patient selection, noting that delgocitinib may be particularly appropriate for patients with moderate to severe CHE who have had an inadequate response to TCSs, or for whom TCSs are not advisable or contraindicated. They also noted that patients with mild CHE for whom TCSs have not yet been utilized, or patients whose disease is being adequately managed by emollients, avoidance strategies, or TCSs, are less appropriate candidates.

The clinician groups noted that initial assessment of response between 3 and 6 months or 16 weeks would be reasonable. The DAO also highlighted that assessment of treatment response often varies among clinicians and depends on clinical practice waiting times, availability of follow-up, and other patient-specific factors. In terms of outcome assessment, the clinician groups added that outcome measures are not strictly defined in clinical practice for CHE, and an informal PGA tool is usually used by the clinicians. The clinician groups agreed that reasons for discontinuation of delgocitinib may include poor efficacy or inadequate response, recurrent flares, worsening or nonresponse of disease despite an adequate therapeutic trial, or intolerance to treatment or side effects.

Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Response
Relevant comparators	
Delgocitinib cream is compared to cream vehicle instead of other commonly used topical therapies for eczema (e.g., vitamin D3 derivatives [calcipotriol] and calcineurin inhibitors [tacrolimus and pimecrolimus]). Is it appropriate to compare delgocitinib to oral alitretinoin, given that not all jurisdictions include alitretinoin as a treatment option?	CDEC acknowledged that while not all jurisdictions include oral alitretinoin on their formularies, such variation is common across treatments in Canada due to provincial differences in access (similar discrepancies occur with access to phototherapy and cyclosporine). Despite these access issues, CDEC considered the comparison to alitretinoin appropriate, as it is currently the only drug with an NOC for hand dermatitis.
Considerations for initiation of therapy	
Most eczema medications require patients to have a score ≥ 16 on the EASI. The primary end point in the submitted studies was the IGA-CHE. IGA-CHE treatment success is defined as a score of 0 or 1 and a ≥ 2-step improvement from	Regarding the use of the IGA-CHE as the primary outcome measure in delgocitinib trials, CDEC stated that the IGA-CHE and the PGA are clinically similar and interchangeable. Thus, the use of the IGA-CHE was considered reasonable.

Drug program implementation questions	Response
baseline at week 16. Given that the studies for delgocitinib used IGA-CHE score as the primary outcome instead of EASI score, is this tool commonly used in clinical practice? Can the PGA be substituted?	
Participants in the submitted studies were adults aged 18 years and older. Could experts comment on the use in the pediatric population? Is there any clinical experience or evidence supporting the use of delgocitinib in children, especially for those seeking alternatives to topical steroids?	CDEC noted that delgocitinib has not been studied or approved for children, and that the pediatric population is outside the scope of this review.
Should delgocitinib be reserved only for patients who experience failure of or intolerance to topical steroids? What is a reasonable time frame to define steroid treatment failure (e.g., 8 weeks)? Should failure of nonsteroidal treatments like calcipotriol or tacrolimus also be considered before initiating delgocitinib? Should systemic therapies such as methotrexate be tried before initiating treatment with delgocitinib?	CDEC acknowledged that delgocitinib should generally be reserved for patients who have experienced failure of or intolerance to topical corticosteroids. An 8-week duration was deemed a reasonable time frame to assess steroid treatment failure. CDEC emphasized that the potency of the steroid used matters: patients experiencing failure of high-potency steroids may not benefit from switching to topical nonsteroidal agents like tacrolimus, whereas failure of low-potency steroids could justify such a switch. Regarding systemic therapies, CDEC advised that methotrexate should not be used before delgocitinib, as this would bypass alitretinoin, which is a more logical and appropriate step in the treatment sequence.
Considerations for prescribing of therapy	
Should prescribing of delgocitinib be restricted to dermatologists?	CDEC expressed that restricting prescribing to dermatologists may not be necessary, as family physicians often manage hand dermatitis. CDEC suggested that family doctors should be allowed to prescribe delgocitinib after patients have experienced failure of topical corticosteroids.
Can delgocitinib be used in combination with a topical calcineurin inhibitor, biologics, and/or oral JAK inhibitor?	CDEC noted that the pivotal trials did not support concurrent use of delgocitinib with other therapies, and no other evidence was submitted. Consequently, CDEC cannot advise on combination use at this time.
Ruxolitinib (Opzelura) received a Do not Reimburse recommendation for atopic dermatitis.	This is a comment from the drug programs to inform CDEC deliberations.
System and economic issues	
Cost per 60 g tube: $636.98 Pan-Canadian budget impact: Year 1: –$5,891,445 Year 2: –$8,981,078 Year 3: –$12,169,822 Total 3-year impact: –$27,042,344	This is a comment from the drug programs to inform CDEC deliberations.

CDEC = Canadian Drug Expert Committee; EASI = Eczema Area and Severity Index; IGA-CHE = Investigator Global Assessment of Chronic Hand Eczema; JAK = Janus kinase; NOC = Notice of Compliance; PGA = Physician Global Assessment.

