Canadian Journal of Health Technologies

Canada's Drug Agency
L'Agence des médicaments du Canada

March 2026 Volume 6 Issue 3

Drugs Health Technologies Health Systems

Reimbursement Recommendation

Nemolizumab (Nemluvio)

Indication: Nemolizumab is indicated for the treatment of adults with moderate-to-severe prurigo nodularis (PN) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Sponsor: Galderma Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Nemluvio?

Canada's Drug Agency (CDA-AMC) recommends that Nemluvio be reimbursed by public drug plans for the treatment of adult patients with moderate to severe prurigo nodularis (PN) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable if certain conditions are met.

Which Patients Are Eligible for Coverage?

Nemluvio should only be covered to treat adult patients with moderate to severe PN, which was diagnosed by a dermatologist, who have had an inappropriate response to an appropriate course of topical prescription therapy, and in alignment with criteria used in the jurisdictions for the initiating, renewing, and prescribing of other advanced systemic treatments for PN.

What Are the Conditions for Reimbursement?

Nemluvio should only be reimbursed if the patient is under the care of a dermatologist with expertise in the management of PN and if the cost of Nemluvio is reduced. Nemluvio should be reimbursed for an initial 6-month period and continued thereafter only if there is documented evidence of a clinically meaningful reduction in itch and lesion count. Nemluvio should not be used in combination with other systemic therapies for PN.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 2 clinical trials showed that, compared with placebo treatment, Nemluvio reduced itching and the number of PN lesions and improved health-related quality of life (HRQoL) in patients with moderate to severe PN.
- Nemluvio may meet important patient needs, including reducing itch, clearing lesions, and improving HRQoL, and it offers an alternative treatment for adult patients with moderate to severe PN.
- Based on the CDA-AMC assessment of health economic evidence, Nemluvio does not represent good value to the health care system at the public list price. The committee determined there was not enough evidence to justify a greater cost for Nemluvio compared with dupilumab or other drugs used in the treatment of moderate to severe PN.
- Based on public list prices, Nemluvio is estimated to cost the public drug plans approximately $186 million over the next 3 years. However, the

Summary

actual budget impact is uncertain, and it is expected to be greater than $40 million in years 1, 2, and 3.

Additional Information

What Is Prurigo Nodularis?

PN is a rare condition that affects the skin causing raised nodules that are extremely itchy. Constant scratching causes tissue damage, scabbing, and scars. PN can lead to reduced quality of life (QoL) because symptoms may disrupt sleep, work, and school, and negatively impact patients' personal and social lives. There are an estimated 6,000 patients with moderate to severe PN in Canada.

Unmet Needs in Prurigo Nodularis

There is no cure for PN, and current therapies often fail to provide adequate itch control. Safe, effective, and easy-to-administer treatments that target the underlying disease remain an important unmet need.

How Much Does Nemluvio Cost?

Treatment with Nemluvio is expected to cost approximately $42,064 per patient for the first year and $39,069 per year in subsequent years for a patient weighing less than 90 kg or approximately $78,137 per year for a patient weighing 90 kg or greater in all years.

Recommendation

The CDA-AMC Canadian Drug Expert Committee (CDEC) recommends that nemolizumab be reimbursed for the treatment of adult patients with moderate to severe PN only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two phase III, double-blind, randomized, placebo-controlled trials (OLYMPIA 1: N = 286 patients; OLYMPIA 2: N = 274 patients) demonstrated that treatment with nemolizumab resulted in added clinical benefit for adult patients with moderate to severe PN compared with treatment with placebo. The primary outcomes from both trials indicated that, after 16 weeks of treatment, reductions in symptom severity and disease severity were meaningful and significantly greater with nemolizumab than with placebo as measured by change from baseline in Peak Pruritus Numeric Rating Scale (PP NRS) score and Investigator's Global Assessment (IGA) success score. Specifically, the proportion of patients with improvement of 4 or more points from baseline in weekly average PP NRS at week 16 was 58.4% in the nemolizumab group and 16.7% in the placebo group (strata-adjusted proportion difference = 40.1%; 95% confidence interval (CI), 29.4% to 50.8%; P value < 0.0001) in the OLYMPIA 1 trial, and 56.3% in the nemolizumab group and 20.9% in the placebo group (strata-adjusted proportion difference = 37.4%; 95% CI, 26.3% to 48.5%; P value < 0.0001) in the OLYMPIA 2 trials. Similarly, the between-group difference in IGA success response at week 16 indicated that patients treated with nemolizumab showed statistically significantly greater improvement in lesion clearance in the OLYMPIA 1 trial (14.6%; 95% CI, 6.7% to 22.6%) and the OLYMPIA 2 trial (28.5%; 95% CI, 18.8% to 38.2%).

In addition, the between-group difference in the Sleep Disturbance Numeric Rating Scale (SD NRS) score showed that patients treated with nemolizumab showed statistically significantly better improvement in sleep than those who received placebo (OLYMPIA 1: 38.0% [95% CI, 27.8% to 48.2%]; OLYMPIA 2: 31.9% [95% CI, 20.7% to 43.2%]), although it is uncertain whether this was clinically meaningful. An assessment of patients' HRQoL using the Dermatology Life Quality Index (DLQI) scale suggested that nemolizumab improves patients' QoL better than placebo, although the analysis did not control for multiplicity. The clinical experts consulted for this review considered the between-group differences in itch reduction, lesion clearance, and HRQoL outcomes clinically meaningful.

Results from a network meta-analysis (NMA) comparing nemolizumab to dupilumab had limitations that precluded the ability to make a firm conclusion on comparative effectiveness. The clinical experts consulted for this review anticipated that the effect of nemolizumab would be comparable to that of dupilumab in clinical practice.

Patients identified effective disease control, with sustained itch relief, minimal side effects, and improved HRQoL, and affordability as key important outcomes. CDEC concluded that nemolizumab may meet most patients' needs, including reducing itch, clearing lesions, and improving HRQoL, and offers an alternative treatment to adult patients with moderate to severe PN.

At the sponsor-submitted price for nemolizumab and publicly listed prices for all other drugs, nemolizumab was more costly than dupilumab. Because there was insufficient evidence to conclusively determine the comparative clinical benefit for nemolizumab versus dupilumab, the total drug cost of nemolizumab should not exceed the total drug cost of dupilumab. Further price reduction may be needed due to uncertainty within the NMA.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with nemolizumab should be reimbursed for adult (≥ 18 years) patients with a confirmed diagnosis of moderate to severe PN and all the following criteria: 1.1. PN diagnosed by a dermatologist 1.2. severe pruritus with PP NRS score ≥ 7 points 1.3. moderate or severe disease as indicated by IGA score ≥ 3 1.4. at least 20 lesions, distributed bilaterally.	Evidence from 2 phase III trials (OLYMPIA 1 and OLYMPIA 2) demonstrated that treatment with nemolizumab resulted in clinically meaningful pruritus response, lesion clearance, and HRQoL in patients with these characteristics.	Jurisdictions may align the initiation, renewal, and prescribing criteria for nemolizumab with those established for other advanced systemic treatments for PN.
2. When therapy with nemolizumab is advisable, patients should have experienced an inadequate response to an appropriate course of prescription topical therapy.	Although the inclusion criteria of the OLYMPIA 1 and OLYMPIA 2 trials did not require patients to have experienced an inadequate response to topical therapy, most patients in the trials had previously received prescription therapy, with the most common being TCS (approximately 53% and 78%, respectively). The trials were placebo-controlled, and there was no evidence suggesting that using nemolizumab as initial therapy before prescription topical therapy for PN would result in clinical benefit.	The clinical experts consulted for this review noted that an appropriate course of topical prescription therapy includes 6 to 8 weeks of high- to super-high–potency TCS or, for patients in whom TCS is not advisable, 6 to 8 weeks of topical calcineurin inhibitors. Although the OLYMPIA 1 and OLYMPIA 2 trials excluded patients treated with other therapies, nemolizumab may be considered an option for adult patients with PN that has not achieved adequate control with topical prescription therapies or when those therapies are not advisable.
3. The response to nemolizumab should be assessed after an initial 6-month treatment period.	Treatment response at 16 weeks was assessed in both OLYMPIA 1 and OLYMPIA 2. Response at 24 weeks was also assessed in Olympia 1. According to the clinical experts consulted for this review, 6 months is a reasonable duration to assess whether initial treatment with nemolizumab is clinically beneficial.	In jurisdictions with limited access to dermatologists, a duration of 12 months for initial authorization could be considered.

