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Reimbursement Recommendation

Spesolimab (Spevigo)

Indication: For the treatment of generalized pustular psoriasis (GPP) in adults and pediatric patients 12 years of age and older and weighing at least 40 kg.

Sponsor: Boehringer Ingelheim (Canada) Ltd.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Spevigo?

Canada's Drug Agency (CDA-AMC) recommends that Spevigo should be reimbursed by public drug plans for the treatment of generalized pustular psoriasis (GPP) in adults and pediatric patients aged 12 years and older and weighing at least 40 kg if certain conditions are met.

Which Patients Are Eligible for Coverage?

Spevigo should only be covered to treat adults and pediatric patients aged 12 years and older, weighing at least 40 kg, and living with GPP. Spevigo should be reimbursed for both the acute treatment of GPP flares and for the prevention of GPP flares for patients with a history of flares according to the European Rare and Severe Psoriasis Expert Network (ERASPEN) criteria.

What Are the Conditions for Reimbursement?

Spevigo should only be reimbursed if prescribed by clinicians (dermatologists or rheumatologists) with expertise in managing GPP and other types of psoriasis. For the prevention of flares, the initial authorization should be for 6 months of treatment. For continued renewal of Spevigo for the prevention of flares, the severity of GPP as measured by the generalized pustular psoriasis physician global assessment (GPPGA) total score at initiation should be maintained (not worsen), patient should experience fewer flares compared to baseline, and the reduction in the number of flares should be sustained. Spevigo should only be reimbursed if there is a reduction in drug price.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 2 pivotal studies (Effisayil-1 and Effisayil-2) demonstrated that treatment with Spevigo resulted in a clinical benefit for patients with GPP compared to placebo. Patients treated with Spevigo (900 mg, single-dose IV infusion) were more likely to experience an improvement and resolution of their flares after 1 week compared to placebo in the Effisayil-1 study. In addition, patients with a history of GPP flares who were treated with Spevigo (600 mg loading dose followed by a maintenance treatment of 300 mg every 4 weeks as subcutaneous [SC] injections) were more likely to have a longer time to the next GPP flare compared to placebo in the Effisayil-2 study.
- Spevigo may meet some patient needs such as providing a treatment with a manageable safety profile, that may resolve symptoms of an acute GPP flare and improve a patient's productivity and quality of life.

Summary

- Based on the CDA-AMC assessment of the health economic evidence, Spevigo does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Spevigo is estimated to cost public drug plans approximately $4.8 million over the next 3 years.

Additional Information

What Is GPP?

GPP is a rare, chronic, severe, and potentially life-threatening skin condition. It is characterized by repeated episodes (flares) of a sudden, rapidly spreading skin rash with pus-filled blisters, crusts, and scales. Additionally, the flare is usually associated with generalized symptoms such as fever, malaise, and fatigue. The incidence rate of GPP in Canada in 2023 was 1.95 per million individuals and the prevalence rate reported was 2.8 to 5.4 per million individuals.

Unmet Needs in GPP

Before the approval of Spevigo, there were no treatments available in Canada that were indicated for the treatment of GPP. In current clinical practice in Canada, GPP is managed by treatments that are indicated for psoriasis (e.g., plaque psoriasis) and are used off label for GPP. There is an urgent need for new treatments that effectively resolve flare episodes and control episodes from returning in patients.

How Much Does Spevigo Cost?

For the treatment of acute flares, Spevigo is expected to cost approximately $21,900 or $43,800 (if 2 doses are required) per flare. As preventive therapy, Spevigo is expected to cost approximately $102,000 in the first year and $95,000 in subsequent years of treatment per patient.

Recommendation

The CDA-AMC Canadian Drug Expert Committee (CDEC) recommends that spesolimab be reimbursed for the treatment of generalized pustular psoriasis (GPP) in adults and pediatric patients aged 12 years and older and weighing at least 40 kg, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

GPP is a rare and serious disease with flares that can be life-threatening. The 2 pivotal studies for spesolimab, Effisayil-1 and Effisayil-2, demonstrated that treatment with spesolimab resulted in a clinical benefit for patients with GPP compared to placebo.

Effisayil-1, a multicentre, randomized, placebo-controlled, double-blind, phase II trial, evaluated the efficacy and safety of spesolimab for the treatment of acute flare of moderate to severe intensity in adults diagnosed with GPP as per the European Rare and Severe Psoriasis Expert Network (ERASPEN) criteria. The Effisayil-1 trial demonstrated that treatment with spesolimab likely results in improved resolution of GPP flares 1 week after treatment (900 mg, single-dose IV infusion) compared to placebo. More specifically, 54.3% of patients in the spesolimab group had a generalized pustular psoriasis physician global assessment (GPPGA) pustulation subscore of 0 (no visible pustules) at week 1 compared to 5.6% in the placebo group (risk difference = 48.7%; 95% confidence interval [CI], 21.5% to 67.2%; superiority P value = 0.0004). Also, the proportion of patients that had a GPPGA total score of 0 or 1 (clear or almost clear skin) was greater in the spesolimab group compared to the placebo group (risk difference = 31.7%; 95% CI, 2.2% to 52.7%; superiority P value = 0.0118).

Effisayil-2, a multicentre, randomized, placebo-controlled, double-blind, phase IIb dose-finding study, evaluated the efficacy and safety of spesolimab for the prevention of GPP flares in patients aged 12 years and older with a history of GPP as per the ERASPEN criteria. The Effisayil-2 study demonstrated that administration of spesolimab (600 mg loading dose followed by maintenance treatment of 300 mg every 4 weeks as subcutaneous [SC] injections) for up to 48 weeks likely results in a benefit based on the time to first GPP flare compared to placebo (hazard ratio [HR] = 0.157; 95% CI, 0.046 to 0.541; superiority P value = 0.0005). Further, spesolimab demonstrated a benefit in the proportion of patients who experienced at least 1 GPP flare-up to 48 weeks of treatment for patients receiving spesolimab compared to placebo (estimated adjusted risk difference = –39.0%; 95% CI, –62.1% to –15.9%; superiority P value = 0.0013).

Patients identified the following unmet needs for the management of GPP: disease symptom control, reduce morbidity and mortality associated with GPP flares, and rapid resolution of cutaneous symptoms of flares. Patients also expressed a need for treatments that are safe and prevent subsequent flares, ultimately leading to an improvement in productivity and quality of life. CDEC concluded that spesolimab meets some of these needs compared to placebo, such as providing a treatment with a manageable safety profile, that may resolve symptoms of an acute GPP flare. CDEC also noted that spesolimab may prevent subsequent flares, although it is challenging to assess in a clinical trial setting due to the unpredictable nature of the condition.

Using the sponsor-submitted price for spesolimab, the incremental cost-effectiveness ratio (ICER) for spesolimab was $431,569 per quality-adjusted life-year (QALY) gained compared with no treatment. At this ICER, spesolimab is not cost-effective at a $50,000 per QALY gained willingness-to-pay threshold for the treatment of GPP in adults and pediatric patients aged 12 years and older and weighing at least 40 kg. A price reduction is required for spesolimab to be considered cost-effective at a $50,000 per QALY gained threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adults and pediatric patients aged 12 years and older and weighing at least 40 kg living with GPP, as per the following criteria: 1.1. diagnosis of GPP based on the ERASPEN criteria. Initiation criteria for the treatment of acute flares and the prevention of flares are further described in condition 2 and 3, respectively.	The Effisayil-1 and Effisayil-2 studies provided evidence of safety and efficacy for use of spesolimab in patients with a diagnosis of GPP based on the consensus diagnostic criteria by ERASPEN. Clinician input indicated that there were no safety concerns with the use of spesolimab in adolescent patients (aged 12 to 18 years and older and weighing at least 40 kg), particularly given the severity of GPP flares.	The 2017 European consensus statement on phenotypes of pustular psoriasis defines GPP as primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques). The statement also notes that GPP can occur with or without systemic inflammation, with or without psoriasis vulgaris and can either be a relapsing (greater than 1 episode) or persistent (greater than 3 months) condition.
2. Reimbursement of spesolimab for the acute treatment of a GPP flare of moderate to severe intensity, as defined by the emergence of all of the following: 2.1. GPPGA total score of at least 3 (moderate to severe GPP flare) 2.2. new or worsening pustules 2.3. GPPGA pustulation subscore greater than 2 (moderate to severe pustules) 2.4. greater than 5% BSA with erythema and the presence of pustules.	Evidence from the Effisayil-1 study demonstrated that treatment with spesolimab likely results in improved resolution of GPP flares with no visible pustules compared to placebo. In the trial, spesolimab was administered upon the emergence of a moderate to severe GPP flare, defined by criteria consistent with conditions 2.1 through 2.4.	—
3. Reimbursement of spesolimab for the prevention of GPP flares, as per the following criteria: 3.1. documented history of at least 2 GPP flares, defined by the ERASPEN criteria 3.2. GPPGA total score of 0 or 1 3.3. no identifiable, modifiable trigger of GPP flares.	Evidence from the Effisayil-2 study demonstrated that spesolimab for the prevention of flares for up to 48 weeks likely results in a benefit based on the time to first GPP flare and the proportion of patients who experienced a GPP flare compared to placebo. Patients enrolled in the Effisayil-2 study were required to have a known and documented history of GPP as per	Input from clinical experts indicated that that the following situations may trigger a flare: infections, stress, withdrawal from corticosteroid treatment, and pregnancy.