Clinical Evidence

Systematic Review

Description of Studies

Three phase III RCTs evaluated the efficacy and safety of delgocitinib cream 20 mg/g in adults with moderate to severe CHE. Two vehicle-controlled trials, the DELTA 1 (N = 487) and DELTA 2 (N = 473) trials, assessed whether delgocitinib improved IGA-CHE treatment success and HECSI scores over 16 weeks compared to vehicle cream. An active-controlled trial, the DELTA FORCE trial (N = 513), compared delgocitinib to oral alitretinoin over 24 weeks in patients with severe CHE, with primary and key secondary outcomes including change in HECSI score, IGA-CHE treatment success, HECSI-75 and HECSI-90, and patient-reported measures such as the Hand Eczema Symptom Diary (HESD) itch score and DLQI.

Across all trials, baseline demographic and disease characteristics were generally well balanced between groups. The mean age of participants ranged from 44 years to 46 years, with most having CHE symptoms for at least 4 to 6 years. The population was predominantly white (more than 90% versus less than 4% Asian, less than 1% Black, and less than 1% Indigenous) and slightly more than half were female (versus approximately 35% male). Baseline severity scores (e.g., HECSI and IGA-CHE scores) were consistent with moderate to severe CHE, and no notable imbalances were observed across treatment arms.

Efficacy Results

Vehicle-Controlled Studies

In the vehicle-controlled DELTA 1 and DELTA 2 trials, delgocitinib cream 20 mg/g twice daily demonstrated superior efficacy to vehicle at week 16 across clinician-reported and patient-reported outcomes.

IGA-CHE treatment success was achieved in 64 of 325 patients (19.7%) receiving delgocitinib versus 16 of 162 patients (9.9%) receiving vehicle (difference = 9.8%; 95% CI, 3.6% to 16.1%, P = 0.0055) in the DELTA 1 trial, and in 91 of 313 patients (29.1%) receiving delgocitinib versus 11 of 159 patients (6.9%) receiving vehicle (difference = 22.2%; 95% CI, 15.8% to 28.5%; P < 0.0001) in the DELTA 2 trial.

More patients treated with delgocitinib had HECSI-75 responses versus those receiving vehicle (DELTA 1 trial: 49.2% [160 of 325 patients] versus 23.5% [38 of 162 patients]; DELTA 2 trial: 49.5% [155 of 313 patients] versus 18.2% [29 of 159 patients]), and more patients treated with delgocitinib had HECSI-90 responses versus those receiving vehicle (DELTA 1 trial: 29.5% [96 of 325 patients] versus 12.3% [20 of 162 patients]; DELTA 2 trial: 31.0% [97 of 313 patients] versus 8.8% [14 of 159 patients]). The mean percentage reduction from baseline in HECSI score also favoured delgocitinib in both studies (DELTA 1: difference = –35.2; 95% CI, –46.7 to –23.8; P < 0.001; DELTA 2: difference = –45.5; 95% CI −56.4 to −34.6; P < 0.001).

A 4-point or greater reduction in HESD itch was reported by 152 of 323 patients (47.1%) receiving delgocitinib versus 37 of 161 patients (23.0%) receiving vehicle in the DELTA 1 trial, and 146 of 309 patients (47.2%) receiving delgocitinib versus 31 of 156 patients (19.9%) receiving vehicle in the DELTA 2 trial.

In terms of QoL, DLQI improvement of 4 points or greater was reported in 227 of 305 patients (74.4%) receiving delgocitinib versus 74 of 148 patients (50.0%) receiving vehicle in the DELTA 1 trial, and 216 of 299 patients (72.2%) receiving delgocitinib versus 70 of 153 patients (45.8%) receiving vehicle in the DELTA 2 trial. Mean DLQI score improved by –7.6 and –7.0 with delgocitinib in the DELTA 1 and DELTA 2 trials, respectively, compared to –3.9 and –3.1 in the vehicle groups; the mean difference was –3.6 (95% CI, –4.7 to –2.6) in the DELTA 1 trial and –3.9 (95% CI, –5.0 to –2.8) in the DELTA 2 trial. HEIS scores also improved more with delgocitinib than with vehicle in the DELTA 1 trial (difference = –0.6; 95% CI, –0.8 to –0.5) and the DELTA 2 trial (difference = –0.8; 95% CI, –1.0 to –0.6). All effects across these outcomes in the DELTA 1 and DELTA 2 trials were considered clinically meaningful.

Active-Controlled Study

In the active-controlled DELTA FORCE trial, delgocitinib demonstrated greater efficacy than oral alitretinoin 30 mg once daily. At week 12, IGA-CHE treatment success was achieved in 68 of 250 patients (27.2%) receiving delgocitinib versus 42 of 253 patients (16.6%) receiving alitretinoin (difference = 10.6%; 95% CI, 3.3% to 17.9%; P = 0.004). Mean change from baseline in HECSI score was –67.6 versus –51.5 at week 12 (difference = –16.1; 95% CI, −23.28 to −8.86; P < 0.001) and –69.6 versus –45.1 at week 24 (difference = −24.5; 95% CI, −32.55 to −16.36; P < 0.001), favouring delgocitinib. HECSI-90 responses were achieved in 96 of 249 patients (38.6%) receiving delgocitinib versus 65 of 250 patients (26.0%) receiving alitretinoin (difference = 12.6%; 95% CI, 4.3 to 20.8; P = 0.003). While the observed differences in HESD itch reduction greater than or equal to 4 points, DLQI, and HEIS were smaller and consistently favoured delgocitinib, they were not judged to be clinically meaningful.