Reimbursement condition	Reason	Implementation guidance
Renewal		
4. Reimbursement of treatment with nemolizumab should be continued after the initial 6 months of treatment if there is a documented change of at least 1 of the following: 4.1. reduction in itch indicated by ≥ 4-point reduction on the PP NRS 4.2. reduction in the number of lesions indicated by an IGA score of 0 or 1 or at least a 2-point improvement from baseline.	The OLYMPIA 1 and OLYMPIA 2 trials used a 4-point reduction in PP NRS as a threshold for clinically meaningful improvement in pruritus, which was supported by input from the clinical experts. In the OLYMPIA 1 and OLYMPIA 2 trials, IGA success was defined as an IGA score of 0 (clear) or 1 (almost clear) and a ≥ 2-point improvement from baseline. The treatment period was 24 weeks and 16 weeks in OLYMPIA 1 and OLYMPIA 2, respectively; follow-up was 8 weeks in both studies.	The clinical experts consulted for this review noted that, in patients with good response to treatment after the initial 6 months, assessments for renewal should occur every year. Nemolizumab could be renewed similarly to other biologics currently reimbursed for the treatment of PN as per the reimbursement criteria for each public drug plan.
5. For subsequent renewal, the clinician must verify that the initial response observed after the first 6 months of nemolizumab therapy has been sustained regarding itch (i.e., on PP NRS score) or lesion clearance (i.e., on IGA score).	This is to ensure that nemolizumab is prescribed for patients with a continued response to treatment.	—
Prescribing		
6. Nemolizumab should be prescribed by dermatologists with expertise in the management of PN.	This is meant to ensure that nemolizumab is prescribed to patients with an accurate diagnosis of PN and there is appropriate monitoring to optimize treatment outcome.	—
7. Nemolizumab should not be used in combination with dupilumab or other systemic therapies for PN.	The OLYMPIA 1 and OLYMPIA 2 trials did not combine nemolizumab with other drugs and CDEC did not review any evidence regarding the efficacy and safety of nemolizumab when used in combination with dupilumab or other systemic therapies for PN.	According to the clinical experts consulted for this review, although these treatments were not permitted as concomitant therapy in the OLYMPIA 1 and OLYMPIA 2 trials, it is likely that nemolizumab would be combined with TCS and intralesional corticosteroids, and nemolizumab could be combined with phototherapy in patients whose disease has not shown an adequate response to other treatments.
Pricing		
8. A reduction in price.	The ICER for nemolizumab plus BSC is $1,124,092 per QALY gained when compared with dupilumab plus BSC. The ICER for dupilumab plus BSC is $105,993 per QALY gained compared to BSC alone. A price reduction of 71% would be required for nemolizumab plus BSC to achieve an ICER of $50,000 per QALY gained compared to BSC alone. Given that BSC was not included as a comparator in the	CDEC concluded there was insufficient evidence to conclusively determine the comparative clinical benefit of nemolizumab vs. dupilumab or other drugs used in the treatment of moderate to severe prurigo nodularis. There is insufficient evidence to justify a higher price for nemolizumab than for other advanced systemic therapies reimbursed for the treatment of PN.

Reimbursement condition	Reason	Implementation guidance
	sponsor's NMA, a higher price reduction may be needed.	
Feasibility of adoption		
9. The economic feasibility of adoption of nemolizumab must be addressed.	At the submitted price, the incremental budget impact of nemolizumab is expected to be greater than $40 million in years 1, 2, and 3.	—
10. The feasibility of adoption of nemolizumab must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption because of the difference between the sponsor's estimate and the CDA-AMC estimate(s).	—

BSC = best supportive care; CDA-AMC = Canada's Drug Agency; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; IGA = Investigator's Global Assessment; NMA = network meta-analysis; PN = prurigo nodularis; PP NRS = Peak Pruritus Numeric Rating Scale, QALY = quality-adjusted life-year; TCS = topical corticosteroids; vs. = versus.

Discussion Points

- **Significant unmet need:** CDEC deliberated on nemolizumab considering the criteria for significant unmet need that are described in the Procedures for Reimbursement Reviews. CDEC discussed the unmet needs identified by patients, acknowledging that PN is a rare disease for which current treatments are used off-label, have limited effectiveness, and are often associated with significant side effects and feasibility issues. Currently, no established treatments are reimbursed for patients with moderate to severe PN whose disease is not adequately controlled with topical prescription therapies or for whom those therapies are not advisable. CDEC determined that although the OLYMPIA 1 and OLYMPIA 2 trials compared nemolizumab to placebo only, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment indicated high certainty with the reported results and the clinical experts considered the gains clinically meaningful. Considering the absence of clinically effective alternatives for moderate to severe PN, CDEC concluded that the available evidence reasonably suggests that nemolizumab has the potential to improve pruritus and lesion clearance in this patient population.
- **Lack of long-term effect data**: CDEC acknowledged that PN is a chronic disease characterized by significant life-impacting pruritic nodules and that patients are likely to receive drug therapy for a lifetime. However, the evidence regarding the efficacy and safety of nemolizumab in patients with PN is mainly short-term, and CDEC noted a higher incidence in new diagnosis or worsening of asthma as an adverse event (AE) of special interest (AESI) in patients treated with nemolizumab. CDEC acknowledged that the harms results reported in the ongoing, single-arm, open-label OLYMPIA long-term extension (LTE) study were consistent with results observed during the OLYMPIA 1 and OLYMPIA 2 trials and noted the need to assess the long-term clinical benefit of nemolizumab in patients with moderate to severe PN.

- **Lack of comparative evidence**: CDEC noted the lack of direct evidence comparing nemolizumab with any active drugs used in the treatment of PN. CDEC discussed the sponsor-submitted NMA noting that dupilumab was the only current relevant comparator among the drugs that were compared to nemolizumab in the NMA. The committee noted that the comparison of nemolizumab with dupilumab was potentially biased in favour of nemolizumab because of differences in treatment duration. CDEC also determined that the effect estimates had uncertainty indicated by wide CIs. Therefore, CDEC concluded that there was insufficient evidence to conclusively determine the comparative clinical benefit of nemolizumab versus dupilumab or to other therapies used in the treatment of moderate to severe PN.
- **Place in therapy**: CDEC noted that although most patients in the OLYMPIA 1 and OLYMPIA 2 trials had previously received topical corticosteroids, the inclusion criteria of both trials did not require participants to have had an inadequate response to previous treatments. Patients were also not allowed to receive topical or systemic therapies for PN during the study, except for rescue purposes. Therefore, CDEC noted a lack of evidence to determine whether nemolizumab should be used as first-line therapy, used as a subsequent-line therapy after inadequate response to conventional treatments used in Canada, or could be used alongside other treatments.
- **Cost-effectiveness versus BSC:** The economic analysis derived measures of relative efficacy between nemolizumab and best supportive care (BSC), defined as topical emollients, topical corticosteroids, and topical calcineurin inhibitors, from an NMA submitted by the sponsor. CDEC noted that the NMA used placebo not BSC as the comparator. The sponsor's economic analysis was predicated on the assumption that placebo and BSC are equivalent, which was not supported by the submitted evidence. Consequently, the incremental cost-effectiveness ratio (ICER) and the price reduction estimated for nemolizumab versus BSC is subject to a high degree of uncertainty, and additional reduction may be needed to achieve cost-effectiveness at a given willingness-to-pay threshold.
- **Cost-effectiveness versus dupilumab:** CDEC noted that the NMA comparing nemolizumab to dupilumab was not restricted to patients with previous experience with topical corticosteroids. This misalignment between the available evidence and the anticipated place in therapy for nemolizumab contributes additional uncertainty to the comparative effectiveness of nemolizumab and dupilumab for patients with moderate to severe PN. Additional price reduction may be required to achieve cost-effectiveness compared to dupilumab.