Reimbursement condition	Reason	Implementation guidance
	the ERASPEN criteria with at least 2 presentations of moderate to severe GPP flares with fresh pustulation (new appearance or worsening) in the past, and a GPPGA score of 0 or 1. The clinical experts noted that GPP flares may be triggered by changes in GPP therapies, such as immunosuppressant doses, or other factors that are modifiable to prevent future flares.	
4. Duration of initial authorization of spesolimab for the prevention of GPP flares is 6 months.	Clinical experts indicated that patients on stable therapy to prevent flares would be monitored every 3 to 6 months.	—
Renewal		
5. For reimbursement of initial renewal of spesolimab for the prevention of flares, the following must be demonstrated 6 months after initiation of spesolimab: 5.1. maintenance of GPPGA total score at initiation 5.2. reduction of flares from baseline.	Based on the assessment of the occurrence of at least 1 GPP flare in the Effisayil-2 study, treatment with spesolimab likely results in a clinically meaningful reduction in the proportion of patients having a flare event up to 48 weeks of treatment compared to placebo.	CDEC noted that for the purpose of renewal for the prevention of flares, the assessment of GPPGA total score should be performed while the patient is not actively flaring.
6. Reimbursement of subsequent renewals of spesolimab for the prevention of flares should be based on an annual assessment where the following must be demonstrated: 6.1. Sustained reduction of flares from the year before treatment to the year after treatment. For patients who experience an absolute reduction of flares in a year, less than 2 acute flares of moderate to severe intensity should be demonstrated for continued renewal.	Input from clinical experts indicated that reducing or eliminating GPP flares is an important outcome for long-term treatment. Further, a clinically meaningful response was defined as a reduction in flares per year while on treatment or less than 2 GPP flares per year.	—
Discontinuation		
7. Reimbursement of spesolimab for the prevention of GPP flares should be discontinued upon occurrence of any of the following: 7.1. need for add-on standard of care treatments for the	In the randomized maintenance treatment phase of the Effisayil-2 study, if a patient received any standard of care prescribed by the investigator due to the worsening of GPP disease, they were required to discontinue the trial treatment. As such, there is no evidence to support the use	Standard of care treatments that are used off label for GPP may include the following: biologics targeting IL (e.g., brodalumab, guselkumab, ixekizumab, secukinumab, bimekizumab, and ustekinumab); biologics targeting TNF alpha (adalimumab, certolizumab pegol, etanercept, and

Reimbursement condition	Reason	Implementation guidance
prevention of flares 7.2. worsening of GPP disease.	of spesolimab in combination with other standard of care treatments for the prevention of GPP flares.	infliximab); and nonbiologic systemic drugs (acitretin, cyclosporine, and methotrexate).
Prescribing		
8. Spesolimab should be prescribed by clinicians (dermatologists or rheumatologists) with expertise in managing GPP and other types of psoriasis.	This is meant to ensure that spesolimab is prescribed for appropriate patients.	—
Pricing		
9. A reduction in price.	The ICER for spesolimab is $431,569 when compared with no treatment. A price reduction of at least 79% would be required for spesolimab to achieve an ICER of $50,000 per QALY gained compared to no treatment	—

BSA = body surface area; CDEC = Canadian Drug Expert Committee; ERASPEN = European Rare and Severe Psoriasis Expert Network; GPP = generalized pustular psoriasis; GPPGA = generalized pustular psoriasis physician global assessment; ICER = incremental cost-effectiveness ratio; IL = interleukin; QALY = quality-adjusted life-years; TNF = tumour necrosis factor.

Discussion Points

- **Eligibility considerations for prevention of flares:** CDEC discussed whether it would be appropriate for a patient to receive SC spesolimab for the prevention of flares if they had previously experienced an acute flare that did not adequately respond to treatment with IV spesolimab. In consultation with the clinical experts, the committee concluded that in this situation, it would not be appropriate to prescribe spesolimab for the prevention of flares.
- **History of flares and eligibility for prevention of flares:** As noted under condition 3.1 (Table 1), a documented history of at least 2 GPP flares is included as 1 of the initiation criteria for spesolimab for prevention of flares. CDEC noted that in the Effisayil-2 study, the eligibility criteria related to the history of flares was based on concomitant GPP treatment at the time of randomization. Patients not receiving treatment had to have at least 2 flares in the past year, and those who started treatment12 weeks or less before randomization had to have a history of flaring on concomitant treatment or due to any of the following: dose modifications, elevated C-reactive protein or white blood cells, asthenia, and myalgia. Feedback from clinical experts indicated that the occurrence and timing of flares is unpredictable, but they also noted that patients who have had at least 2 prior flares are at a higher risk of having a third flare, especially in a situation where a trigger is known, and depending on flare severity. Given the severe nature of GPP flares and the challenge associated with anticipating the next flare, CDEC recommended that the relevant time frame to assess the history of GPP flares should be at the discretion of the treating physician.

- **No evidence for combination use**: CDEC noted the lack of evidence for the use of spesolimab in combination with off-label treatments that are used for GPP as part of standard of care before the introduction of spesolimab. The committee acknowledged the rarity of GPP and limited guidance available for the treatment of GPP, which may result in variable approaches to treatment; however, CDEC noted that in the Effisayil trials, the following medications were not permitted: biologics, phototherapy, topical corticosteroids, systemic immunomodulating treatments (e.g., corticosteroids and cyclophosphamide), tofacitinib, apremilast and other systemic psoriasis treatments (e.g., fumarates and any other drug known to possibly benefit psoriasis), photochemotherapy (e.g., psoralen plus ultraviolet A therapy [PUVA]), interleukin (IL)-36R inhibitors, and investigational products for psoriasis. As such, CDEC concluded that there is no evidence to support the use of spesolimab in combination with these treatments.
- **Evidence gaps:** CDEC discussed the importance of symptom resolution between flares, and reduction in hospitalization and mortality in the context of a condition involving potentially life-threatening flares. Pain associated with flares was identified as an outcome of interest to this review; however, the effect of spesolimab (900 mg, single-dose IV infusion) on the change in pain from baseline to week 4 based on a visual analogue scale (VAS) was considered very uncertain when compared to placebo. Regarding a reduction in hospitalization and mortality, evidence was not available to assess the impact of treatment with spesolimab on these outcomes. CDEC also noted a lack of long-term data beyond these 2 studies, particularly for the use of spesolimab for the prevention of flares which is limited to 48 weeks. Given the unpredictable and severe nature of GPP, CDEC noted it is important to continue monitoring patients and consider the risks and benefits of continued treatment.
- **Current standard of care:** CDEC discussed ethical and equity considerations related to the current reliance on off-label therapies to treat GPP flares and provide long-term maintenance. They acknowledged that patients with GPP may receive inadequate care due to the variability in access to these off-label therapeutics across jurisdictions, inconsistent efficacy in GPP, and contraindication in some patients. The committee discussed the potential that spesolimab fills an unmet need for a targeted treatment option for GPP; however, they also recognized that in the absence of comparative data, how spesolimab fills an unmet need when considered in the context of standard of care (available off-label therapies) is unclear.
- **Special populations:** CDEC discussed ethical considerations in the use of spesolimab for the treatment of acute GPP flares and long-term prevention of their re-emergence, including those related to its use in adolescents, and patients who are pregnant. They acknowledged that clinical experts noted that, while spesolimab is not intended for use in patients who are pregnant, providers may still choose to use spesolimab given the potentially life-threatening nature of acute GPP flares. Further, CDEC noted that while clinical experts expected that there is likely no difference in the efficacy of spesolimab between adolescents and adults, the safety and efficacy of IV spesolimab in patients aged 12 to 17 years is presently uncertain due to the absence of trial data for this population.

As such, the committee recognized the importance of having robust consent conversations to help adolescents, and patients who are pregnant, weigh potential risks and benefits.

- **Cost-effectiveness:** The committee discussed the economic evidence for spesolimab and noted that it was associated with 4.60 incremental QALYs at an additional cost of $1,986,465 compared to no treatment. The committee noted that current clinical practice in Canada includes several off-label treatments for both the prevention and treatment of GPP flares; however, there is no direct or indirect evidence comparing spesolimab to treatments used in clinical practice in Canada. As such, the cost-effectiveness of spesolimab compared to current clinical practice is unknown. The clinical evidence used to inform the economic model likely overestimated the treatment effect associated with spesolimab and underestimated the comparator cost by assuming no treatment or associated costs. As a result of the uncertainty in the economic evidence, the ICER estimated by Canada's Drug Agency (CDA-AMC) is uncertain.

Background

GPP is a rare, chronic, severe, and potentially life-threatening neutrophilic skin disease characterized by recurrent episodes (GPP flares) of widespread eruption of sterile, macroscopically visible pustules that occur frequently with or without systemic inflammation. Although GPP can present with chronic skin involvement (e.g., painful erythema or scaling) similar to psoriasis vulgaris, it has a distinct pathophysiology involving the dysregulation of the immune system leading to the activation of immune cells surrounding the abnormality in the IL-36 pathway. Flares are characterized by the sudden onset of rapidly disseminating cutaneous eruption and sterile pustules, crusts, and scales combined with systemic symptoms, such as fever and general malaise with fatigue. Systemic symptoms and extracutaneous manifestations such as arthritis, uveitis and neutrophilic cholangitis, acute respiratory distress syndrome, and cardiovascular septic shock often accompany significant flares. GPP onset can occur at any age, including childhood; the median age of diagnosis is approximately 50 years. Risk factors for GPP include mutations in IL-36, smoking, obesity, anxiety disorder, or recent systemic corticosteroid.

There is an urgent unmet need for treatment that resolve GPP flares and help achieve rapid and effective control of recurrent episodes in patients. In Canada, there are no published guidelines identified at the time of this review for the management and prevention of GPP flares, and spesolimab is the only treatment approved in Canada that is indicated for the treatment of GPP. Current treatment options currently used in clinical practice in Canada are indicated for psoriasis (e.g., plaque psoriasis) and used off label for GPP.

Spesolimab is a humanized antagonistic immunoglobulin G1 (IgG1) antibody that blocks IL-36 signalling by binding to IL-36R. Spesolimab has been approved by Health Canada for the treatment of GPP in adults and pediatric patients aged 12 years and older and weighing at least 40 kg. The recommended dose of spesolimab solution for infusion to treat a GPP flare is a single dose of 900 mg (two 450 mg, 7.5 mL vials) administered as an IV infusion. If flare symptoms persist, an additional 900 mg dose may be administered 1 week after the initial dose. The recommended dose of spesolimab for GPP flare prevention is an SC

loading dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) administered subcutaneously every 4 weeks. If a patient experiences a GPP flare while receiving spesolimab as prevention treatment, the GPP flare may be treated with IV spesolimab. Four weeks after treatment for a GPP flare with IV spesolimab, SC spesolimab can be initiated or reinitiated at 300 mg (two 150 mg injections) administered every 4 weeks. In this case, an SC loading dose is not required. Spesolimab has not been previously reviewed by CDA-AMC.