These outcomes were exploratory and not adjusted for multiplicity.

Harms Results

Across the DELTA 1, DELTA 2, and DELTA FORCE trials, delgocitinib cream 20 mg/g twice daily demonstrated a favourable safety profile. In the vehicle-controlled studies (the DELTA 1 and DELTA 2 trials), the proportion of patients experiencing at least 1 AE was similar between groups: 45.2% with delgocitinib versus 50.6% with vehicle in the DELTA 1 trial, and 45.5% versus 44.7% in the DELTA 2 trial. Most AEs were mild to moderate. The most commonly reported AEs included COVID-19, nasopharyngitis, and headache.

In the active-controlled DELTA FORCE study, AEs occurred in 76.1% of patients receiving oral alitretinoin versus 49.4% of patients receiving delgocitinib. Notable AEs such as headache (32.4% versus 4.0%), nausea (5.7% versus 0.4%), dry skin (3.6% versus 1.2%), and hypercholesterolemia (3.6% versus 0%) occurred more frequently with alitretinoin than with delgocitinib.

Serious adverse events (SAEs) were infrequent across all studies, occurring in less than or equal to 2.0% of patients receiving delgocitinib in all trials, compared to less than or equal to 4.9% of patients receiving alitretinoin in the DELTA FORCE trial. No SAEs led to major safety concerns or deaths. AEs leading to treatment discontinuation were also rare with delgocitinib (≤ 1.2%) but notably higher with alitretinoin (10.1%). No AEs of special interest occurred in the delgocitinib groups, while 1 patient in the alitretinoin group experienced deep vein thrombosis. No deaths occurred in any of the trials.

Critical Appraisal

The vehicle-controlled DELTA 1 and DELTA 2 trials were methodologically robust, with low risk of bias across outcomes. Randomization, allocation concealment, and blinding were well executed, and outcome assessments used instruments that were overall validated (although some were validated within the sponsored study) and aligned with the trial objectives. Missing data were minimal and handled appropriately using standard imputation methods. In contrast, the DELTA FORCE trial employed an open-label design, in which patients and treating physicians were aware of treatment allocation; however, efficacy assessments were conducted by blinded assessors to mitigate potential detection bias. Differential dropout rates between treatment arms (36% for alitretinoin versus 13% for delgocitinib) likely reflect differences in tolerability and clinical effects inherent to systemic versus topical products. However, this degree of imbalance raises concerns about attrition bias, particularly for longer-term and subjective outcomes, and the direction of this bias would likely favour delgocitinib.

The trials enrolled patients consistently with the Health Canada indication for delgocitinib, with baseline characteristics reflective of the intended population. However, the underrepresentation of racial and geographic diversity, exclusion of patients with significant comorbidities, and controlled trial setting may modestly limit generalizability. Nonetheless, the intervention and comparator regimens, background care, and outcomes assessed were aligned with Canadian clinical practice, supporting the overall applicability of findings to the real-world setting.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. Table 3 and Table 4 present the summary of findings for these relevant outcomes.

Table 3: Summary of Findings for Delgocitinib vs. Cream Vehicle for Patients With CHE

Outcome and follow-up	Patients (studies), N	Absolute effects	Certainty	What happens
Severity of CHE				
IGA-CHE treatment success, n (%) Follow-up: 16 weeks	2 RCTs, 959 patients	DELTA 1 trial: • Delgocitinib: 64 of 325 patients (19.7%) • Vehicle: 16 of 162 patients (9.9%) • Difference: 10 more patients per 100 treated (95% CI, 4 to 16) DELTA 2 trial: • Delgocitinib: 91 of 313 patients (29.1%) • Vehicle: 11 of 159 patients (6.9%)	High[a]	Delgocitinib results in a clinically meaningful increase in treatment success as defined by IGA-CHE score when compared to cream vehicle.