Background

PN is a rare neuroimmune inflammatory skin disease characterized by chronic itch (≥ 6 weeks), a history and signs of repeated scratching (e.g., excoriation and scars), and multiple localized or generalized hyperkeratotic, symmetrically distributed pruritic nodules on the extensor surfaces of the extremities and trunk. Exact incidence and prevalence estimates for Canada are unknown; however, based on the expected prevalence of PN published in a study by Bahloul et al. (2024), there are an estimated 6,000 patients with

moderate to severe PN in Canada. PN can occur in all age groups without sex predilection although it primarily affects older adults, with approximately 69% of patients aged 51 years and older.

PN leads to significantly reduced QoL because symptoms, such as itch and skin lesions, impact patients' personal and social lives. The negative impact on QoL from PN is primarily driven by the increased incidence and intensity of pruritus. Furthermore, patients with PN may be affected by insomnia and general sleep disturbances, a higher level of absenteeism (full days or partial days), decreased productivity, or presenteeism (showing up to work even when not able to perform effectively) and lower work performance. Other disruptions in day-to-day activities for patients with PN due to their symptoms include getting dressed, self-care or personal hygiene, planning activities, and chores.

PN is associated with the presence of comorbidities, such as chronic obstructive pulmonary disease (COPD), chronic hepatitis C, HIV, and atopic dermatitis, increasing the burden in patients with these. It is estimated that approximately 43% of patients with PN are initially misdiagnosed. Given the burden of PN and its associated comorbidities, patients with PN have high rates of health care utilization and specialty care.

According to clinical experts consulted by CDA-AMC, PN is often initially managed with high-potency topical corticosteroids. Other initial treatment options include topical calcineurin inhibitors or anesthetics, oral antihistamines, intralesional corticosteroid injections, topical capsaicin, and UV light treatment (phototherapy). The clinical experts consulted for this review commented that systemic immunosuppressants, such as cyclosporine and methotrexate, may be prescribed for severe or treatment-resistant PN. Other medications that may be considered to treat PN include gabapentin, pregabalin, carbamazepine, doxepin, mirtazapine, mycophenolate mofetil, and low-dose naltrexone. The clinical experts highlighted that PN is difficult to treat, the aforementioned treatment options may provide only partial or short-term symptomatic relief, and their use is often limited by side effects and feasibility issues. International guidelines detail several medication options for the treatment of PN, most of which have limited evidence supporting efficacy and are used off-label. In Canada, dupilumab is currently the only treatment indicated for PN. The clinical experts agreed with patient and clinician groups that there is a need for highly effective, disease-modifying, systemic PN therapies that provide sustained relief, are safe for long-term use, and are convenient and accessible.

The Health Canada–approved indication for nemolizumab is for the treatment of adults with moderate to severe PN whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The sponsor submitted the drug for this review before receiving a Health Canada Notice of Compliance. The CDA-AMC review reflects the sponsor's requested reimbursement, which is aligned with the approved indication. Nemolizumab is a humanized IgG2 monoclonal antibody. It is available as a powder and solvent solution for subcutaneous injection as 30 mg per 0.49 mL in a single-dose, prefilled, dual-chamber pen. The dosage recommended in the product monograph differs based on patient body weight. The recommended dosage of nemolizumab for patients weighing less than 90 kg is an initial dose of 60 mg (two 30 mg injections) followed by 30 mg given every 4 weeks. The recommended dosage for patients weighing 90 kg or more is an initial dose of 60 mg (two 30 mg injections) followed by 60 mg given every 4 weeks.

Sources of Information Used by the Committee

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

- a review of 2 phase III, randomized, double-blind, placebo-controlled studies in adult patients with PN; 1 LTE study; and 1 sponsor-submitted indirect treatment comparison (ITC)
- patients' perspectives gathered by 1 patient group, the Canadian Skin Patient Alliance (CSPA)
- input from public drug plans that participate in the reimbursement review process
- two clinical specialists with expertise diagnosing and treating patients with PN
- input from 2 clinician group(s), the Atlantic Dermatology Group and the Dermatology Association of Ontario (DAO)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Group Input

A single patient group, the CSPA, provided input for this submission. CSPA is a national charity organization that supports the health and well-being of people across Canada affected by skin, hair, and nail conditions through collaboration, advocacy, and education. Information regarding the experiences of people living with PN was compiled from a patient and caregiver survey from September 12 to November 29, 2024. A total of 9 survey responses were received from Canada. None of the patients had experience with nemolizumab.

Five survey respondents indicated that they had PN for less than 5 years, and most reported severe (n = 3) or moderate (n = 1) PN. Respondents indicated that their PN diagnosis impacted family relationships, intimate relationships, work life, mental health, social life, daily activities, sleep, self-esteem, finances, and sex life. Respondents highlighted the following symptoms of the disease: itchy skin, itchy bumps (nodules), burning or stinging skin, scratching, pain, and hyperpigmentation (dark spots).

The caregiver respondent reported that the disease impacted their loved ones with regards to family balance and relationships, mental health, and intimacy. Additionally, they shared that it was difficult having to encourage their loved ones to continue taking treatments for PN.

The respondents indicated that effectiveness, lack of side effects, and affordability as the top 3 unmet needs. Other important aspects included treatments that are easy to take or apply and conducive to the patient's schedule. The caregiver respondent noted the cost of medication as an important unmet need.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts consulted by CDA-AMC expressed an unmet need for disease-modifying systemic therapies for PN that are highly effective in achieving treatment goals (e.g., itch relief, treatment of lesions), provide sustained disease control and symptom relief, are safe for short-term and long-term use across

diverse patient populations (e.g., all ages, those with comorbidities), and are convenient and accessible. The clinical experts commented that, along with dupilumab, nemolizumab is expected to cause a shift if the current treatment paradigm for PN in Canada. The clinical experts expected that traditional therapies (e.g., topical corticosteroids) would still be used for initial management of PN and stated that nemolizumab would be best suited for patients with moderate to severe or refractory PN, particularly those with persistent pruritus and a large number of chronic lesions that have not responded to conventional treatments.

According to the clinical experts, patients who are least suited for nemolizumab would be those with mild PN or mild symptoms that can be managed with conventional treatments. The clinical experts stated that nemolizumab or dupilumab would likely be preferred systemic treatment options over systemic immunosuppressants. They also noted that nemolizumab would likely be combined with some existing PN treatments, such as topical or intralesional corticosteroids. According to the clinical experts, treatment response in patients with PN is assessed in clinical practice based on improvement in the number of lesions, reduction in pruritus, and improvement in QoL, and physicians may prioritize these outcomes differently. They noted that assessing treatment response in clinical practice does not usually use the grading tools as stringently as used in clinical trials. The clinical experts stated that response would typically be assessed 3 to 6 months after initiation of PN treatment and at the same interval while the disease remains active, with annual follow-up once the disease is controlled.

When deciding to discontinue treatment with nemolizumab, the clinical experts would evaluate whether the patient had achieved the desired clinical outcomes within a 6-month time frame. The clinical experts consulted for this review identified that a clinically important response would be a decrease in lesion count from 20 or more at the start of therapy to 5 or fewer, or a decrease in peak itch severity by at least 4 points (out of 10) on the PP NRS. The clinical experts also acknowledged that decisions to stop treatment in patients with a partial response would consider whether the patient wanted to continue therapy and if any other effective treatment options are available. Additional factors for discontinuation may include serious AEs (SAEs) or the emergence of comorbidities requiring other treatments. The clinical experts agreed that, due to the complexity of diagnosing PN, it is essential that treatment of PN with nemolizumab be limited to dermatologists.

Clinician Group Input

Two clinician groups, Atlantic Dermatology Group and the DAO, provided their input for this submission. Input from Atlantic Dermatology Group was provided by 5 clinicians, and information was gathered from sessions related to PN at the recent European Academy of Dermatology and Venerology in Amsterdam (September 2024) and from the literature. Input from the DAO was provided by 7 clinicians, and the information was gathered from clinical trial data, available literature retrieved through PubMed, and experience with nemolizumab use in clinical trials in Canada.