Sources of Information Used by the Committee

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

- a review of 2 studies: 1 randomized, placebo-controlled, double-blind, phase II trial in adults (aged 18 to 75 years) with GPP presenting with acute flares of moderate to severe intensity and 1 randomized, placebo-controlled, double-blind, phase IIb trial in adult and pediatric patients aged 12 years and older with a history of GPP
- patients' perspectives gathered by 1 patient group (the Canadian Psoriasis Network and the Canadian Association of Psoriasis Patients – consolidated as Psoriasis Canada)
- input from public drug plans that participate in the reimbursement review process
- 4 clinical specialists with expertise diagnosing and treating patients with GPP
- input from 1 clinician group (Origins Dermatology Centre)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to spesolimab.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Input was received from 1 patient group, Psoriasis Canada, a single, national, psoriatic disease organization. Psoriasis Canada gathered information from a virtual GPP summit of 7 participants, including 2 patients with diagnosed GPP, conducting interviews with 3 patients and 1 caregiver and conducting a survey with 10 respondents who were interested in attending the GPP virtual summit but were not able to do so. Psoriasis Canada explained that the severity of flares and symptoms of GPP can vary across patients and experiences. Emergency department visits or inpatient care may be required depending on the level of skin impacted and the degree of systemic involvement. More severe involvement can lead to serious complications including heart failure, renal failure, and sepsis. Psoriasis Canada added that living with GPP, even without active flares, can present challenges. For example, people with this condition may experience poor self-image, difficulty with intimacy, disruptions in school and work life, burden on personal finances, stigma and discrimination, feelings of isolation, and difficulties accessing diagnosis, care, and treatment throughout different times in their lives. Psoriasis Canada explained that patients' lives can be completely

disrupted during GPP flares as a result of missing work, being bedridden, being hospitalized, and being dependent on caregivers during severe flares.

Psoriasis Canada noted that important treatment outcomes reported by patients with GPP are symptom reduction, reduced frequency and severity of flares, management of symptoms between flares, access to appropriate care and treatment, and the ability to control GPP to reduce the stress about the next flare.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

According to the clinical experts consulted during the review, there is an unmet need for new treatments that rapidly resolve flare symptoms during acute flares and also prevent GPP flares from reoccurring. Prior to the Health Canada approval of spesolimab, treatment options used in clinical practice to resolve acute flares and prevent recurrent flares were treatments indicated for plaque psoriasis and used off label for patients with GPP. The experts consulted noted examples of treatments that are used in the acute flare setting, which include methotrexate, cyclosporine, and acitretin. Other treatments preferentially considered for patients presenting with life-threatening flares were fast-acting biologics indicated for psoriasis such as biologics that target IL-17 (e.g., secukinumab, ixekizumab, bimekizumab, and brodalumab) or tumour necrosis factor (TNF) alpha (e.g., adalimumab, certolizumab pegol, or infliximab). For long-term control and flare prevention, the experts noted that oral therapies or biologics such as those that target IL-23 or IL-12 and IL-23 (e.g., risankizumab, guselkumab, or ustekinumab) are considered.

The ideal treatment goal for acute flares is one that will resolve flares; improve erythema, pustulation, and accompanying systemic symptoms (such as fever and arthritis); and prevent mortality. For patients with a history of recurrent GPP flares, or for those with the risk of GPP flares, the ideal treatment goal will be to limit flares and reduce pain which will eventually lead to improved patient quality of life.

The experts anticipate that spesolimab will shift the current GPP treatment paradigm. According to the experts, spesolimab would be appropriate as first-line therapy for the treatment of flares and the prevention of flares in patients with a definitive diagnosis of GPP due to its unique mechanism of action, an IL-36 receptor inhibitor designed to treat and prevent GPP flares.

The experts highlighted that spesolimab will be appropriate for patients presenting with an acute flare of GPP. According to the experts, it would be best not to reserve this medication for those who are intolerant to other options or for whom other medications are contraindicated given the rapid onset of GPP and the associated risks of undertreatment, including hospitalization, respiratory failure, septic shock, and death. For flare prevention, spesolimab would also be appropriate for patients for whom no modifiable trigger was identified for the flare of GPP, given that flares can be associated with abrupt withdrawal of immunosuppressive medications such as prednisone or cyclosporine, and other medications such as terbinafine or amoxicillin.

According to clinical experts, the evaluation of the response to therapy in clinical practice will be based on whether patients are being treated for an acute flare or if the goal is to prevent the reoccurrence of flares.

The experts noted that resolving erythema and pustulation, including skin pain and systemic symptoms, will be an ideal therapeutic outcome for acute flares. The experts noted that given the spectrum and severity of GPP, a meaningful response requires near-complete resolution of the flare to eliminate the risk of severe complications that may require hospitalization and place the patient at increased risk of mortality. A reduction in mortality associated with GPP would also be considered a good measure of the success of a therapy on a population level. The experts indicated that spesolimab may be discontinued after the resolution of an acute flare, although if there is a history of recurrent flares or the patient is at a higher risk of another GPP flare, spesolimab may be used after the acute flare to prevent the recurrence of flares. The experts expressed that a physician, such as a dermatologist with expertise in the diagnosis and experience in the treatment of GPP and other subtypes of psoriasis, is necessary for treating and managing GPP.

Clinician Group Input

One clinician group provided input for this submission, the Origins Dermatology Centre. The Origins Dermatology Centre services urban, rural, and Indigenous populations in an underserviced area, focusing on medical and general dermatology. One clinician was the author of this input, who gathered information from literature resources, clinical experience, and input from experienced nurses.

According to the Origins Dermatology Centre, treatment goals would include fast control of acute flares, controlling signs and symptoms (e.g., fever, malaise, pain, itch, swelling, and pustules), and controlling and preventing systemic worsening or collapse as a part of the disease process. Long-term goals would include encouraging sustained responses, including preventing flares, keeping patients out of the hospital, disease control, improving quality of life impact, and creating a favourable and advantageous safety profile.

The Origins Dermatology Centre explained that in Canada, there are no current guidelines or approved therapies for the treatment of GPP until spesolimab became available. Current off-label systemic treatments (systemic immunosuppressants and biologic therapy) for plaque psoriasis have proven inadequate to control chronic and acute forms of GPP. The Origins Dermatology Centre added that based on a survey reported by Strober et al. (2021), dermatologists treating GPP reported that there are high rates of relapse with current off-label therapies, and treatments are slow to control flares. Further, most patients will relapse within 1 year of treatment. The clinician group also noted that the use of broad oral systemic immunosuppressants often used for this condition comes with side effects such as cytopenia, liver and renal toxicity, and increased risk of infection among others (e.g., methotrexate or cyclosporine) which limits both their short- and long-term use in this disease.

The Origins Dermatology Centre stated that there is an unmet need for approved, studied, safe, and effective targeted options for the treatment of patients living with GPP. The clinician group believed that the drug under review would be a first-line therapy for those diagnosed with GPP, noting that patients experiencing active disease, flares, systemic symptoms, and hospitalization would be most in need of intervention.

According to the Origins Dermatology Centre, clinical response over time, disease progression, and adjunctive therapy use may be considered when deciding to discontinue treatment with spesolimab.

Based on the clinician group input, hospitals and IV infusion clinics are the appropriate setting for treatment with spesolimab, and once the diagnosis is confirmed, specialists in the field of dermatology, internal medicine, and emergency medicine could prescribe and monitor effectively.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for spesolimab:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues.

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	
The sponsor states that reimbursed treatments are currently used off label in practice in Canada, which would include biologic drugs and nonbiologic systemic drugs. However, the Health Canada drug product monographs for methotrexate and cyclosporine do not define the type of psoriasis indicated, other than stating for severe, disabling psoriasis. This could be interpreted to mean they are indicated for severe psoriasis of any subtype, including GPP which is a severe form of psoriasis. Similarly, the Health Canada drug product monograph for acitretin notes it is indicated for severe psoriasis, including pustular types. 1. Would you agree that there are no off-label comparators used in Canada for the treatment or prevention of GPP flares, suitable for comparison to spesolimab? 2. If you disagree, which medication(s) do you feel would be a suitable comparator?	1. The clinical experts highlighted that no other medications have been specifically studied for treating and preventing GPP flares. Conventional therapies are indicated for other diseases and are used off label for GPP. The experts noted that although the product monographs for methotrexate and cyclosporine highlight potential use in psoriasis vulgaris, psoriasis does not encompass GPP, and there is no direct evidence of their efficacy in patients with GPP. 2. The experts cited the availability of evidence supporting the use of off-label biologics in GPP. The expert considered the following suitable comparators. Biologics targeting IL (e.g., brodalumab, guselkumab, ixekizumab, secukinumab, bimekizumab, and ustekinumab); biologics targeting TNF alpha (adalimumab, certolizumab pegol, etanercept, and infliximab); and nonbiologic systemic drugs (acitretin, cyclosporine, and methotrexate). CDEC defers to the expertise of the clinical experts. CDEC notes that the Health Canada monograph for methotrexate includes the following indication “Severe disabling psoriasis/psoriatic arthritis.”

Drug program implementation questions	Response
Many of the therapies historically used for treatment of GPP are reimbursed for plaque psoriasis and include biologics that target IL and TNF alpha, in addition to nonbiologic medications such as acitretin, cyclosporine, and methotrexate. Access to public funding is limited, given the reimbursed indication for restricted biologic therapies is plaque psoriasis.	Comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
There is a 2017 European consensus statement by ERASPEN to define diagnostic criteria; however, there is a lack of consensus among experts in Canada, resulting in diagnosis relying on expert examination. The reimbursement request includes the use of a GPPGA scoring system, requiring patients presenting with acute flares to have a GPPGA total score of greater than or equal to 2. The GPPGA is the Generalized Pustular Psoriasis Physician Global Assessment score. 1. Is the GPPGA currently used in clinical practice? 2. Are there potential barriers to asking for this score? 3. Should any other scores, such as DLQI, be obtained as a baseline?	1. The clinical experts highlighted that GPPGAs are currently not used in clinical practice for GPP. The experts noted the following barriers to not using the scoring system: limited time allotted for individual patient appointments and lack of familiarity with the score. 2. The experts anticipate that clinicians will adopt the GPPGA scoring system if this is a prerequisite for patient access to treatment. 3. The experts indicated that DLQI and PSS are ancillary scores that can support GPPGA scores in assessing treatment success. However, these outcomes will not supersede GPPGA. For example, 1 of the clinical experts indicated that the DLQI scores may be considered less relevant given that the majority of patients with GPP will be managed in the setting of an acute flare. Considering the severe and life-threatening nature of an acute flare, the clinical expert suggested that the patient is unlikely to have clearly defined opinions related to how their skin impacts their daily life over the last 7 days. CDEC notes that based on the clinical trial data, GPPGA appears to be the most reliable assessment.
The requested indication is for the treatment and prevention of flares in both adult and pediatric patients aged ≥ 12 years; however, patients younger than 18 years were excluded from the Effisayil-1 study. In addition, patients weighing less than 40 kg were excluded from the preventive treatment study (Effisayil-2). • Regarding the weight restriction for patients weighing less than 40 kg, do you have safety concerns, and do you see this as a potential barrier to treatment?	Despite the weight limitations outlined in the studies, the experts consulted did not anticipate safety concerns for using spesolimab to treat patients aged 12 years and older with GPP. The experts cited evidence on biologics used to treat psoriasis and atopic dermatitis, showing no clinically meaningful differences between adolescents and adults. CDEC defers to the expertise of the clinical experts. CDEC also notes that the Health Canada–approved indication for patients aged at least 12 years and weighing at least 40 kg.
The Effisayil trials had a multitude of exclusions with regards to comorbidities, including the following conditions: • patients with SAPHO syndrome, primary erythrodermic psoriasis vulgaris, or AGEP triggered by drug usage • patients with primary plaque psoriasis vulgaris without presence of pustules or with pustules that were restricted to psoriatic plaques • patients with severe, progressive, or uncontrolled hepatic disease (defined as > 3-fold ULN elevation in AST or ALT or alkaline phosphatase, or > 2-fold ULN	1. The clinical experts consulted were not concerned that the comorbidities listed as exclusion criteria in both trials (Effisayil-1 and Effisayil-2) would impact spesolimab use in patients with GPP in current practice. According to the experts, GPP is a life-threatening condition; thus, treatment will be chosen based on the potential risk of death from acute flares. The experts stated that some patients in their practice have died from using methotrexate, but they have not reported cases of mortality associated with the use of an IL-23 inhibitor. 2. According to the experts, patients with severe active infections such as TB, viral hepatitis, or systemic bacterial or fungal infections would not be suitable candidates for spesolimab. There