Outcome and follow-up	Patients (studies), N	Absolute effects	Certainty	What happens
		• Difference: 22 more patients per 100 treated (95% CI, 16 to 29)		
HECSI-90, n (%) Follow-up: 16 weeks	2 RCTs, 959 patients	DELTA 1 trial: • Delgocitinib: 96 of 325 patients (29.5%) • Vehicle: 20 of 162 patients (12.3%) • Difference: 17 more patients per 100 treated (95% CI, 10 to 24) DELTA 2 trial: • Delgocitinib: 97 of 313 patients (31.0%) • Vehicle: 14 of 159 patients (8.8%) • Difference: 22 more patients per 100 treated (95% CI, 15 to 29)	High[a]	Delgocitinib results in a clinically meaningful increase in patients with a HECSI-90 response when compared to cream vehicle.
HECSI-75, n (%) Follow-up: 16 weeks	2 RCTs, 959 patients	DELTA 1 trial: • Delgocitinib: 160 of 325 patients (49.2%) • Vehicle: 38 of 162 patients (23.5%) • Difference: 26 more patients per 100 treated (95% CI, 17 to 34) DELTA 2 trial: • Delgocitinib: 155 of 313 patients (49.5%) • Vehicle: 29 of 159 patients (18.2%) • Difference: 31 more patients per 100 treated (95% CI, 23 to 40)	High[a]	Delgocitinib results in a clinically meaningful increase in patients with a HECSI-75 response when compared to cream vehicle.
HECSI score, change from baseline Follow-up :16 weeks	2 RCTs, 959 patients	DELTA 1 trial: • Delgocitinib, mean (SE): –56.5 (3.4) • Vehicle, mean (SE): –21.2 (4.8) • Difference: –35.2 points (95% CI, –46.7 to –23.8) DELTA 2 trial: • Delgocitinib, mean (SE): –58.9 (3.2) • Vehicle, mean (SE): –13.4 (4.5) • Difference: –45.5 points (95% CI, –56.4 to –34.6)	High[b]	Delgocitinib results in a clinically meaningful reduction in HECSI score from baseline when compared to cream vehicle.

Outcome and follow-up	Patients (studies), N	Absolute effects	Certainty	What happens
Symptom reduction				
HESD itch reduction ≥ 4 points, n (%) Follow-up: Week 16	2 RCTs, 949 patients	DELTA 1 trial: • Delgocitinib: 152 of 323 patients (47.1%) • Vehicle: 37 of 161 patients (23.0%) • Difference: 24 more patients per 100 treated (95% CI, 16 to 33) DELTA 2 trial: • Delgocitinib: 146 of 309 patients (47.2%) • Vehicle: 31 of 156 patients (19.9%) • Difference: 27 more patients per 100 treated (95% CI, 19 to 36)	High[a]	Delgocitinib results in a clinically meaningful increase in patients with itch reduction of ≥ 4 points in the HESD when compared to cream vehicle.
HRQoL				
DLQI score, change from baseline Follow-up: 16 weeks	2 RCTs, 948 patients	DELTA 1 trial: • Delgocitinib, mean (SE): –7.6 (0.3) • Vehicle, mean (SE): –3.9 (0.4) • Difference: –3.6 points (95% CI, –4.7 to –2.6) DELTA 2 trial: • Delgocitinib, mean (SE): –7.0 (0.3) • Vehicle, mean (SE): –3.1 (0.5) • Difference: –3.9 points (95% CI, –5.0 to –2.8)	High[c]	Delgocitinib results in a clinically meaningful reduction in DLQI score from baseline when compared to cream vehicle.
HEIS, change from baseline Follow-up: 16 weeks	2 RCTs, 948 patients	DELTA 1 trial: • Delgocitinib, mean (SE): –1.5 (0.1) • Vehicle, mean (SE): –0.8 (0.1) • Difference: –0.6 points (95% CI, –0.8 to –0.5) DELTA 2 trial: • Delgocitinib, mean (SE): –1.5 (0.1) • Vehicle, mean (SE): –0.6 (0.1) • Difference: –0.8 points (95% CI, –1.0 to –0.6)	High[d]	Delgocitinib results in a clinically meaningful reduction in HEIS score from baseline when compared to cream vehicle.
Harms				
AEs Follow-up: 16 weeks	2 RCTs, 960 patients	In the DELTA 1 trial, 45.2% of patients receiving delgocitinib experienced at least 1 AE,	High[e]	Delgocitinib results in little to no difference in the number of patients

Outcome and follow-up	Patients (studies), N	Absolute effects	Certainty	What happens
		compared to 50.6% in the vehicle group. In the DELTA 2 trial, AEs occurred in 45.5% of patients treated with delgocitinib and 44.7% in the vehicle group.		with at least 1 AE when compared to cream vehicle. The magnitude of a meaningful effect is uncertain.
SAEs Follow-up: 16 weeks	2 RCTs, 960 patients	In the DELTA 1 trial, SAEs occurred in 1.8% of patients receiving delgocitinib and 1.9% of patients receiving vehicle. In the DELTA 2 trial, SAEs were reported in 1.6% and 1.9% of patients in the delgocitinib and vehicle groups, respectively.	Moderate[e]	Delgocitinib likely results in little to no difference in the number of patients with at least 1 SAE when compared to cream vehicle. The magnitude of a meaningful effect is uncertain.
AESIs Follow-up: 16 weeks	2 RCTs, 960 patients	No AESIs occurred in the DELTA 1 and DELTA 2 trials.	Moderate[e]	Delgocitinib likely results in little to no difference in the number of patients with at least 1 AESI when compared to cream vehicle. The magnitude of a meaningful effect is uncertain.