Both clinician groups highlighted that currently there are no specific clinical practice guidelines for PN in Canada. They indicated that current therapies include topical treatments, such as corticosteroids and emollients; dupilumab; and off-label regimens (systemic immunosuppressants, thalidomide, lenalidomide, tricyclic antidepressants, JAK inhibitors, neurokinin 1 receptor antagonists, and monoclonal antibodies

targeting IL-4 pathways). The DAO also highlighted that nondrug treatments, such as UVB phototherapy and psychosocial therapy, have been attempted with limited availability and success in addressing the psychological burden of PN and improving overall QoL. The Atlantic Dermatology Group further highlighted evidence from a systematic review that concluded although phototherapy, corticosteroids, cyclosporin, and methotrexate offer viable options, the potential benefits are limited because of the risk of relapse and potential side effects.

The DAO highlighted the following unmet needs in PN treatment: therapies that provide rapid and sustained relief from severe itch, improve skin lesions and address the psychosocial impacts of the disease, address poor tolerance and/or inconvenience using current treatments, and target the underlying neuroimmune mechanisms driving PN. The Atlantic Dermatology Group clinicians noted the need for therapy that provides clinically significant reductions in itch, improvements in physician global assessment of skin lesions, and improved QoL.

The Atlantic Dermatology Group indicated that nemolizumab will cause a shift in the current treatment paradigm because it can be used as first-line therapy in patients with PN or in patients with an inadequate response to or intolerance of dupilumab, topical corticosteroids, or phototherapy. They also noted that nemolizumab would be used as a stand-alone treatment. However, the DAO indicated that nemolizumab would fit as a targeted second-line or third-line option following failure of or insufficient response to topical therapies and phototherapy.

The DAO clinician group noted that patients best suited for treatment with nemolizumab would be those who have not experienced adequate relief from topical therapies or phototherapy, are unable to access these treatments, have moderate to severe PN, have persistent and intense pruritus, have widespread nodular lesions, or have significant impairment in QoL. The Atlantic Dermatology Group highlighted those patients with moderate to severe PN with an itch score of at least 7 points and at least 20 lesions would be in most need and best suited for treatment. The DAO group further noted nemolizumab treatment would not be suitable for patients with contraindications, such as a known hypersensitivity to nemolizumab; with milder disease that responds to topical steroids; or with conditions that significantly compromise immune function unless the benefits outweigh risks.

The DAO clinician group noted that, to identify patients who would most likely respond to nemolizumab, a clinician assessment of the intensity and persistence of itch, the extent of nodular lesions, and the impact on daily functioning and QoL was sufficient. However, the Atlantic Dermatology Group noted that no clinical, pathological, or chemical markers exist to identify patients who are most likely to exhibit a response to treatment.

The Atlantic Dermatology Group noted that misdiagnoses were unlikely if treatment is managed by dermatologists in their clinical practice, and emphasized the consideration of other diagnoses (i.e., pemphigoid nodularis, mastocytosis, lichen planus, nodular scabies, arthropod bites, lymphocytoma cutis, lymphomatoid papulosis, amyloidosis, reticulohistiocytosis, and cutaneous T-cell lymphoma). However, the DAO indicated that PN may be underdiagnosed or misdiagnosed as other pruritic dermatoses, and that clinician education and awareness are key to improving diagnostic accuracy.

Both clinician groups noted that a 4-point improvement in a patient's PP NRS score should be used to determine if the patient is responding to treatment. The Atlantic Dermatology Group and DAO noted a physician IGA of clear or almost clear and a reduction of at least 2 points from baseline, respectively, are outcomes used to determine treatment response. In addition, the Atlantic Dermatology Group highlighted that measurement of DLQI should also be assessed; the DAO highlighted the subjective feedback on daily comfort and sleep quality also be assessed.

Both clinician groups agreed that treatment discontinuation should be considered if there is a lack of meaningful reduction in PP NRS score or there are persistent nodular lesions as assessed by the IGA. The Atlantic Dermatology Group noted that treatment should be discontinued after 6 months of therapy if there is a lack of response. Additional criteria for discontinuation were noted by the DAO, including significant AEs (hypersensitivity, injection site reaction, long-term safety including recurrent infections). Disease progression (worsening lesions, skin infections) and patient-reported dissatisfaction were also noted as important factors requiring treatment reassessment and, in cases where systemic immunosuppressants or other biologics are required to manage refractory disease, nemolizumab would not be an optimal choice.

The Atlantic Dermatology Group indicated that PN should be managed by dermatologists experienced in the diagnosis and management of PN as well as experienced in the use of biologics. They also noted that dermatologists should be experienced in measurement of DLQI, IGA, counting nodules, and PP NRS. The DAO clinician group noted that, in addition to dermatologists, allergists or immunologists may also be involved in managing patients with PN when PN overlaps with other atopic or immune-mediated conditions. They highlighted that the diagnosis, treatment initiation, and monitoring of patients require the expertise and oversight of specialists; however, nemolizumab may be prescribed in various clinical settings (community clinics, hospital outpatient departments, and specialty dermatology or allergy clinics) and administered by the patient at home.

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 nemolizumab:

- 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

Implementation issues	Response
Relevant comparators	
Other implementation issues regarding relevant comparators (e.g., access and funding, covered population) Comments for awareness: • The sponsor notes that dupilumab is currently the only biologic therapy indicated for PN. • Dupilumab is currently under review by CDA-AMC for PN and is not publicly reimbursed for this indication. Question for clinical experts: • Are there other drugs with similar clinical effects as nemolizumab in PN that should be considered relevant comparators?	The clinical experts consulted for this review commented that dupilumab would be the most relevant comparator to nemolizumab; there are no other drugs with similar clinical effects that should be considered relevant comparators. CDEC acknowledged the clinical experts' input, noting that other drugs and procedures are currently used as second-line therapies for PN.
Considerations for initiation of therapy	
Disease diagnosis, scoring, or staging for eligibility Key inclusion criteria for the pivotal trials: • aged ≥ 18 years • PN diagnosis for ≥ 6 months • weekly average PP NRS ≥ 7 • ≥ 20 pruriginous nodular lesions on the body with a bilateral distribution • IGA ≥ 3 (i.e., moderate or severe rating). The sponsor notes: "Diagnosis of PN requires a physical examination and assessment of clinical presentation of symptoms. In some cases, a biopsy may be required to examine tissue for confirmation of diagnosis, and to distinguish from other skin conditions." Questions for clinical experts or CDEC: • Should patients have to meet all of the key trial inclusion criteria to be eligible to receive nemolizumab? • When should a biopsy be required to confirm a diagnosis of PN? ◦ What results would be confirmatory of PN?	The clinical experts commented that a PN diagnosis for at least 6 months would be reasonable given that most patients would have had this condition for months to years. The clinical experts commented that, at the time of determining patient eligibility, having a specific itch score requirement may not be necessary; the criterion of severe itching would be suitable because patients with moderate to severe PN would be experiencing severe itch. However, the clinical experts acknowledged that using a PP NRS score at baseline may be useful to allow for objective follow-up in determining clinical improvement in itch severity. The clinical experts expressed that fulfillment of both disease severity criteria may not be necessary because patients with 20 or more lesions would also have an IGA score of 3 or higher. The clinical experts suggested that eligibility criteria could state "≥ 20 pruriginous nodular lesions on the body with a bilateral distribution *and/or* IGA ≥ 3" or state only 1 of these criteria. The clinical experts noted that PN is a clinical diagnosis. The clinical experts commented that if PN is diagnosed by a dermatologist, a biopsy is not required to confirm the diagnosis. PN on biopsy can be similar to other chronic itch or excoriating disorders, and biopsy results are not entirely specific to PN. CDEC noted that the PP NRS score is not disease-specific; therefore, it would be useful to combine PP NRS score and other trial criteria, especially because other skin conditions were excluded from the OLYMPIA 1 and OLYMPIA 2 trials. CDEC acknowledged the clinical experts' input regarding biopsy results not being entirely specific to PN.