Drug program implementation questions	Response
elevation in total bilirubin) • patients with congestive heart disease • patients with active systemic infections (fungal and bacterial disease) during the last 2 weeks before receiving first drug administration • patients at increased risk of infectious complications • patients with relevant chronic or acute infections including HIV or viral hepatitis • patients known to have active or latent TB. 1. Do you feel the conditions listed as exclusions in the Effisayil trials would be contraindications to the use of spesolimab? 2. If not all, which ones would you consider to be contraindications?	is also evidence showing that spesolimab may cause liver injury. Therefore, patients with severe, progressive, or uncontrolled hepatic disease would be contraindicated. Patients with heart failure would also be contraindicated due to the volume of fluid infused associated with treatment with spesolimab. The expert noted that GPP flare onset is progressive and nonresponsive to traditional therapies; thus, treating physicians must weigh the risk of death due to GPP vs. the risk of medication administration. In this scenario, the only absolute contraindication would be anaphylaxis to spesolimab. CDEC defers to the expertise of the clinical experts.
There are no guidelines for treatment of GPP and all traditionally used treatments are considered by the sponsor to be off label. • Are there any treatments you would expect to use before initiating treatment with spesolimab?	The clinical experts indicated that spesolimab will be used as first-line therapy. The experts noted that a trial-and-error scenario with other drugs was not recommended due to the severity and potential life-threatening nature of GPP flares. In flare prevention, the clinical experts stated that due to the paucity of studies looking at alternative drugs for GPP flare prevention, there is uncertainty as to whether other drugs should be used before initiating treatment with spesolimab. One expert noted that biologics approved for psoriasis have been used successfully for GPP flare prevention in jurisdictions like Japan. Therefore, the choice of therapy for flare prevention will depend on cost and access to treatment. The experts also noted that if spesolimab is available at the same price as other biologics, they will opt for spesolimab as the first-line treatment. In a scenario where difficulties exist in accessing spesolimab, they will consider other drugs indicated for psoriasis for long-term flare prevention. CDEC defers to the expertise of the clinical experts.
Consider alignment with biologic drugs previously granted a positive recommendation through CDEC for the indication of plaque psoriasis, with regards to the need for establishing baseline characteristics for assessing response to treatment. For example, PASI vs. GPPASI, and DLQI or other comparable parameters.	Comment from the drug programs to inform CDEC deliberations.
Considerations for continuation or renewal of therapy	
It is unclear what outcomes would be useful for assessing continuation of therapy as many were used in the studies. 1. Which ones would be applicable in real-world practice settings? GPPGA, GPPASI 75, absence or reduction of flares, PSS, DLQI, or others. 2. How should clinically meaningful response be defined using objective parameters?	1. According to the experts, any treatment should be geared toward achieving a GPPGA of 0 or at least a complete resolution of erythema and pustulation. The experts further stated that desquamation may continue for longer periods and thus may not be a good marker of treatment success. 2. Both experts considered reducing or eliminating flares an important outcome for long-term treatment. One expert noted that they would objectively define a clinically meaningful response as the absolute reduction of flares (i.e., flares per year before spesolimab minus flares per year with spesolimab) or less

Drug program implementation questions	Response
	than 2 flares per year. PSS or DLQI were considered valuable assessments but would not supersede the clinical assessment. CDEC defers to the expertise of the clinical experts.
Consider alignment with biologic drugs previously granted a positive recommendation through CDEC for the indication of plaque psoriasis, with regards to requiring PASI or GPPASI, DLQI, or other comparable parameters.	Comment from the drug programs to inform CDEC deliberations.
Considerations for discontinuation of therapy	
The trial treatment was discontinued upon the initiation of drugs prescribed by an investigator, with exceptions of treatments such as topical steroids, methotrexate, cyclosporine, retinoids during the flare treatment periods (4 weeks after IV infusion, day 1). • At what point would you choose to discontinue treatment with spesolimab?	The clinical experts noted that treatment discontinuation with spesolimab will depend on the treatment phase. In a scenario where spesolimab is used to treat flares, both experts noted that discontinuation would occur after 1 or 2 infusions (2 doses), 1 week apart from each other in the case of a complete response, as measured by GPPGA = 0. In a scenario where spesolimab is used to treat and prevent relapse or flares, the experts agreed to discontinue treatment if there was no significant change from baseline in flare recurrence. The experts noted that treatment would be discontinued if a patient has experienced 2 or more flares at 3 to 6 months of treatment or there is a lack of overall clinical improvement (based on GPPGA or GPPASI scores). CDEC defers to the expertise of the clinical experts.
Consider aligning with biologics previously granted a positive recommendation through CDEC for the indication of plaque psoriasis, with regards to requiring PASI or GPPASI, DLQI, or other comparable parameters.	Comment from the drug programs to inform CDEC deliberations.
Considerations for prescribing of therapy	
As per the drug product monograph, treatment with spesolimab should be initiated by physicians experienced in the management of patients with inflammatory skin diseases. This is a rare disease, with an estimated prevalence of 2.77 cases per million individuals in Canada. Depending on the amount of specialized training required, accessing an experienced physician may be challenging in some areas.	Comment from the drug programs to inform CDEC deliberations.
At this time, most therapies used for GPP are considered off label with only SOC being publicly available. • Are there any biologic or systemic therapies that you would expect to be used in combination with spesolimab?	Both experts consulted highlighted that there are patients in practice who have concurrent psoriasis that also appear to be prone to GPP flares. According to the experts, these patients will require other therapies in addition to spesolimab to control the totality of the psoriasis. The experts anticipate that a portion of patients treated with spesolimab will require adjuvant or combination therapy with biologics or oral drugs geared at treating psoriasis, some will include biologics targeting IL (e.g., brodalumab, guselkumab, ixekizumab, secukinumab, bimekizumab, risankizumab, and ustekinumab), biologic drugs targeting TNF alpha (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab); nonbiologic systemic drugs (acitretin, cyclosporine, and methotrexate), and phototherapy. The experts also noted that in the event of treatment failure with

Drug program implementation questions	Response
	spesolimab, medications including acitretin, cyclosporine, and anti-psoriasis biologics will be started to manage an acute flare. The experts noted that for GPP flare prevention, they do not anticipate any medications to be used in combination. CDEC defers to the expertise of the clinical experts.
Generalizability	
Can patients with GPP who are currently in remission on an off-label biologic drug transition to spesolimab?	According to clinical experts, patients could be transitioned from an off-label biologic to spesolimab; however, the experts do not anticipate this scenario happening frequently. Both experts noted that if patients are doing well on an off-label biologic and are currently in remission, they will not advise transitioning patients to spesolimab unless in the event of a flare. CDEC defers to the expertise of the clinical experts.
Care provision issues	
The IV spesolimab requires access to a hospital or infusion clinic for administration by a trained health care professional. The SC spesolimab does require training, for patient or caregiver, to administer.	Comment from the drug programs to inform CDEC deliberations.
Anti-TB medication should be considered before initiating spesolimab in patients with latent TB or a history of TB in whom an adequate course of treatment cannot be confirmed.	Comment from the drug programs to inform CDEC deliberations.
System and economic issues	
The BIA was developed to encompass the full Health Canada indication rather than the requested deviation to the indication. This may affect the actual impact.	Comment from the drug programs to inform CDEC deliberations.
The sponsor has noted that they are offering a patient support program which will limit the impact on public funded health care resources during treatment of flares with IV spesolimab and noted that the patient support program will also be available for the preventive treatment with SC spesolimab. The program limitations remain undefined.	Comment from the drug programs to inform CDEC deliberations.

AGEP = acute generalized exanthematous pustulosis; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CDEC = Canadian Drug Expert Committee; DLQI = Dermatology Life Quality Index; ERASPEN = European Rare and Severe Psoriasis Expert Network; GPP = generalized pustular psoriasis; GPPASI = Generalized Pustular Psoriasis Area and Severity Index; GPPGA = Generalized Pustular Psoriasis Physician Global Assessment; IL = interleukin; PSS = Psoriasis Symptom Scale; SC = subcutaneous; SOC = standard of care; SAPHO = synovitis, acne, pustulosis, hyperostosisosteitis, and osteitis; TB = tuberculosis; TNF alpha = tumour necrosis factor alpha; ULN = upper limit of normal; vs. = versus.

Clinical Evidence

Systematic Review

Description of Studies

The systematic review included 2 pivotal studies (Effisayil-1 and Effisayil-2). Effasyil-1 evaluated the use of IV spesolimab as a treatment for acute GPP flares whereas Effsayil-2 evaluated the use of SC spesolimab for the prevention of flares.