AE = adverse event; AESI = adverse event of special interest; CHE = chronic hand eczema; CI = confidence interval; DLQI = Dermatology Life Quality Index; HECSI = Hand Eczema Severity Index; HEIS = Hand Eczema Impact Scale; HRQoL = health-related quality of life; HESD = Hand Eczema Symptom Diary; IGA-CHE = Investigator Global Assessment of Chronic Hand Eczema; MID = minimal important difference; RCT = randomized controlled trial; SAE = serious adverse event; SE = standard error; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in these footnotes.

[a]A clinically meaningful effect of at least 3 patients improved per 100 treated was established as the threshold for clinical importance; hence, the body of evidence was not rated down for imprecision. IGA-CHE success was defined as a score of 0 or 1 with at least a 2-step improvement from baseline. Differences in effect estimates were detected between the DELTA 1 and DELTA 2 trials; however, this was likely explained by differences in patients' baseline risk factors. Furthermore, both estimates and CIs showed a meaningful effect; therefore, we did not rate down for inconsistency.

[b]A MID of 20 was established as the threshold of clinical importance for the HECSI values, hence the body of evidence was not rated down for imprecision.

[c]DLQI MID of 4 points.

[d]HEIS MID of 0.6 points.

[e]A threshold of clinical importance to determine the magnitude of effect was not possible to obtain. For SAEs and AESIs, we rated down 1 level for imprecision because the magnitude of effect was uncertain and there were few or no events.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence.[16]

Table 4: Summary of Findings for Delgocitinib vs. Alitretinoin for Patients With CHE

Outcome and follow-up	Patients (studies), N	Absolute effects	Certainty	What happens
Severity of CHE				
IGA-CHE treatment success, n (%) Follow-up: 12 weeks	1 RCT, 503 patients	Delgocitinib: 68 of 250 patients (27.2%) Alitretinoin: 42 of 253 patients (16.6%) Difference: 11 more patients per 100 treated (95% CI, 3 to 18)	Moderate[a,b]	Delgocitinib likely results in a clinically meaningful treatment success, as defined by IGA-CHE score, when compared to alitretinoin.
HECSI-90, n (%) Follow-up: 12 weeks	1 RCT, 499 patients	Delgocitinib: 96 of 249 patients (38.6%) Alitretinoin: 65 of 250 patients (26.0%) Difference: 13 more patients per 100 treated (95% CI, 4 to 21)	Moderate[a,b]	Delgocitinib likely results in a clinically meaningful increase in patients with a HECSI-90 response when compared to alitretinoin.
HECSI, change from baseline Follow-up: 12 weeks	1 RCT, 499 patients	Delgocitinib, mean (SE): −67.6 (3.37) Alitretinoin, mean (SE): −51.5 (3.36) Difference: −16.1 (95% CI, −23.28 to −8.86)[c]	Moderate[a,c]	Delgocitinib likely results in a clinically meaningful reduction in HECSI score from baseline when compared to alitretinoin.
Symptom reduction				
HESD itch score, change from baseline Follow-up: 12 weeks	1 RCT, 476 patients	Delgocitinib, mean (SE): −3.0 (0.22) Alitretinoin, mean (SE): −2.4 (0.21) Difference: −0.7 (95% CI, −1.12 to −0.20)[d]	Moderate[a,d]	Delgocitinib likely results in little to no difference in HESD itch score when compared to alitretinoin.
HRQoL				
DLQI, change from baseline Follow-up: 12 weeks	1 RCT, 466 patients	Delgocitinib, mean (SE): −7.5 (0.5) Alitretinoin, mean (SE): −5.8 (0.5) Difference: −1.8 (95% CI, −2.8 to −0.7)[e]	Moderate[a,e]	Delgocitinib likely results in little to no difference in DLQI score when compared to alitretinoin.
HEIS, change from baseline Follow-up: 12 weeks	1 RCT, 468 patients	Delgocitinib, mean (SE): −1.4 (0.1) Alitretinoin, mean (SE): −1.1 (0.1) Difference: −0.3 (95% CI, −0.5 to −0.1)[f]	Moderate[a,f]	Delgocitinib likely results in little to no difference in HEIS score when compared to alitretinoin.
Harms				
AEs Follow-up: 24 weeks	1 RCT, 513 patients	AEs occurred in 49.4% of patients treated with delgocitinib and 76.1% of those receiving alitretinoin. The most common AEs in the alitretinoin group were headache (32.4%), nasopharyngitis (13.8%), lip dryness (3.2%), and nausea (5.7%), while the most frequent AEs in the delgocitinib group	Moderate[g]	Delgocitinib likely results in fewer AEs compared with alitretinoin, although the magnitude and clinical importance of this effect are uncertain.

Outcome and follow-up	Patients (studies), N	Absolute effects	Certainty	What happens
		were nasopharyngitis (11.9%) and headache (4.0%).		
SAEs Follow-up: 24 weeks	1 RCT, 513 patients	SAEs were reported in 2.0% of patients in the delgocitinib group and 4.9% in the alitretinoin group. All SAEs resolved by the end of the study, and none led to long-term harm.	Moderate[g]	Delgocitinib likely results in fewer SAEs when compared to alitretinoin. The magnitude of this effect is uncertain.
AESI Follow-up: 24 weeks	1 RCT, 513 patients	One patient (0.4%) in the alitretinoin group experienced an AESI (a postoperative DVT, which resolved). No AESIs were reported in the delgocitinib group.	Moderate[g]	Delgocitinib likely results in little to no difference in AESIs when compared to alitretinoin. The magnitude of this effect is uncertain.