Implementation issues	Response
Prior therapies required for eligibility Relatively small proportions of patients in the pivotal trials received prior therapies for PN, aside from topical corticosteroids. Question for clinical experts or CDEC: • Should patients be required to have an inadequate response to any drug treatments used off-label for PN (e.g., topical corticosteroids, systemic nonsteroidal immunosuppressants) to be eligible to receive nemolizumab? • Should patients be required to have an inadequate response to phototherapy, where available?	The clinical experts stated that it is reasonable that all patients should have tried moderate- to high-potency topical corticosteroids before starting nemolizumab, especially considering these are likely to have been prescribed by family physicians before patients were able to see a dermatologist. The clinical experts commented that patients should not be required to have received methotrexate or cyclosporine due to the high failure rate and associated side effects and monitoring requirements associated with these medications (cyclosporine is also not a safe long-term treatment option in PN). It would be preferred to offer patients nemolizumab before prescribing methotrexate or cyclosporine. The clinical experts commented that it is not reasonable that patients should be required to have tried phototherapy to receive treatment with nemolizumab. There are barriers to access and patients' ability to adhere to phototherapy. CDEC acknowledged the clinical experts' input.
Consistency with initiation criteria associated with other drugs reviewed by CDA-AMC in the same therapeutic space It is expected that a CDA-AMC recommendation will be issued for dupilumab before nemolizumab is reviewed by CDEC. Comment for CDEC: • Consider alignment with initiation criteria for dupilumab, as applicable or appropriate.	This is a comment from the drug programs to inform CDEC deliberations. CDEC commented that the evidence base for dupilumab is substantially different than for nemolizumab. However, it would be reasonable to align initiation and renewal criteria of the 2 drugs as permitted in each jurisdiction.
Considerations for continuation or renewal of therapy	
Challenges related to assessment and monitoring of therapeutic response The primary end points in the pivotal trials were: • proportion of participants with an improvement of ≥ 4 from baseline in PP NRS at week 16 • proportion of participants with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point improvement from baseline) at week 16. The draft product monograph notes: "Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks." Questions for clinical experts or CDEC: • What level of improvement in primary and/or secondary trial end points should patients have to achieve to receive continued therapy? ◦ Should improvements need to be maintained indefinitely? • At what time point(s) should assessments for treatment renewal occur? • Under what circumstances should patients with a partial response be able to continue treatment beyond 16 weeks?	The clinical experts consulted for this review commented that itch response is the key consideration for continuation of therapy. Criteria for continuation of therapy could include itch response and/or improvement in the number of lesions; however, it should not be a requirement to fulfill both criteria for continuation of treatment. The clinical experts considered itch response to be at least a 4-point improvement in PP NRS score from baseline. One clinical expert commented that improvement in the number of lesions could be measured as an IGA score of 0 or 1. The other clinical expert suggested that either an IGA score of 0 or 1 or a 2-point improvement in IGA score from baseline could be used as a measure of improvement in the number of lesions. The clinical experts commented that assessment for treatment renewal (i.e., response to treatment) should occur 4 to 6 months following the initiation of nemolizumab. The clinical experts noted that assessment at 6 months is preferable; 1 clinical expert specified that assessment of lesions should occur at this time point and not at 4 months. For patients with good response to treatment at the initial assessment, the clinical experts commented that the second follow-up assessment would occur at 6 months or 1 year (the clinical experts suggested different time points), and annually thereafter. The clinical experts agreed that, for patients whose PD does

Implementation issues	Response
	not maintain good response to therapy (as previously defined), treatment with nemolizumab should be discontinued. Regarding continued treatment beyond 16 weeks in patients whose PD has partial response, 1 clinical expert commented these patients should be assessed at 24 weeks instead; if treatment response (as previously defined) has not been achieved at this point, improvement thereafter is unlikely. The other clinical expert commented that all patients should be allowed up to 24 weeks to experience full response; patients with partial response at 16 weeks should be seen again at 24 weeks, by which point treatment response (as previously defined) should be achieved to be able to continue treatment. CDEC acknowledged the clinical experts' input, noting that measures of improvement should be aligned with the OLYMPIA 1 and OLYMPIA 2 trial outcomes.
Consistency with renewal criteria associated with other drugs reviewed by CDA-AMC in the same therapeutic space It is expected that a CDA-AMC recommendation will be issued for dupilumab before nemolizumab is reviewed by CDEC. Comment for CDEC: • Consider alignment with renewal criteria for dupilumab, as applicable or appropriate.	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for discontinuation of therapy	
Consistency with discontinuation criteria associated with other drugs reviewed by CDA-AMC in the same therapeutic space It is expected that a CDA-AMC recommendation will be issued for dupilumab before nemolizumab is reviewed by CDEC. Comment for CDEC: • Consider alignment with discontinuation criteria for dupilumab, as applicable or appropriate.	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for prescribing of therapy	
Concerns related to combination usage Patients in the pivotal trials received nemolizumab monotherapy. Question for clinical experts or CDEC: • Should patients be able to use nemolizumab in combination with other treatments for PN (e.g., off-label therapies or other advanced therapies like dupilumab)?	The clinical experts commented that it is likely that nemolizumab would be combined with topical corticosteroids and intralesional corticosteroids. Although less likely, nemolizumab could be combined with phototherapy in patients with an inadequate response. Nemolizumab may be combined with methotrexate in very severe cases. Combining nemolizumab and cyclosporine therapy would be very unlikely. It is very unlikely that multiple biologics would be combined. CDEC commented that there is no evidence from the OLYMPIA 1 and OLYMPIA 2 trials for the use of nemolizumab in combination with any other PN therapy.

Implementation issues	Response
Consistency with prescribing criteria associated with other drugs reviewed by CDA-AMC in the same therapeutic space It is expected that a CDA-AMC recommendation will be issued for dupilumab before nemolizumab is reviewed by CDEC. Comment for CDEC: • Consider alignment with prescribing criteria for dupilumab, as applicable or appropriate.	This is a comment from the drug programs to inform CDEC deliberations.
Generalizability	
Populations of interest matching the indication but with insufficient data Patients with any of the following were excluded from the pivotal trials: • active atopic dermatitis (signs and symptoms other than dry skin) in the last 3 months • chronic pruritus resulting from another active condition other than PN • neuropathic and psychogenic pruritus. Question for clinical experts or CDEC: • Should such patients be ineligible to receive nemolizumab?	One clinical expert noted that approximately 30% of patients with PN also have atopic dermatitis and that patients with atopic dermatitis alongside moderate to severe PN should not be ineligible to receive nemolizumab (i.e., patients with atopic dermatitis in the absence of moderate to severe PN should be ineligible to receive nemolizumab). The other clinical expert commented that all patients with atopic dermatitis and PN should be eligible to start nemolizumab. One clinical expert commented that patients with chronic pruritus resulting from another active condition in the absence of moderate to severe PN should be ineligible to receive nemolizumab, noting that PN can occur alongside other itchy conditions (e.g., uremic pruritus, atopic dermatitis). Regarding the use of nemolizumab in patients with chronic pruritus resulting from another active condition than PN, the other clinical expert described that this should be left to the discretion of the dermatologist. The clinical expert highlighted this as a reason why nemolizumab should only be prescribed by dermatologists who are able to manage these other conditions and that dermatologists would not unsafely prescribe nemolizumab if a patient is diagnosed with another itchy dermatosis. Both clinical experts stated that their aforementioned comments would also be applicable in the context of neuropathic and psychogenic pruritus. CDEC acknowledged the clinical experts' input, noting that it underscores the importance of combining the PP NRS score with other conditions for initiation of treatment.
Populations outside the indication or reimbursement request but of interest to jurisdictions The pivotal trials only included adult patients, and the draft product monograph notes, "The safety and efficacy of Nemluvio in pediatric patients with PN have not been established." Question for clinical experts or CDEC: • Should pediatric patients be ineligible to receive nemolizumab?	One clinical expert stated that, for the time being, pediatric patients should be ineligible to receive nemolizumab, noting a lack of phase III studies conducted in the pediatric population. The clinical expert highlighted that PN is extremely rare in children. The other clinical expert stated that they cannot comment on the use of nemolizumab in pediatric patients. CDEC agreed with the clinical expert's feedback.