Effisayil-1 is a multicentre, randomized, placebo-controlled, double-blind, phase II trial designed to evaluate the efficacy, safety, and tolerability of IV spesolimab administered as a single dose compared to placebo in adults (aged 18 to 75 years) with GPP presenting with an acute flare of moderate to severe intensity who had received a diagnosis of GPP as per the ERASPEN criteria. Patients were randomized to treatment with spesolimab or placebo if they experienced a GPP flare of moderate to severe intensity, defined by the emergence of the following: a GPPGA total score of 3 or more, new or worsening pustules, a GPPGA pustulation subscore of 2 or more, and involvement of 5% or more of the body surface area with erythema and the presence of pustules. Patients were enrolled across 37 centres in 12 countries, with none in Canada. In total, 53 patients who presented with a GPP flare of moderate to severe intensity were randomized (2:1) to receive either IV spesolimab (900 mg, single dose) (n = 35 patients) or placebo (n = 18 patients). The primary end point was the proportion of patients with a GPPGA pustulation subscore of 0 at the end of week 1. The key secondary end point assessed the proportion of patients with a GPPGA total score of 0 or 1 at the end of week 1. Other secondary end points of note for this review included change from baseline in pain VAS. The final database lock date was April 1, 2021. The mean age in the spesolimab group was 43.2 years versus 42.6 years in the placebo group. In total, 60.0% and 83.3% of participants were female (40.0% and 16.7% were male) in the spesolimab and placebo groups, respectfully. Numerical differences were observed in both arms of the trial in race (people of Asian ethnicity, 45.7% for spesolimab and 72.2% for placebo; white, 54.3% for spesolimab and, 27.8% for placebo); GPPGA pustulation subscore (score of 2, 17.1% for spesolimab versus 27.8% for placebo; score of 3, 45.7% for spesolimab versus 38.9% for placebo; score of 4, 37.1% for spesolimab versus 33.3% for placebo), and past or present occurrence of psoriasis (yes, 68.6% for spesolimab versus 77.8% for placebo).

Effisayil-2 is a multicentre, randomized, placebo-controlled, double-blind, phase IIb dose-finding study designed to evaluate the efficacy and safety of SC spesolimab for the prevention of GPP flares in adult and pediatric patients aged 12 years and older with a history of GPP. Three doses were evaluated: low dose (spesolimab 300 mg loading dose followed by maintenance treatment of 150 mg every 12 weeks as SC injections), medium dose (spesolimab 600 mg loading dose followed by maintenance treatment of 300 mg every 12 weeks as SC injections), and high dose (HD) (spesolimab 600 mg loading dose followed by 300 mg subcutaneously, administered every 4 weeks). Only efficacy results for the HD have been reported for this review as the other doses were not included under the recommended dosage approved by Health Canada. Patients enrolled in the Effasyil-2 study were required to have a known and documented history of GPP, experienced at least 2 GPP flares, and a GPPGA score of 0 or 1 (clear or almost clear) at randomization. Patients were also required to be between the ages of 12 and 75 years with a documented history of

GPP per the ERASPEN criteria. The study was conducted across 71 sites in 23 countries, with no sites in Canada. In total, 30 patients were randomized into the HD group and 31 patients into the placebo group. The primary hypothesis was a dose-finding assessment followed by the assessment of time to the first GPP flare at week 48 and a key secondary end point of the proportion of patients with at least 1 GPP flare at week 48. The final database lock date was January 13, 2023. Patients who were enrolled were between the ages of 14 to 75 years (8 patients were adolescents). The mean (standard deviation [SD]) age at randomization in the HD spesolimab group was 40.2 years (16.4) versus 39.5 years (14.0) for placebo; 70.0% versus 54.8% of patients identified as Asian, 30.0% versus 45.2% were white, 3.3% versus 9.7% were of Hispanic or Latino ethnicity, 60.0% versus 58.1% were female, and 40.0% versus 41.9% were male in the HD spesolimab and placebo groups, respectively. At baseline, the mean weight was 68.7 kg (SD = 22.9) versus 75.73 kg (SD = 23.92) and body mass index was 25.6 kg/m^2 (SD = 7.3) versus 26.9 kg/m^2 (SD = 8.3) in the HD spesolimab and placebo groups, respectively. The proportion of patients who had a GPPGA pustulation score of 0 (clear) was 67.7% in both the HD spesolimab and placebo groups, and a GPPGA pustulation score of 1 (almost clear) was 33.3% in the HD spesolimab group and 32.3% in the placebo group. The mean (SD) Dermatology Life Quality Index (DLQI) total score was 11.1 (6.9) in the HD spesolimab group versus 7.2 (5.6) in the placebo group. Numerical differences were observed in the HD spesolimab group compared to the placebo group for race (proportion of patients of Asian ethnicity, 70% in the HD spesolimab group versus 54.8% in the placebo group), concurrent plaque psoriasis (23.3% in the HD spesolimab group versus 32.3% in the placebo group), presence of potential pathogenic IL-36RN variation (23.3% in the HD spesolimab group versus 12.9% in the placebo group), and prior use of at least 1 biologic therapy (20% in the HD spesolimab group versus 29% in the placebo group).

Patients who completed treatment with spesolimab in both trials were permitted to participate in the Effisayil-ON long-term, open-label extension trial; however, results were not available at the time of this review.

Efficacy Results

Effisayil-1

The Proportion of Patients With a GPPGA Pustulation Subscore of 0 at Week 1

Clinical experts, patient groups, and other interested parties considered a GPPGA pustulation subscore of 0 (i.e., no visible pustules) a critical outcome for decision-making and deliberations. At the April 1, 2021, data cut-off date, the primary objective of the Effisayil-1 trial, the proportion of patients with GPPGA pustulation subscore of 0, was met. More specifically, 54.3% of patients who received a single dose of IV spesolimab experienced an improvement in flare resolution (GPPGA pustulation subscore of 0) 1 week following treatment compared to 5.6% of patients who received placebo, corresponding to a risk difference of 48.7% (95% CI, 21.5% to 67.2%; P = 0.0004) in favour of spesolimab. Three sensitivity analyses were carried out on the primary end point (specifically using alternative methods to handle missing data, and analysis of additional estimands [where death or any use of escape medication, before observing the week 1 primary end point was considered a nonresponse]). Findings from all sensitivity analyses were consistent with the main analysis of the primary end point.

The Proportion of Patients With a GPPGA Total Score of 0 or 1 at Week 1

A GPPGA total score of 0 or 1 (i.e., clear or almost clear skin) was also identified as an outcome of importance to clinical experts, patient groups, and clinician groups. In total, 42.9% of patients who received single dose IV spesolimab achieved clear or almost clear skin (i.e., GPPGA total score of 0 or 1) after 1 week compared to 11.1% of patients in the placebo group corresponding to a risk difference of 31.7% (95% CI, 2.2% to 52.7%; P = 0.0118) in favour of spesolimab. The sensitivity analyses that were conducted were consistent with the main analysis.

Change From Baseline in Pain VAS Score at Week 4

Pain VAS scores were identified as a clinically important patient-reported outcome. In total, 88.9% of patients in the placebo group were considered nonresponders for pain VAS score compared to 42.9% in the spesolimab group due to the use of escape medication, open-label (OL) spesolimab at day 8, or rescue medication with spesolimab before week 4. There was a decrease in median change from baseline of −22.45 in the spesolimab group, representing a decrease in pain, whereas in the placebo group, the median was not calculable due to the use of escape medication, open-label spesolimab at day 8, or rescue medication with spesolimab before week 4.

Effisayil-2

By the January 13, 2023, data cut-off, confirmatory testing of the secondary objective was conducted.

Time to First the GPP Flare-Up to Week 48

The time to first GPP flare-up was considered a critical outcome by clinical experts, patient groups for decision-making, and deliberations regarding GPP flare prevention in adults and pediatric patients aged 12 years and older. As per the analysis of time to first GPP flare following 48 weeks of treatment, the risk of GPP flare was lower among patients who received SC spesolimab relative to patients who received placebo, based on an HR of 0.157 (95% CI, 0.046 to 0.541; P = 0.0005). Four sensitivity analyses (to assess whether the use of rescue medication with spesolimab or investigator-prescribed standard of care (SOC) was considered a GPP flare [i.e., event or treatment failure]) were conducted for the primary end point. Findings from all sensitivity analyses were consistent with the main analysis of the primary end point.

Occurrence of 1 or More GPP Flare-Up to Week 48

The proportion of patients experiencing 1 or more flares was also considered a critical outcome by clinical experts, patient groups, and other interested parties for decision-making and deliberations for GPP flare prevention in adults and pediatric patients aged 12 years and older. The key secondary end point was met by the January 13, 2023, data cut-off date. The estimated adjusted risk difference by week 48 was −39.0% (95% CI, −62.1% to −15.9%; superiority P = 0.0013) in favour of the HD spesolimab group than the placebo group.

Time to First Worsening of DLQI Up to Week 48

Health-related quality of life (HRQoL) was assessed based on the time to first worsening of DLQI to 48 weeks following initiation of treatment with SC spesolimab. Of note, first worsening of DLQI was defined as a 4-point increase in total score from baseline. Use of rescue medication, or investigator-prescribed SOC,

was also considered as the onset worsening of HRQoL. Patient groups identified HRQoL as an outcome of importance. In total, in the HD spesolimab group and in the placebo group, 27 patients had a DLQI worsening up to week 48 of treatment. In total, 23% of patients in the HD spesolimab group reported DLQI worsening at up to week 48 compared to 65% in the placebo group. The estimated HR for risk of DLQI worsening up to 48 weeks was 0.259 (95% CI, 0.109 to 0.620). The estimated risk difference for DLQI worsening in the HD spesolimab group versus the placebo group was −42.4% (95% CI, −64.3% to −20.4%) in favour of the HD spesolimab group.

Harms

Effisayil-1

In Effisayil-1, adverse events (AE) were reported before the nonrandomized administration of spesolimab and up to week 1 (herein referred to as the week 1 analysis) and following any spesolimab up to week 12 in addition to the residual effect period (herein referred to as the week 12 analysis). Of note, the week 12 analysis included AEs observed in patients following treatment with any spesolimab verum (double-blind or nonrandomized) up to 16 weeks after the last spesolimab administration, end of study, or treatment in the extension trial, whichever was earlier.