AE = adverse event; AESI = adverse event of special interest; CHE = chronic hand eczema; CI = confidence interval; DLQI = Dermatology Life Quality Index; HECSI = Hand Eczema Severity Index; HEIS = Hand Eczema Impact Scale; HRQoL = health-related quality of life; HESD = Hand Eczema Symptom Diary; IGA-CHE = Investigator Global Assessment of Chronic Hand Eczema; MID = minimal important difference; RCT = randomized controlled trial; SAE = serious adverse event; SE = standard error; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in these footnotes.

[a]Rated down 1 level due to risk of bias in the DELTA FORCE study, an open-label study with outcome completion rates higher in the delgocitinib group (86.6%) vs. the alitretinoin group(64.1%), with a differential dropout rate of approximately 22%. Discontinuations in the alitretinoin group were mainly due to AEs and lack of efficacy. Although sensitivity analyses were conducted, the missingness is likely related to the outcome.

[b]A clinically meaningful effect of at least 3 patients improved per 100 treated was established as the threshold for clinical importance; hence, the body of evidence was not rated down for imprecision. IGA-CHE success was defined as a score of 0 or 1 with at least a 2-step improvement from baseline.

[c]A MID of 20 was established as the threshold of clinical importance for the HECSI values; therefore, the body of evidence was not rated down for imprecision.

[d]A value of ≥ 4-point reduction for HESD itch score was used as the threshold for a clinically meaningful result (MID). The effect estimate and CI do not include this threshold; there was precision in the result as it falls within a trivial or no-effect zone (between thresholds).

[e]DLQI change of ≥ 4 points was established as the threshold for a meaningful effect or MID. The effect estimate and CI do not include this threshold; there was precision in the result as it falls within a trivial or no-effect zone (between thresholds).

[f]For the HEIS, the MID was established at ≥ 0.6 points difference. The effect estimate and CI do not include this threshold; there was precision in the result as it falls within a trivial or no-effect zone (between thresholds).

[g]Certainty rated down 1 level for imprecision due to absence of effect estimates with CIs and lack of established thresholds for clinical importance. These limitations preclude a high-certainty judgment.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence.[16]

Long-Term Extension Studies

Description of Studies

The DELTA 3 study was a phase III, open-label, multisite extension phase of the DELTA 1 and DELTA 2 trials, conducted to assess the long-term safety and efficacy of twice-daily applications of delgocitinib cream 20 mg/g as needed (based on IGA-CHE score) in patients who completed 1 of the 2 pivotal phase III trials with delgocitinib cream 20 mg/g or cream vehicle. Together, the parent trials and the DELTA 3 extension trial provided 52 weeks of efficacy and safety data. The baseline visit (day 1, week 0) of this extension trial coincided with the end-of-treatment visit (week 16) of the parent trials.

Eligible patients for the DELTA 3 extension trial were those who completed the treatment period in the DELTA 1 or DELTA 2 parent trial. Participants who discontinued treatment with delgocitinib early, used rescue

medication, or experienced any AE during participation in the parent trial that precluded further treatment with delgocitinib were not eligible to participate in the DELTA 3 trial. From baseline to week 36, patients were treated on an as-needed basis with delgocitinib cream 20 mg/g twice daily. If a patient had an IGA-CHE score of 2 or higher at any time during the trial, the investigator dispensed delgocitinib cream and instructed the patient to start treatment with twice-daily applications. When the patient achieved an IGA-CHE score of 0 (clear) or 1 (almost clear), the patient could stop treatment.

The primary outcome of the DELTA 3 extension study was the number of treatment-emergent adverse events (TEAEs) from baseline up to week 38. SAEs, AEs leading to discontinuation, and deaths were also reported. Long-term efficacy outcomes, including IGA-CHE score and HECSI score, were reported as secondary outcomes, whereas HESD itch score and DLQI score were reported as tertiary outcomes for the extension phase.

Patient Disposition

Of the 810 screened patients, 801 patients were eligible to participate in the DELTA 3 study and were therefore included in the patient safety analysis. Among these 801 patients, 560 belonged to the previous delgocitinib group and 241 to the previous cream vehicle group. From the previous delgocitinib group, 88 patients (15.7%) discontinued from the study, and from the previous cream vehicle group, 49 patients (20.3%) discontinued from the study. A total of 664 patients completed the treatment period, 472 (84.3%) from the previous delgocitinib group and 192 (79.7%) from the previous cream vehicle group.