Implementation issues	Response
Care provision issues	
Management of adverse effects In the pivotal trials, atopic dermatitis was reported as an AE with nemolizumab more frequently than with placebo (which seems odd given the sponsor is also seeking NOC for atopic dermatitis). Question or comment for clinical experts or CDEC: • If a patient develops atopic dermatitis while receiving nemolizumab for PN and their PN is responding well to nemolizumab, should they be eligible to receive a concurrent advanced therapy for atopic dermatitis?	One clinical expert commented that patients who develop atopic dermatitis while receiving nemolizumab for PN should have their treatment switched to another agent (e.g., dupilumab can be used for both atopic dermatitis and PN); therefore, it would not make sense to add dupilumab to nemolizumab when dupilumab monotherapy would be sufficient. The other clinical expert also noted that it would be unlikely that multiple biologics would be combined; the likely approach would be to find 1 biologic that is effective for both conditions. CDEC agreed with the clinical experts' feedback.
System and economic issues	
Concerns regarding the anticipated budget impact and sustainability Comment for awareness: • The sponsor notes that nemolizumab for the treatment of moderate to severe PN is anticipated to have a cumulative 3-year budget impact to publicly drug plans of $138.9 million, with budget impact ranging from $72.2 to $299.9 million, with results being sensitive to estimates on the prevalence of PN in Canada.	This is a comment from the drug programs to inform CDEC deliberations.

CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; IGA = Investigator's Global Assessment; NOC = Notice of Compliance; PN = prurigo nodularis; PP NRS = Peak Pruritus Numeric Rating Scale.

Clinical Evidence

Systematic Review

Description of Studies

The OLYMPIA 1 (N = 286) and OLYMPIA 2 (N = 274) trials were both phase III, randomized, double-blind, placebo-controlled studies investigating the efficacy and safety of nemolizumab for the treatment of adult patients with PN. The studies were conducted in a total of 16 countries (77 sites for OLYMPIA 1; 55 sites for OLYMPIA 2), including 8 sites in Canada that randomized a total of 44 patients. In both trials, patients were randomized 2:1 to receive nemolizumab or matched placebo by subcutaneous injection every 4 weeks. The treatment period was 24 weeks in the OLYMPIA 1 trial and 16 weeks in the OLYMPIA 2 trial; follow-up was 8 weeks in both studies.

The primary end points in the OLYMPIA 1 and OLYMPIA 2 trials were the proportion of patients with at least a 4-point improvement from baseline in PP NRS score and the proportion of patients with IGA success at week 16. The PP NRS is an 11-point scale used for the assessment of maximum itch intensity during the previous 24 hours, in which 0 indicates "no itch" and 10 indicates "worst itch imaginable." IGA was used to assess lesion clearance, with response defined as a score of 0 ("clear") or 1 ("almost clear") and at least a 2-point reduction from baseline at week 16.

Key secondary and other secondary end points included measures of improvement in the SD NRS score, itch reduction (PP NRS score), lesion clearance (IGA success), and HRQoL (DLQI score). The SD NRS is an 11-point scale, with 0 indicating no sleep loss and 10 indicating no sleep at all due to the symptoms of the skin disease (PN). The DLQI total score was calculated as the sum of the score for each question, resulting in a minimum score of 0 and a maximum score of 30; a higher total score indicates a greater impairment in QoL. Harms outcomes were also assessed.

Patients eligible for participation in both OLYMPIA pivotal trials were adults aged 18 years or older with a clinical diagnosis of PN for at least 6 months with pruriginous nodular lesions on the upper limbs, lower limbs, and/or trunk; at least 20 nodules on the entire body with bilateral distribution; and an IGA score of at least 3 (indicating moderate or severe global severity); and severe pruritus, as defined by a PP NRS score of at least 7 points. In the OLYMPIA 1 and OLYMPIA 2 trials, the majority of patients were female, white, and between ages 18 and 65 years. Patients were not eligible for participation in the trials if they had uncontrolled or exacerbated asthma, COPD, chronic bronchitis, certain infections, or active atopic dermatitis within the previous 3 months.

Efficacy Results

Improvement of at Least 4 Points From Baseline in PP NRS Score at Weeks 16 and 24

In the OLYMPIA 1 trial, the proportion of patients with improvement of at least 4 points from baseline in weekly average PP NRS score at week 16 was 58.4% in the nemolizumab group and 16.7% in the placebo group (strata-adjusted proportion difference = 40.1%; 95% CI, 29.4% to 50.8%; P value < 0.0001). For the same end point in the OLYMPIA 2 trial, the proportion of patients was 56.3% in the nemolizumab group and 20.9% in the placebo group (strata-adjusted proportion difference = 37.4%; 95% CI, 26.3% to 48.5%; P value < 0.0001). The proportion difference between groups was statistically significant in favour of nemolizumab in both trials, and the clinical experts consulted by CDA-AMC considered the differences to be clinically meaningful. Results at week 24 in the OLYMPIA 1 trial were roughly maintained with those reported at week 16.

IGA Success at Weeks 16 and 24

In the OLYMPIA 1 trial, the proportion of patients with IGA success at week 16 was 26.3% in the nemolizumab group and 7.3% in the placebo group (strata-adjusted proportion difference = 14.6%; 95% CI, 6.7% to 22.6%; P value = 0.0025). For the same end point in the OLYMPIA 2 trial, the proportion of patients with IGA success was 37.7% in the nemolizumab group and 11.0% in the placebo group (strata-adjusted proportion difference = 28.5%; 95% CI, 18.8% to 38.2%; P value < 0.0001). The proportion difference between groups was statistically significant in favour of nemolizumab in both trials, and the clinical experts consulted by CDA-AMC considered the differences to be clinically meaningful. Results at week 24 in the OLYMPIA 1 trial were consistent with those reported at week 16.

Improvement of at Least 4 Points From Baseline in SD NRS Score at Week 16

In the OLYMPIA 1 trial, the proportion of patients with improvement of at least 4 points from baseline in weekly average SD NRS score at week 16 was 50.0% in the nemolizumab group and 11.5% in the placebo

group (strata-adjusted proportion difference = 38.0%; 95% CI, 27.8% to 48.2%; P value < 0.0001). For the same end point in the OLYMPIA 2 trial, the proportion of patients with improvement of at least 4 points from baseline in weekly average SD NRS score was 51.9% in the nemolizumab group and 20.9% in the placebo group (strata-adjusted proportion difference = 31.9%; 95% CI, 20.7% to 43.2%; P value < 0.0001). The proportion difference between groups was statistically significant in favour of nemolizumab in both trials (input regarding the clinical meaningfulness of these differences was not received from the clinical experts consulted by CDA-AMC).

Improvement of at Least 4 Points From Baseline in DLQI Score at Week 16 and Week 24

In the OLYMPIA 1 trial, the proportion of patients with an improvement of at least 4 points from baseline in DLQI total score at week 16 was 70.5% in the nemolizumab group and 42.7% in the placebo group (strata-adjusted proportion difference = 27.5%; 95% CI, 15.8 to 39.2; P value < 0.0001), and at week 24, the proportions were 71.1% and 35.4%, respectively (strata-adjusted proportion difference = 35.5%; 95% CI, 23.9% to 47.2%). In the OLYMPIA 2 trial, the proportion of patients with an improvement of at least 4 points from baseline in DLQI total score at week 16 was 74.9% in the nemolizumab group and 39.6% in the placebo group (strata-adjusted proportion difference = 37.4%; 95% CI, 25.7% to 49.0%; P value < 0.0001). The clinical experts consulted by CDA-AMC considered the differences to be clinically meaningful.

There were no published between-group minimal important difference values provided by the sponsor for the PP NRS, IGA success, and DLQI end points assessed by GRADE; as such, the thresholds used to judge the target of certainty in the GRADE assessment is based on input from the clinical experts consulted by CDA-AMC.

Harms Results

In the OLYMPIA 1 trial, at least 1 AE was reported in 71.7% of patients in the nemolizumab group and 65.3% of patients in the placebo group. The most common AEs (nemolizumab versus placebo) were COVID-19 (8.0% versus 14.7%), nasopharyngitis (6.4% versus 8.4%), headache (7.0% versus 2.1%), cough (4.8% versus 5.3%), dyspnea (3.2% versus 5.3%), neurodermatitis (9.6% versus 20.0%), and eczema (5.3% versus 1.1%). At least 1 serious AE (SAE) was reported in 8.6% of patients in the nemolizumab group and 10.5% of patients in the placebo group; AEs leading to study drug withdrawal occurred in 4.8% and 3.2% of patients, respectively. One patient in the placebo group died during the OLYMPIA 1 trial. At least 1 AESI was reported in 17.1% of patients in the nemolizumab group and 18.9% of patients in the placebo group. The most commonly reported AESI in the nemolizumab and placebo groups was infections (10.7% and 16.8%, respectively). The AESI of newly diagnosed asthma or worsening of asthma was reported in 3.7% of patients in the nemolizumab group and 2.1% of patients in the placebo group.