Based on the week 1 analysis, the incidence of AEs of any grade was numerically higher in the spesolimab group (77.1%) compared to the placebo group (66.7%) before administering nonrandomized spesolimab. The most frequently reported AEs during week 1 were pustular psoriasis (37.1% in the spesolimab group versus 38.9% in the placebo group) and pyrexia (5.7% in the spesolimab group versus 22.2% in the placebo group). Overall, most AEs were mild (grade 1) or moderate (grade 2), while the AEs of 2 patients (11.1%) in the placebo group and 6 patients (17.1%) in the spesolimab group were classified as severe (grade 3). Grade 3 AEs in the spesolimab group included anemia, pustular psoriasis, and arthritis during week 1. Based on the week 12 analyses (after receiving any spesolimab) (i.e., at randomization, on day 8 as OL spesolimab, or as rescue treatment later), 91.4% of patients initially randomized to spesolimab and 93.8% of patients initially randomized to placebo on day 1 experienced at least 1 AE up to week 12. The most frequently reported AEs overall up to week 12 were pustular psoriasis (57.1% in the spesolimab group versus 43.8% in the placebo group), pyrexia (8.6% in the spesolimab group versus 12.5% in the placebo group), and vomiting (11.4% in the spesolimab group versus 6.3% in the placebo group).

For the week 1 analysis, the most frequently reported serious AE (SAE) overall was pustular psoriasis (11.4% in the spesolimab group versus 16.7% in the placebo group). All other SAEs (arthritis, drug-induced liver injury, drug reaction with eosinophilia and systemic symptoms [DRESS] and urinary tract infection) were only experienced by 1 patient in each category. After receiving spesolimab, the most frequently reported SAEs were pustular psoriasis and DRESS in 9 and 2 patients, respectively. One patient in the spesolimab group was reported as having experienced AE of special interests (drug-induced liver injury and DRESS) before the administration of nonrandomized spesolimab. After receiving any spesolimab (randomized or rescue), 1 patient initially randomized to placebo on day 1 experienced latent tuberculosis. No patients discontinued treatment due to AEs and deaths were reported in the study.

Effisayil-2

The proportion of patients experiencing any AEs were comparable in both groups (86.7% in the HD spesolimab group and 86.7% in the placebo group). The most frequently reported AEs (≥ 10% in either group) were pustular psoriasis (10.0% patients receiving HD spesolimab versus 53.3% placebo), psoriasis (13.3% for HD spesolimab versus 10.0% placebo), and injection site erythema (16.7% in HD spesolimab versus 3.3% placebo). Overall, most patients experienced AEs of mild (grade 1) or moderate (grade 2) intensity. The most frequently reported AE of the worst intensity (grade 3) overall was pustular psoriasis, reported in 9 patients (9.7%) in the combined spesolimab dose groups and 4 patients (13.3%) in the placebo group.

In total, 10% of patients with HD spesolimab and 3.3% of patients with placebo reported 1 or more SAEs during the randomized treatment period of the study. The most reported SAE was pustular psoriasis (3.2%) in the total spesolimab group (1 patient in each spesolimab dose group) compared to none in the placebo group. SAEs reported in the HD spesolimab group included pustular psoriasis, breast cancer, and cholelithiasis (1 patient each). AEs of special interest were not reported in the HD spesolimab group. AEs leading to study discontinuation occurred in 10% of patients treated with HD spesolimab, and included pustular psoriasis, psoriasis, and breast cancer (1 patient, 3.3% for each AE) — no patients in the placebo group discontinued treatment due to AEs. There were no reports of death during the study.

Critical Appraisal

Effisayil-1 and Effisayil-2 were multicentre phase II and IIB randomized controlled trials (RCTs), respectively. The risk of bias related to randomization and treatment allocation concealment was considered low in both studies. There were numerical differences observed in some factors in both studies (Effisayil-1: sex, race, GPPGA pustulation subscore and present or past occurrence of psoriasis; Effisayil-2: race, concurrent plaque psoriasis, IL-36RN variation, GPPGA total score and prior use of at least 1 biologic therapy), possibly due to the small sample size, which was expected due to the rarity of the disease. The clinical experts consulted during the review did not anticipate that these noted differences would bias findings.

Both trials were double-blind, and steps were implemented to maintain blinding of patients and investigators before data cut-offs. However, there is the potential that patients could have inferred the group to which they were assigned, evidenced by differences observed in efficacy and harms in the spesolimab group relative to the placebo group. The presence and direction of any bias is uncertain. Statistical analyses for the primary outcome in Effisayil-1 were based on the exact Suissa–Shuster z pooled test, and analyses in Effisayil-2 were based on the stratified Cochran-Mantel-Haenszel test, using the intention to treat population. Missing data were imputed as nonresponders (for binary outcomes), and the last observation carried forward method was used for continuous outcomes. The statistical tests implemented in both studies were considered appropriate. Sensitivity analyses conducted in both trials showed that missing data were unlikely to bias the results for the primary outcome. Outcomes investigated in both trials were generally accepted and aligned with clinical practice.

Concerning external validity, the characteristics of the patients enrolled in both trials were considered representative of patients in Canada. Most patients enrolled across the 2 trials identified as Asian or white.

No key patient groups were excluded. Both trials excluded patients with different conditions, such as synovitis, acne, pustulosis, hyperostosisosteitis, and osteitis (SAPHO) syndrome, primary erythrodermic psoriasis vulgaris, and acute generalized exanthematous pustulosis triggered by drug usage, which may impact the generalizability of findings from both trials to that patient population in current practice. However, the clinical experts consulted did not anticipate that these exclusion criteria would impact the generalizability of findings to patients in current practice. In both trials, placebo was the comparator without an approved treatment for GPP. Placebo was considered an appropriate comparator in both trials since current drugs used for the treatment of GPP in practice are indicated for plaque psoriasis and currently used off label for GPP. The use of other SOC therapies (biologics and systemic modulating drugs for GPP and other conditions such as plaque psoriasis) was restricted in the randomized phase of both trials but allowed as rescue therapy in scenarios where patients experienced a flare recurrence or did not improve following treatment with spesolimab. These procedures were considered appropriate and aligned with the approved Health Canada product monograph. The experts anticipate that a few patients will require up to 2 doses of IV spesolimab in practice to ensure complete resolution of flares. The experts also noted that patients with concomitant comorbidities (plaque psoriasis) may require other medications to treat their symptoms other than GPP flare. The treatment assessment duration in the trials was considered appropriate and reflective of clinical practice. There was limited information at the time of this review to conclude on the long-term efficacy and safety of spesolimab for patients living with GPP, as the open-label study which enrolled patients from Effisayil-1 and Effisayil-2 is ongoing.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform the CDA-AMC's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refer to internal validity or risk of bias), indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of a clinically important effect based on the threshold informed by the clinical expert consulted by CDA-AMC for the following outcomes: the proportion of patients with GPPGA pustulation subscore of 0, the proportion of patients with GPPGA total score of 0 or 1, change from baseline in pain VAS scores, and time to worsening of the DLQI up to week 48. The clinical experts could not provide a clinically meaning threshold for time to first GPP flare, the proportion of patients with the occurrence of 1 or more GPP flares, and SAEs; thus, the null was used.

Results of GRADE Assessments

The GRADE assessments included an evaluation of the main outcomes considered important by clinicians, patient groups, and interested parties. The selection of outcomes for the 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. The following list of outcomes was finalized in consultation with expert committee members. The selection of outcomes for the 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. The following list of outcomes was finalized in consultation with expert committee members and was assessed using GRADE: the proportion of patients with GPPGA pustulation subscore of 0, the proportion of patients with GPPGA total score of 0 or 1, change from baseline in pain VAS scores, time to first GPP flare, and the proportion of patients with the occurrence of 1 or more GPP flares, time to worsening in DLQI, and SAEs.

Table 3 and Table 4 present the GRADE findings for spesolimab versus placebo for the Effisayil-1 and Effisayil-2 studies, respectively.

Table 3: Summary of Findings for Spesolimab Versus Placebo for the Treatment of Acute GPP Flares in Adults (Effisayil-1)

Outcome and follow-up	Patients (studies), N	Relative effect	Absolute effects			Certainty	What happens
			Placebo	Spesolimab	Difference		
GPPGA pustulation subscore							
Proportion of patients with a GPPGA pustulation subscore of 0 Follow-up: 1 week	53 (1 RCT)	NR	6 per 100	54 per 100 (95% CI, 38.2 to 69.5)	49 more per 100 (from 22 more to 67 more)	Moderate[a]	Spesolimab (900 mg single dose, infusion) likely results in a clinically meaningful increase in the proportion of patients with a GPPGA pustulation subscore of 0 after 1 week of treatment when compared with placebo.
GPPGA total score							
Proportion of patients with a GPPGA total score of 0 or 1 Follow-up: 1 week	53 (1 RCT)	NR	11 per 100	43 per 100 (95% CI, 28.0 to 59.1)	32 more per 100 (from 2 more to 53 more)	Moderate[b]	Spesolimab (900 mg single dose, infusion) likely results in a clinically meaningful increase in the proportion of patients with a GPPGA total score of 0 or 1 after 1 week of treatment when compared with placebo.
Pain VAS							
CFB in pain VAS Follow-up: 4 weeks	50 (1 RCT)	Patients with pain VAS response (responders): • Spesolimab: 57.1 per 100 • Placebo: 11 per 100 • Difference: the sponsor reported this was not calculable Median (IQR): • Spesolimab: −22.45 (−70.41 to no response) • Placebo: no response				Very low[c]	The effect of spesolimab (900 mg single dose infusion) on CFB in pain VAS is very uncertain when compared with placebo.
Harms							
Proportion of patients with SAEs before nonrandomized spesolimab Follow-up: 1 week	53 (1 RCT)	NR	16.7 per 100	14.3 per 100 (NR)	NR	Low[d]	Spesolimab may result in little to no difference in the proportion of patients experiencing 1 or more SAEs after week 1 compared to placebo.

AE = adverse event; CFB = change from baseline; CI = confidence interval; GPP = generalized pustular psoriasis; GPPGA = Generalized Pustular Psoriasis Physician Global Assessment; IQR = Interquartile range; NR = not reported; RCT = randomized controlled trial; SAE = serious adverse event; VAS = visual analogue scale.

[a]A conservative threshold of 15 to 20 patients per 100 was suggested by the clinical experts consulted as clinically meaningful, minimally important difference between groups due to the rare nature of GPP and the lack of available treatments in current settings. Rated down −1 for imprecision. Although all values within the 95% CI were considered clinically important, the sample size is small, raising concerns for prognostic imbalance and a potential that the true effect is overestimated.