Baseline Characteristics

The baseline characteristics were similar to those of the parent trials. IGA-CHE and HECSI scores at the parent trial baseline were similar between the treatment groups. There were some differences in terms of IGA-CHE score at the extension trial baseline between the previous delgocitinib and cream vehicle groups. Median HECSI score, HESD itch and pain scores, HESD score, and DLQI score had decreased baseline values in both treatment groups compared to the parent trial baseline values. The distribution of CHE subtypes at the parent trial baseline was similar between the groups, with the exception of vesicular hand eczema (pompholyx) (11.3% versus 5.8% in the previous delgocitinib and cream vehicle groups, respectively).

Efficacy Results

In the DELTA 3 study, efficacy outcomes were generally maintained or improved over 36 weeks of as-needed delgocitinib use. Among patients who had received delgocitinib in the parent trials, IGA-CHE treatment success was stable (24.6% at extension baseline; 30.0% at week 36). In those previously treated with vehicle, IGA-CHE success increased from 9.1% to 29.5% over the same period.

HECSI scores declined further in both groups during the first 16 weeks and then stabilized. Mean HECSI score in the delgocitinib group fell from 23.9 to 14.8; in the former vehicle group, it fell from 46.8 to 16.8. Correspondingly, HECSI-75 response increased from 51.8% to 58.6% in the delgocitinib group and from 23.7% to 51.5% in the vehicle group. HECSI-90 response also improved, reaching 36.6% in the delgocitinib group and 35.7% in the former vehicle group by week 36.

Symptom relief was sustained, with HESD itch reductions of at least 4 points in 52.4% (versus 50.6% at baseline) and HESD pain reductions in 55.4% (versus 51.9%) of patients in the delgocitinib group. Improvements were also observed in the former vehicle group (itch: 26.3% to 41.3%; pain: 32.3% to 43.3%).

Patient-reported HEIS and DLQI scores showed modest continued improvement in the delgocitinib group and early gains that stabilized in the former vehicle group, supporting durability of treatment benefit over the extension period.

Harms

Overall, 495 patients (61.8%) reported at least 1 AE, with similar rates in those previously treated with delgocitinib (61.1%) and those previously receiving vehicle (63.5%). The most common AEs (≥ 5%) were COVID-19 and nasopharyngitis. While infection rates were slightly higher during on-treatment periods than off-treatment periods, the difference was not clinically meaningful.

SAEs were infrequent (3.4%), with no major differences by treatment phase or prior treatment group. Nine patients permanently discontinued the study drug due to AEs (most of which were nonserious), and rates were comparable across groups. One AE of special interest, eczema herpeticum, occurred during an on-treatment period in a patient with atopic dermatitis. Three deaths were reported, none of which were considered related to the study drug.

Critical Appraisal

The open-label extension phase design of the DELTA 3 trial may have biased the reporting of some end points because awareness of the study treatment received may have influenced the perception of improvement and/or harms by patients and clinicians, particularly for outcomes that are subjective in measurement and interpretation. As part of the eligibility criteria for the open-label extension phase, patients had to complete 1 of the prior studies, which may potentially allow for selection bias. Given that all patients were taking delgocitinib during the open-label extension phase, there was no relevant randomized comparison group (i.e., for any active comparator of interest), which precludes causal conclusions.

Given that the patients who took part in the DELTA 3 trial were originally from the DELTA 1 or DELTA 2 parent studies and the eligibility criteria remained the same, it is reasonable to expect that the same limitations to generalizability are relevant to the open-label extension (OLE) study. For instance, because the participants were predominantly white (approximately 91%), the results from these trials may not be generalizable to other racial groups, which may be commonly seen at some centres in North America and Europe. One of the eligibility criteria in the extension phase was that patients who experienced any AE during participation in the parent trial that precluded further treatment with delgocitinib were not eligible to participate in the DELTA 3 trial. While this reflects, to some extent, what would be expected in clinical practice (as patients who do not experience a treatment response or who discontinue due to AEs are unlikely to continue treatment), it also leads to enrichment of patients who tolerate and respond to delgocitinib. As a result, the generalizability of the DELTA 3 study to the overall population is uncertain.

Indirect Comparisons

Description of Studies

Due to limited head-to-head evidence, the sponsor submitted 2 ITCs to support the comparative efficacy and safety of delgocitinib for CHE. A Bayesian NMA compared delgocitinib to phototherapy (PUVA) and oral alitretinoin using data from 7 RCTs, including the DELTA 1, DELTA 2, and DELTA FORCE trials. A MAIC was also conducted to compare delgocitinib with dupilumab, using individual patient data from the DELTA 1 and 2 trials and aggregate data from the LIBERTY-AD-HAFT study, a trial in patients with atopic hand and foot eczema.

Efficacy Results

In the NMA, delgocitinib demonstrated higher odds of achieving an IGA-CHE or PGA 0 or 1 end point response compared to vehicle (overall response [OR] = 2.92; 95% credible interval [CrI], 2.06 to 4.21), PUVA (OR = 2.73; 95% CrI, 1.43 to 5.25), and alitretinoin (OR = 1.88; 95% CrI, 1.23 to 2.93) at the primary end point. Results were consistent at week 12 sensitivity analyses and across severity subgroups. Delgocitinib also showed improved odds of achieving a HECSI-90 response compared to vehicle (OR = 3.59; 95% CrI, 2.49 to 5.28) and alitretinoin (OR = 1.79; 95% CrI, 1.22 to 2.62). The MAIC found no significant difference between delgocitinib and dupilumab in achieving a IGA-CHE or Hand and Foot Investigator's Global Assessment score of 0 or 1 ([redacted]) or HECSI-90 response ([redacted]), with wide CIs reflecting imprecision.