In the OLYMPIA 2 trial, at least 1 AE was reported in 61.2% and 53.8% of patients in the nemolizumab and placebo groups, respectively. In the OLYMPIA 2 trial, the most common AEs (nemolizumab versus placebo) were headache (6.6% versus 4.4%), neurodermatitis (3.8% versus 11.0%), and dermatitis atopic (5.5% versus 0%). At least 1 SAE was reported in 2.2% of patients in the nemolizumab group and 5.5% of patients in the placebo group; AEs leading to study drug withdrawal occurred in 2.7% and 2.2% of patients, respectively. No patient deaths occurred during the OLYMPIA 2 trial. At least 1 AESI was reported in 11.5%

of patients in the nemolizumab group and 9.9% of patients in the placebo group. The most commonly reported AESI in the nemolizumab and placebo groups was infections (5.5% versus 6.6%). The AESI of newly diagnosed asthma or worsening of asthma was reported in 2.7% of patients in the nemolizumab group and 1.1% of patients of patients in the placebo group.

Critical Appraisal

The OLYMPIA 1 and OLYMPIA 2 trials were both multicentre, phase III, randomized, double-blind, placebo-controlled studies. Methods of randomization and treatment allocation were adequate. Reported baseline characteristics were generally balanced across the nemolizumab and placebo groups in both trials. Some differences between arms were noted; however, the clinical experts consulted on this review did not anticipate those differences would impact the interpretation of the results. For both pivotal trials, the prespecified sample size was achieved, and the screening failure rates approached or slightly exceeded the expected rates. Both trials were powered for the primary end points of the proportion of patients with at least a 4-point improvement in PP NRS score and the proportion of patients with IGA success (both at week 16). The multiple testing procedure included all primary and key secondary end points. Analyses of other secondary end points were not adjusted for multiplicity; therefore, conclusions cannot be made regarding statistical significance for these end points. Loss to follow-up was low, and rates of discontinuation were similar between treatment arms in both studies. Due to differences in treatment response between arms (e.g., reduction in pruritus), patients and investigators could have become aware of treatment allocation, which may have introduced bias for subjective end points such as PP NRS and DLQI. In both trials, there was a disproportionate use of rescue treatment between study arms, with a higher percentage of patients in the placebo arms requiring rescue therapy than in the nemolizumab arms. This imbalance in rescue treatment could have exaggerated the itch reduction response with placebo, thereby minimizing the comparative benefit of nemolizumab. In contrast, the clinical experts consulted by CDA-AMC did not expect the differences between rescue therapy use between groups to impact the interpretation of the efficacy results.

The clinical experts stated that the characteristics of the patients randomized in the OLYMPIA pivotal trials were a reasonable reflection of patients who would receive nemolizumab for moderate to severe PN in Canada. In both OLYMPIA trials, most patients were white, and patients with certain medical conditions (e.g., active atopic dermatitis, uncontrolled asthma, chronic infections) were not eligible. These factors present potential generalizability limitations. The trial populations do not adequately represent the racial diversity of patients with PN. In addition, the clinical experts noted that PN generally affects older people with comorbidities, such as eczema, severe asthma, or hepatitis, who may qualify for treatment with nemolizumab in clinical practice. Topical and systemic medications and procedures were prohibited during the trials, and nemolizumab was given as monotherapy (unless rescue therapy was used). The clinical experts expressed that, although nemolizumab may be used on its own in clinical practice, it is likely that concomitant treatments such as topical or intralesional corticosteroids would also be prescribed as needed. An important limitation of the OLYMPIA 1 and OLYMPIA 2 trials is that nemolizumab was compared to placebo, which does not represent the standard of care for treatment of PN. The clinical experts noted that dupilumab would be the most relevant comparator to nemolizumab for the indication under review. However, dupilumab was

not indicated for treatment of PN at the time of the OLYMPIA 1 and OLYMPIA 2 trials. The main efficacy and harms outcomes assessed in the OLYMPIA 1 and OLYMPIA 2 trials align with outcomes of importance identified by patients and clinicians.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for 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:

- pruritus response (proportion of patients with an improvement of ≥ 4 points from baseline in PP NRS score)
- global severity of PN (proportion of patients with IGA success)
- HRQoL (proportion of patients with an improvement of ≥ 4 points in DLQI)
- harms (AESI of newly diagnosed asthma or worsening of asthma).

Table 3: Summary of Findings for Nemolizumab vs. Placebo for Patients With Moderate to Severe Prurigo Nodularis

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Pruritus response				
Proportion of patients with an improvement of ≥ 4 points from baseline in PP NRS[a] Follow-up: 16 weeks	560 (2 RCTs)	OLYMPIA 1 • Nemolizumab: 584 per 1,000 • Placebo: 167 per 1,000 • Strata-adjusted proportion difference: 401 more per 1,000 (95% CI, 294 to 508 more per 1,000) OLYMPIA 2 • Nemolizumab: 563 per 1,000 • Placebo: 209 per 1,000 • Strata-adjusted proportion difference: 374 more per 1,000 (95% CI, 263 to 485 more per 1,000)	High[b]	Nemolizumab results in a clinically important increase in the proportion of patients with at least a 4-point improvement in PP NRS score at 16 weeks compared with placebo.
Global severity of PN				
Proportion of patients with IGA success[c] Follow-up: 16 weeks	560 (2 RCTs)	OLYMPIA 1 • Nemolizumab: 263 per 1,000 • Placebo: 73 per 1,000 • Strata-adjusted proportion difference: 146 more per 1,000 (95% CI, 67 to 226 more per 1,000) OLYMPIA 2 • Nemolizumab: 377 per 1,000 • Placebo: 110 per 1,000 • Strata-adjusted proportion difference:	High[b]	Nemolizumab results in a clinically important increase in the proportion of patients with IGA success at 16 weeks compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		285 more per 1,000 (95% CI, 188 to 382 more per 1,000)		
HRQoL				
Proportion of patients with an improvement of ≥ 4 points in DLQI[d] Follow-up: 24 weeks	286 (1 RCT)	OLYMPIA 1 • Nemolizumab: 711 per 1,000 • Placebo: 354 per 1,000 • Strata-adjusted proportion difference: 355 more per 1,000 (95% CI, 239 to 472 more per 1,000)	Moderate[b,e]	Nemolizumab likely results in a clinically important increase in the proportion of patients with at least a 4-point improvement in DLQI score at 24 weeks compared with placebo.
Proportion of patients with an improvement of ≥ 4 points in DLQI[d] Follow-up: 16 weeks	274 (1 RCT)	OLYMPIA 2 • Nemolizumab: 749 per 1,000 • Placebo: 396 per 1,000 • Strata-adjusted proportion difference: 374 more per 1,000 (95% CI, 257 to 490 more per 1,000)	Moderate[b,e]	Nemolizumab likely results in a clinically important increase in the proportion of patients with at least a 4-point improvement in DLQI score at 16 weeks compared with placebo.
Harms				
Proportion of patients with newly diagnosed asthma or worsening of asthma Follow-up: 24 weeks (OLYMPIA 1) 16 weeks (OLYMPIA 2)	556 (2 RCTs)	OLYMPIA 1[f] • Nemolizumab: 37 per 1,000 • Placebo: 21 per 1,000 OLYMPIA 2[f] • Nemolizumab: 27 per 1,000 • Placebo: 11 per 1,000	Low[g]	Nemolizumab may result in an increase in newly diagnosed asthma or worsening of asthma when compared with placebo. The clinical importance of the increase is unclear.

CI = confidence interval; DLQI = Dermatology Life Quality Index; HRQoL = health-related quality of life; IGA = Investigator's Global Assessment; PN = prurigo nodularis; PP NRS = Peak Pruritus Numeric Rating Scale; RCT = randomized controlled trial; vs. versus.