[b]A conservative threshold of 15 to 20 patients per 100 was suggested by the clinical experts consulted as clinically meaningful, minimally important difference between groups due to the rare nature of GPP and the lack of available treatments in current setting. Rated down −1 for imprecision. The 95% CI included values that were considered not clinically meaningful by the clinical experts consulted.

[c]In absence of a threshold for clinical importance, the null was used. Rated down −1 for serious imprecision due to noncalculable events in the placebo arm. Rated down −2 for risk of bias due to the use of escape medications, open-label spesolimab, or rescue medication in the PBO group, rendering the effect uninterpretable. Pain VAS is a subjective outcome and there is a potential for bias due to reporting, if the patients inferred what group they were in.

[d]Rated down −2 for very serious imprecision. The effect may be unstable as it is informed by few events.

Source: Effisayil-1 Clinical Study Report Details included in the table are from the sponsor's Summary of Clinical Evidence.

Table 4: Summary of Findings for Spesolimab HD Group Versus Placebo Group for the Prevention of GPP Flares in Adults and Pediatric Patients Aged 12 Years and Older (Effisayil-2)

Outcome and follow-up	Patients (studies), N	Relative effect	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Spesolimab HD	Difference		
Time to first GPP flare							
Time to first GPP flare (weeks) Follow-up: 48 weeks	61 (1 RCT)	Patients with GPP flares: • Spesolimab HD: 10.0 per 100 • Placebo: 51.6 per 100 Median (95% CI) weeks to first flare: • Spesolimab HD: NE (NE to NE) • Placebo: 37.3 (4.0 to NE) HR = 0.157; 95% CI, 0.046 to 0.541				Moderate[a]	Spesolimab, 600 mg loading dose followed by 300 mg subcutaneous every 4 weeks, likely results in a clinically meaningful increase in the time to first GPP flare compared to placebo.
Occurrence of ≥ 1 GPP flares							
Probability of GPP flare occurrence Follow-up: 48 weeks	61 (1 RCT)	NR	51.6 per 100	12.7 per 100 (95% CI, 5 to 28.9)	39 fewer per 100 (62.1 to 15.9 fewer)	Moderate[a]	Spesolimab, 600 mg loading dose followed by 300 mg subcutaneous every 4 weeks, likely results in a clinically meaningful reduction in the proportion of patients having a flare event up to 48 weeks of treatment compared to placebo.
Time to first DLQI worsening							
Time to first 4-point worsening of DLQI Follow-up: 48 weeks	61 (1 RCT)	Patients with DLQI worsening: • Spesolimab HD: 24.7 per 100 (95% CI, 12.6 to 45.1)				Low[b]	Spesolimab, 600 mg loading dose followed by 300 mg subcutaneous every 4 weeks, may result in a clinically meaningful reduction in the

Outcome and follow-up	Patients (studies), N	Relative effect	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Spesolimab HD	Difference		
		• Placebo: 64.5 per 100 (95% CI, 48.1 to 80.6) • Difference: 42.4 fewer per 100 (95% CI, 64.3 to 20.4 fewer) Median weeks to first DLQI worsening: • Spesolimab HD: NE (NE to NE) • Placebo: 16.0 (95% CI, 4.0 to NE) HR = 0.259 (95% CI, 0.109 to 0.620)					proportion of patients with at least a 4-point DLQI worsening at week 48 when compared with placebo.
Harms							
SAEs Follow-up: 48 weeks	60 (1 RCT)	NR	3.3 per 100	10 per 100 (NR)	NR	Low[c]	Spesolimab, 600 mg loading dose followed by 300 mg subcutaneous every 4 weeks, may result in increase in SAEs when compared with placebo. The clinical relevance of the increase is uncertain.

AE = adverse event; CI = confidence interval; DLQI = dermatology life quality index; GPP = generalized pustular psoriasis; HD = high dose; HR = hazard ratio; NE = not estimable; NR = not reported; RCT = randomized controlled trial; SAE = serious adverse event.

[a]The clinical experts could not provide a clinically important threshold, so the null was used. Rated down −1 for imprecision. Although all values within the 95% CI did not include the null, the sample size was considered small, raising concern for prognostic imbalance and a potential that the true effect is overestimated. According to the clinical experts, the estimated between-group differences were clinically important.

[b]A 15% to 20% threshold was used as per clinical expert input. Rated down −1 for imprecision. Although all values within the 95% CI were considered clinically important, the sample size is small, raising concerns for prognostic imbalance and a potential that the true effect is overestimated. Rated down −1 for risk of bias. There is a risk that patients may have detected in the treatment to which they were assigned due to differences in efficacy between groups, and the outcome is subjective. According to the clinical experts, the estimated between-group difference was clinically important. Due to prior failure [from original source] of the statistical hierarchy (for Psoriasis Symptom Scale), results for DLQI are considered as supportive evidence.

[c]Rated down −2 for very serious imprecision. The effect may be unstable as it is informed by few events.

Source: Effisayil-2 Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Ethical Considerations

Patient group, clinician group, and drug plan input, as well as consultation with clinical experts were reviewed to identify ethical considerations specific to the use of spesolimab by IV and SC infusion in adult patients with GPP.

Diagnosis, Treatment, and Experiences of People Living With GPP

- Living with GPP presents significant physical and psychosocial burdens for patients and their caregivers. During a severe GPP flare, for instance, patients are at an elevated risk of mortality (2% to 16%) due to the systemic impacts on cardiac, lung, and renal function. Beyond this, clinical experts, clinician group, and patient group input all highlighted how recurrent GPP flares can involve the spontaneous, rapid onset of inflammatory pustules, diffuse erythema, and pruritus that are painful. GPP flares can also be highly disruptive to people's lives and daily activities. Patients may need to be hospitalized or become bedridden and unable to work, participate in social activities, or maintain physical intimacy. Patient group input and clinical experts described long-term impacts of GPP on mental health and well-being, including experiences of diminished self-esteem, depression, and anxiety between flares.
- Clinical experts indicated that people experiencing their first GPP flare would likely present to their local emergency department for assessment and diagnosis by a medical dermatologist (if available). However, patient group input noted that some individuals may experience delays in receiving an accurate diagnosis, at times requiring multiple hospital visits and self-advocacy with their family doctors to obtain a referral to a specialist familiar with GPP. While delays in diagnosis are uncommon, GPP is a very rare skin condition with little public awareness. As result, some people may experience delayed diagnosis and thereby delayed access to appropriate care and treatment.
- Clinical experts described how the timely diagnosis and treatment of GPP (whether for an acute flare or long-term flare prevention) could be further hampered by growing gaps in access to publicly funded dermatology services across Canada. This may be exacerbated for people with GPP living in rural or remote areas where specialized dermatology services are more limited. While telehealth services could help bridge some of these gaps by connecting family doctors and emergency departments with specialists, limited geographic availability of hospitals with dermatology specialists and infusion centres needed to treat acute flares, and/or provide preventive therapy with current treatment options remains a challenge and leads to ongoing disparities in access to appropriate dermatological care. Patient group input indicated that, for this reason, having a treatment option that limited the need to travel would be ideal.
- There is currently no targeted treatment option indicated for the treatment of acute GPP flares or long-term management and prevention of flares. Instead, in cases of severe GPP flares, providers use a variety of off-label, fast-acting biologics (i.e., IL-17 and TNF alpha inhibitors) indicated for plaque psoriasis. Similarly, other off-label psoriasis biologics (e.g., IL-23, and IL-12 and L-23 inhibitors) and nonbiologic systemic therapies are used to support long-term management and flare prevention. The absence of targeted therapy is further complicated by the lack of consensus

guidelines regarding the treatment of GPP flares or long-term management of GPP in Canada. As such, clinical experts and clinician group input indicated that current practice is inadequate due to inconsistent efficacy of off-label treatment options in GPP, their contraindication in some patients (e.g., people who are pregnant), and variability in access to these therapies across jurisdictions. Further, given the absence of treatment options indicated and reimbursed specifically for GPP, clinical experts highlighted experiences of moral distress in having to misrepresent patients' diagnoses to gain access to off-label treatments indicated for psoriasis.

- Clinical experts, patient group, and clinician group input all indicated treatment goals for GPP include rapid control of acute flares that not only alleviates symptoms quickly, but that also mitigates potential for long-term systemic damage or mortality due to prolonged flares. Additionally, all expressed an interest in preventive treatment options that could reduce the frequency and severity of GPP flares and improve the overall quality of life for people with GPP.

Clinical Evidence Used in the Evaluation of Spesolimab

- Spesolimab was evaluated in the 2 randomized, placebo-controlled, double-blind, phase II Effisayil-1 (N = 53) and phase IIb Effisayil-2 (N = 123) trials. The Effisayil-1 trial evaluated the safety, efficacy, and tolerability of a single dose of IV spesolimab for acute GPP flares of moderate to severe intensity in adults aged 18 to 75 years. Trial results suggest that patients receiving spesolimab likely experienced better outcomes for the primary end point (resolution of acute GPP flares with no visible pustules after 1 week of treatment) when compared to placebo. The Effisayil-2 trial evaluated the safety and efficacy of spesolimab by SC injections for the prevention of GPP flares in patients aged 12 to 75 years with a history of GPP. Like the Effisayil-1 trial, results suggest people treated with SC spesolimab likely experienced better outcomes for the primary end point (time to first GPP flare-up to week 48) when compared to placebo. Experiences of AEs (e.g., pustular psoriasis, fever, or infection) and SAEs (e.g., pustular psoriasis) were high across both active treatment and placebo arms of the Effisayil-1 and Effisayil-2 trials. However, clinical experts indicated that no new safety concerns were identified. They considered the safety profile manageable given the potentially life-threatening nature of severe GPP flares.
- The long-term extension study for the Effisayil-1 and Effisayil-2 trials (Effisayil-ON long-term) is ongoing, with limited information available during this review. Although clinical experts indicated that the placebo comparator was warranted due to the absence of other treatment options specific to GPP, the long-term efficacy and harms of spesolimab relative to any comparator (including commonly used off-label therapies) are presently unknown. The lack of long-term evidence for safety and efficacy, as well as comparative effectiveness, highlights the importance of robust consent conversations and presents challenges in decision-making for clinical and health systems, including consideration of opportunity costs.
- Clinical experts indicated that the trial populations were broadly generalizable to those seen in practice. However, they also suggested that the Effisayil-1 trial excluded patients that may have been more likely to experience drug-induced side effects – particularly for people living with hepatic disease. Though acknowledging the importance of narrow inclusion and exclusion criteria in trial

settings, 1 clinical expert suggested that in the event of a severe, life-threating GPP flare, providers would consider whether to prescribe spesolimab on a case-by-case assessment of risk benefit, especially as other off-label biologics may be similarly hepatotoxic. Similarly, while the product monograph notes that spesolimab by IV and SC infusions are indicated for the treatment of GPP in patients aged 12 years and older, the Effisayil-1 trial did not include patients aged 12 to 17 years. As such, there is no clinical evidence regarding the efficacy and safety of IV spesolimab in this population. However, clinical experts were comfortable with using it despite this absence and noted that existing evidence on the use of biologics for plaque psoriasis in pediatric patients suggests there is no clinically meaningful difference in safety between adolescents and adults. Regardless, they added that it is important to collect more real-world data in excluded or absent populations from the trials to support future clinical decision-making. Registry data on people who were pregnant was mentioned as of particular interest. In the absence of evidence regarding the efficacy and safety of IV spesolimab in these populations, it will be important for clinical providers to facilitate consent conversations that transparently recognize the absence of data.