Harms Results

The NMA indicated that delgocitinib was associated with lower odds of discontinuations due to AEs compared to vehicle (OR = 0.21; 95% CrI, 0.08 to 0.45), PUVA (OR = 0.09; 95% CrI, 0.03 to 0.32), and alitretinoin (OR = 0.09; 95% CrI, 0.04 to 0.21). These findings were consistent across severity-based sensitivity analyses. No harms data were included in the MAIC.

Critical Appraisal

The NMA was conducted using prespecified methods and included trials with generally low risk of bias. However, key limitations include heterogeneity in outcome definitions (e.g., stricter criteria for IGA-CHE response in DELTA trials), variation in disease severity and treatment duration across studies, and absence of closed loops, precluding formal consistency testing. Despite sensitivity analyses, residual concerns about effect modification remain. The network was sparse, particularly for phototherapy, and some outcomes (e.g., HECSI-90, cumulative response) could not be evaluated across all arms.

The MAIC used appropriate statistical methodology and adjusted for known effect modifiers (age, sex, race, HECSI score, CHE subtype). However, differences in underlying populations (CHE versus atopic hand and foot eczema), end point definitions, and the exclusion of harms limit its interpretability. The effective sample size was reduced after matching, leading to wide CIs and increased uncertainty.

Overall, both ITCs provided exploratory comparative data, but findings should be interpreted cautiously due to methodological and population-level differences.

Economic Evidence

Economic Evaluation and Budget Impact

- Delgocitinib is available as a topical cream (20 mg/g) sold in 60 g tubes. At the submitted price of $636.98 per tube, the cost per year of delgocitinib is expected to range from $637 to $5,096 per patient, based on the Health Canada–recommended dosage[1] and the maximum consumption based on discontinuation rules assumed by the sponsor and clinical expert feedback.
- Clinical efficacy in the economic analysis for delgocitinib versus alitretinoin and delgocitinib versus phototherapy was derived from the DELTA 1,[2] DELTA 2,[2] DELTA 3,[3] DELTA FORCE,[4] and ALPHA[5] trials, as well as the NMA conducted by the sponsor. Evidence from the DELTA FORCE trial indicated that delgocitinib showed superior efficacy in rates of IGA-CHE treatment success and improvements in HECSI score when compared with alitretinoin among adult patients with moderate to severe CHE, particularly among those who have not experienced a response to TCSs and are seeking nonsystemic alternatives. The DELTA FORCE trial showed improvements in QoL end points compared to alitretinoin; however, these were not considered clinically meaningful. The NMA suggested delgocitinib may be more effective than phototherapy and alitretinoin for key outcomes such as IGA-CHE success and HECSI-90 response. For delgocitinib versus dupilumab, clinical efficacy was informed by a sponsor-submitted MAIC, which did not identify a meaningful and precise difference between delgocitinib and dupilumab for the same outcomes. However, both the NMA and MAIC were limited by methodological concerns, including sparse data, residual confounding, and differences in outcome definitions, reducing confidence in the findings.
- The results of the CDA-AMC base case suggest the following:
  - Delgocitinib is predicted to be associated with higher costs to the health care systems than alitretinoin (incremental costs = $1,862) and phototherapy (incremental costs = $4,174), primarily driven by increased costs associated with treatment acquisition.
  - Delgocitinib is not predicted to be associated with life-year gains versus any comparator. Delgocitinib is predicted to be associated with a gain of 0.04 quality-adjusted life-years (QALYs) compared to alitretinoin and 0.05 QALYs compared to phototherapy, over a 30-year time horizon. These results are primarily driven by the incremental QALYs accrued in the response states.
  - The incremental cost-effectiveness ratio (ICER) of delgocitinib in the CDA-AMC base case compared to alitretinoin was $47,393 per QALY gained, and $79,192 per QALY gained compared to phototherapy. More than 90% of the QALY differences between delgocitinib and the comparators were accrued in the extrapolated period.
  - The results of the CDA-AMC base case are highly uncertain due to the lack of comparative evidence for several model inputs and the lack of long-term clinical evidence. The estimated ICERs were highly sensitive to the assumptions around how delgocitinib is dispensed. The cost-effectiveness of delgocitinib compared to immunosuppressants and other relevant comparators excluded from the model is unknown. Finally, the cost-effectiveness of delgocitinib versus

dupilumab is uncertain, given limitations in the evidence presented and uncertainties regarding delgocitinib's place in therapy relative to dupilumab.

- The sponsor-submitted BIA was associated with major limitations that precluded an accurate estimation of the budget impact.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed

Meeting date: September 24, 2025

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@cda-amc.ca.