Clinical Use of Spesolimab

- Clinical experts considered spesolimab a potentially paradigm shifting treatment in the care of people with GPP due to its unique mechanism of action focused on the IL-36 signalling pathway involved in GPP pathogenesis. As a targeted therapy that may alleviate some challenges associated with current off-label treatment options (e.g., their varying efficacy, inconsistent jurisdictional availability, and their contraindication in some patients), clinical experts uniformly expressed willingness to prescribe IV spesolimab as a first-line treatment for patients experiencing acute GPP flares and SC spesolimab as a first-line option for long-term prevention of GPP flares. They described personal experiences observing rapid resolution of GPP flares with spesolimab in their own patients as supporting this decision and highlighted their satisfaction with efficacy and safety results of the Effisayil-1 and Effisayil-2 studies. Clinical experts believed it would be inappropriate to require patients to not succeed using other off-label options before accessing spesolimab for these reasons and because it would unnecessarily expose patients to an elevated risk of mortality. However, for patients who were already well managed with off-label biologics, clinical experts indicated that they would only consider shifting to SC spesolimab for long-term maintenance following treatment of an acute flare with IV spesolimab.
- As pregnancy is a known trigger for GPP flares, some people with GPP require treatment for acute flares during pregnancy. While the product monograph has indicated that the use of spesolimab (IV or SC) should be avoided in people who are pregnant, clinical experts indicated that this guidance may not be followed in practice. Instead, they suggested decisions to use spesolimab in people who are pregnant would be contextual and assessed on a case-by-case basis according to a patient's individual risk benefit, especially given the potentially life-threatening nature of acute flares. This raises an ethical consideration in that there is currently no evidence for the use of spesolimab in people who are pregnant. Additionally, there is some risk that it could cross the placental barrier as a monoclonal antibody and affect the unborn fetus. However, clinical experts noted that this risk was

not unique to spesolimab. For example, other biologics currently used off label to control GPP flares were likely to have similar safety profiles in people who are pregnant, and some systemic therapies are contraindicated in people who are pregnant. As the sole treatment option specifically targeting the causal pathway of GPP, experts assumed spesolimab would have the best risk benefit for people with GPP. Regardless, all highlighted the importance of having clear conversations with patients who are pregnant that could help them weigh the potential risks and benefits of proceeding with spesolimab in the event of an acute flare.

Health Systems Impact

- Clinical experts and clinician group input both suggested that public reimbursement of spesolimab may alter or limit the use of some health care resources associated with long-term flare prevention and treatment of acute GPP flares. However, there is presently no evidence demonstrating these impacts. This raises ethical considerations for health care planning and resource allocation, including how to fairly distribute or share potential risks and benefits associated with reimbursing a therapy where the long-term value is currently unknown. Nonetheless, clinical experts suggested that the reimbursement of SC spesolimab for long-term flare prevention may lead to decreased reliance on trialling off-label biologics and systemic medications. Similarly, they expected that the preventive use of SC spesolimab may lessen hospital admissions and associated health care resources allocated to treating GPP flares. In the event of an acute flare, clinical experts suggested that IV spesolimab for treatment of acute flares delivered in outpatient settings or emergency departments may limit the need for hospital or intensive care unit admissions. This could have an overall benefit for health care resource utilization.
- The fragmentation of the health care system can present challenges for reimbursement and equitable access to spesolimab. For example, spesolimab may be funded through different budget streams: hospital budgets for the treatment of acute flares with IV spesolimab in hospital, provincial formularies for both the treatment of acute flares with IV spesolimab in outpatient infusion centres, and for long-term prevention using SC spesolimab for self-administration. Clinical experts suggested that this could lead to logistical challenges and potential gaps in coverage and inequities in financial support for patients. For example, if IV spesolimab is only covered through hospital budgets, people living in rural or remote locations with limited access to hospital services may not be able to access spesolimab by IV or SC infusion if they do not have private insurance because of lack of public coverage.
- Clinical experts indicated that some people with GPP may be living in locations with limited to no access to infusion centres necessary for outpatient delivery of IV spesolimab for acute flares. As such, the option to self-administer SC spesolimab at home may be considered equity enhancing for patients living in rural or remote locations with limited access to infusion.
- The sponsor has indicated the presence of a patient support program to aid in the implementation of spesolimab in Canada (e.g., outpatient administration at infusion centres and support navigating reimbursement opportunities). While the sponsor has indicated providing compassionate and free goods (i.e., medication at no charge to the patient) to patients unable to afford IV spesolimab, it is

unclear whether these include travel supports for patients residing far from infusion centres, a noted challenge to the equitable provision of timely care for people with GPP. Drug program input indicated the need to further clarify the parameters of this program with the sponsor should spesolimab be recommended for reimbursement.

Economic Evidence

Cost and Cost-Effectiveness

Table 5: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target populations	The treatment of GPP, including treatment of flares with a GPPGA total score of ≥ 2, and, prevention of flares, in adults and pediatric patients aged 12 years and older.
Treatment	Spesolimab
Dose regimen	For treatment of acute flares: a single dose of 900 mg administered as an IV infusion. If flare symptoms persist, an additional 900 mg dose may be administered 1 week after the initial dose. For prevention of flares: 1 loading dose of 600 mg, followed by 300 mg administered subcutaneously every 4 weeks.
Submitted price	Spesolimab: • Two 450 mg vials per package, $21,900.00 per package • Two 150 mg prefilled syringes per package, $7,300.00 per package
Submitted treatment cost	For the treatment of a flare: $21,900 per patient per treatment ($43,800 per patient if 2 doses are administered) For the prevention of flares: $95,229 per patient per year[a]
Comparator	No treatment
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (69 years)
Key data source	Effisayil-1 informed the efficacy and safety for the treatment of GPP flares Effisayil-2 informed the efficacy and safety for the prevention of GPP flares
Key limitations	• The sponsor compared spesolimab to no treatment for both preventive therapy and treatment of acute GPP flares in their analysis. However, current clinical practice in Canada includes several off-label treatments in both treatment settings. Clinical experts consulted by CDA-AMC indicated that the majority of patients would be treated with the best available care. The clinical benefits of spesolimab were likely overestimated when compared with no treatment, given what is expected in clinical practice when patients receive treatment. • The sponsor applied an excess mortality rate of 5.3% each time a patient experienced a GPP flare, based on a study of patients who died following hospital admission during a GPP flare. However, the majority of GPP flares are managed in an outpatient setting, and most patients at risk of flare-related

Component	Description
	mortality would be treated in a hospital. By applying the flare-related mortality rate to all patients experiencing a flare in the model, the sponsor has applied the excess mortality rate to patients being treated for flares in both an outpatient and hospital setting. As a result, the sponsor has likely overestimated the flare-related mortality in the submitted model. • The model structure was not in line with clinical practice. Clinical experts consulted by CDA-AMC noted that spesolimab may be provided along with adjuvant therapy, acute treatment changes would occur within 24 to 48 hours in clinical practice, and that re-treatment with spesolimab for a second acute flare when spesolimab was ineffective for the first acute flare would be unlikely. • The sponsor assumed that the treatment effect of spesolimab for preventive therapy observed in the 48 weeks of trial data in Effisayil-2 would persist indefinitely over a 69-year time horizon. The actual duration of the treatment effect of spesolimab is unknown. • The sponsor excluded administration costs for spesolimab and thus underestimated the total costs associated with spesolimab.
CDA-AMC reanalysis results	• To account for the identified key limitations, CDA-AMC revised how flare-related mortality was included in the model and included treatment administration costs for IV spesolimab. We were unable to address limitations associated with the lack of comparison with treatments used in clinical practice, the model structure, or treatment waning. • In the CDA-AMC base case, the ICER for spesolimab was $431,569 per QALY gained compared to no treatment (incremental cost = $1,986,465; incremental QALYs = 4.60). A price reduction of at least 79% would be required for spesolimab to be considered cost-effective compared to no treatment at a willingness-to-pay threshold of $50,000 per QALY gained.

CDA-AMC = Canada's Drug Agency; GPP = generalized pustular psoriasis; GPPGA = generalized pustular psoriasis global assessment; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

[a]The sponsor assumed the same cost for preventive spesolimab treatment in the first and subsequent years.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: using both prevalence and incidence of GPP was inappropriate, the prevalence of GPP in Canada was likely underestimated, and the market uptake of spesolimab was likely underestimated.

Our reanalysis revised the epidemiological approach and the flare treatment market uptake of spesolimab. In the CDA-AMC base case, the budget impact of reimbursing spesolimab for the Health Canada indicated population is estimated to cost $560,297 in year 1, $1,594,793 in year 2, and $2,620,204 in year 3, for a 3-year budgetary impact of $4,775,294. Due to the uncertainty in the coverage rate for people younger than 65 years, and the market share for spesolimab in the preventive setting, CDA-AMC conducted scenario analyses to assess the impact of alternative assumptions on the expected budget impact of spesolimab. In these scenarios, the budget impact was sensitive to the coverage rate of those aged younger than 65 years and the market uptake of spesolimab in a preventive setting; the 3-year budget impact increased by 74% and 36% compared to the CDA-AMC base case, respectively, in these scenarios.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, 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: October 23, 2024

Regrets: 3 expert committee members did not attend.

Conflicts of interest: 1 expert committee member did not participate due to considerations of conflict of interest.

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

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