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

[a]The PP NRS was a patient-reported, daily scale that asked patients for a unit score on an 11-point scale (0 to 10) in which 0 was "no itch" and 10 was "worst itch imaginable." The PP NRS was used as an assessment of the maximum intensity of pruritus during the previous 24 hours; patients were asked to rate their itch at the worst moment during that time period. Based on clinical expert input, the threshold for a clinically important between-group difference was 200 per 1,000 for the proportion of patients with at least a 4-point reduction from baseline at 16 weeks.

[b]The thresholds used to judge the target of certainty in the GRADE assessments were based on input from clinical experts.

[c]The IGA is a 5-point scale used by the investigator to evaluate the global severity of PN. Based on review of the patient's skin, the investigator assigned a score of 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), or 4 (severe). Treatment response (IGA success) was defined as a score of 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline. Based on clinical expert input, the threshold for a clinically important between-group difference was 150 per 1,000 for the proportion of patients with an IGA success at 16 weeks.

[d]The DLQI is a patient-reported, 10-item questionnaire covering domains of symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment used to measure how much a patient's skin problem has affected their life over the past week. Patients rated each question on a scale ranging from 0 (not at all) to 3 (very much). The DLQI total score was calculated as the sum of the scores for all questions, resulting in a minimum score of 0 and a maximum score of 30; a higher total score indicated a greater impairment in quality of life. Based on clinical expert input, the threshold for a clinically important between-group difference for the proportion of patients with at least a 4-point reduction from baseline was 200 per 1,000 at 24 weeks and 150 to 200 per 1,000 at 16 weeks.

[e]No statistical tests were performed. Rated down 1 level due to serious study limitations (the potential for unblinding with a self-reported measure).

[f]Between-group difference and corresponding 95% CI results were not available.

[g]No statistical tests were performed. There is no known minimal important difference, so the target of certainty appraisal was any effect. Rated down 2 levels due to very serious imprecision; between-group differences and CIs were not available, so it is unknown if the CIs include the possibility of no difference, fewer harms, or increased harms. Clinical experts consulted by CDA-AMC commented that it is possible that a higher incidence of worsening of asthma may occur in clinical practice than reported in the OLYMPIA pivotal trials.

Sources: Sponsor's Summary of Clinical Evidence, OLYMPIA 1 Clinical Study Report, OLYMPIA 2 Clinical Study Report, sponsor's response to request for additional information. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Study

Description of Study

The OLYMPIA LTE (NCT04204616) is an ongoing, phase III, prospective, single-arm, multicentre, open-label study to evaluate the long-term safety and efficacy of nemolizumab in adult patients with PN. The efficacy results summarized in this review are from interim analysis 2 (data available as of July 21, 2024) supplemented with data from interim analysis 1 (data cut-off date: March 10, 2023). Patients from a previous phase IIa study who completed all screening assessments 28 days before the baseline visit or first dose of study drug were eligible to enrol. Also, patients from the phase III trials (OLYMPIA 1 and OLYMPIA 2) were eligible to enrol within 56 days following their last visit.

Each patient's participation in the study will be up to 196 weeks. The study consists of a screening period (up to 4 weeks), a treatment period (up to 184 weeks with final dose administered), and an 8-week follow-up period.

Dose received (1 or 2 injections) in the LTE study was based on the patient's body weight and previous treatment assignment in the nemolizumab PN studies.

For patients who enrolled from the phase IIa study:

- Patients weighing less than 90 kg at baseline received 30 mg nemolizumab (with a 60 mg loading dose at baseline) every 4 weeks.
- Patients weighing 90 kg or more at baseline received 60 mg nemolizumab (two 30 mg injections; no loading dose) every 4 weeks.

For patients who enrolled from the phase III studies:

- The day 1 or baseline dose in the LTE study was based on the blinded study treatment assigned during the pivotal trial to maintain the blinding of the study. Therefore, patients received either 2 blinded 30 mg injections of nemolizumab or 1 blinded 30 mg injection of nemolizumab and 1 blinded placebo injection.
- After day 1, the same dosing regimen used as in the phase III study (1 or 2 subcutaneous injections of 30 mg nemolizumab, based on patient weight at baseline of the phase III study).

Key efficacy outcomes included IGA success (defined as an IGA score of 0 [clear] or 1 [almost clear]), improvement in PP NRS, SD NRS, and DLQI.

No sample size calculation was performed, but approximately 450 patients were planned to be enrolled in this study, depending on the rollover rate from the lead-in studies. The safety population consisted of all patients who received at least 1 dose of nemolizumab (blinded or open label). All efficacy analyses were performed on the safety population and were descriptive in nature. The efficacy analyses were carried out using observed cases without imputing missing data. For binary secondary end points, efficacy data collected on or after the use of rescue therapy was treated as treatment failure, with the exception of observed cases analysis (in which observed data were used regardless of the use of rescue therapy).

All efficacy assessments were summarized by LTE treatment and previous treatment at each analysis visit. Data were summarized under the following headings for efficacy:

- continuous nemolizumab (patients with a < 12-week interval between the last nemolizumab dose in the lead-in study and the first dose in the LTE study [N = 307] was used to evaluate the persistence of nemolizumab effect)
- placebo to nemolizumab (included patients who never received nemolizumab before the LTE study)
- re-treatment (patients with a ≥ 12-week interval between the last nemolizumab dose in the lead-in study and the first dose in the LTE study [N = 27],was used to assess any loss of response).

Overall, 508 patients entered the LTE study. The mean age of patients was 55.40 years, and mean body weight was 82.44 kg. Most patients were white (87.20%) and female (60.40%). Overall, 32.10% of patients had a moderate IGA score and 15.70% of patients had a severe IGA score. A higher proportion of patients were in the placebo-to-nemolizumab group (moderate: 43.10%; severe: 31.60%) than the continuous nemolizumab group (moderate: 26.10%; severe: 6.20%). At lead-in baseline, patients' weekly average PP NRS score was 8.49 points, weekly average SD NRS score was 7.09 points, and mean DLQI total score was 16.90 points. The majority of patients had no atopy background (continuous nemolizumab group: 64.20%; placebo-to-nemolizumab group: 64.90%). Average time since PN diagnosis was 101.63 months.

Efficacy Results

IGA Success From LTE Baseline

The proportion of patients with IGA success (defined as an IGA score of 0 [clear] or 1 [almost clear]) at LTE baseline was 40.1% for patients who were continuing treatment with nemolizumab (the continuous nemolizumab group) and 12.6% for patients who transitioned from placebo to treatment with nemolizumab (the placebo-to-nemolizumab group). At week 28, the proportion of patients with IGA success was similar across the 2 groups (continuous nemolizumab group: 53.3%; placebo-to-nemolizumab group: 56.3%). Continuous improvements in skin clearance at week 100 were observed among the 2 groups (continuous nemolizumab group: 73.4%; placebo-to-nemolizumab group: 75.2%).

Improvement of at Least 4 Points From Baseline Lead-In in PP NRS Score

More than 80% of patients experienced at least a 4-point improvement in PP NRS score at week 28 in the continuous nemolizumab group (88.8%) and placebo-to-nemolizumab group (82.4%). At week 100, results indicated consistent improvement in itch relief in the continuous nemolizumab group (92.1%) and placebo-to-nemolizumab group (94.1%); however, sample sizes steadily decreased over time.

Improvement of at Least 4 Points From Baseline Lead-In in SD NRS Score

Following nemolizumab treatment in the LTE study, the proportion of patients with an improvement of at least 4 points from baseline lead-in in SD NRS score generally increased over time across all patients and within each group. A consistent improvement of at least 4 points from baseline lead-in was observed across the groups at week 100 (continuous nemolizumab group: 86.4%; placebo-to-nemolizumab group: 87.3%). However, sample sizes steadily decreased over time.

Improvement of at Least 4 Points From Baseline Lead-In in DLQI Score

At week 28, the proportion of patients achieving at least a 4-point improvement from baseline lead-in in DLQI score was 87.8% and 90.5% in the continuous nemolizumab and the placebo-to-nemolizumab groups, respectively. Continuous improvements were observed in patients in both groups at week 52 (continuous nemolizumab group: 90.1%; placebo-to-nemolizumab group: 91.0%) and week 100 (continuous nemolizumab group: 89.9%; placebo-to-nemolizumab group: 93.1%).

Harms Results

A total of 407 patients (80.1%) experienced at least 1 AE during the overall study period. The most frequently reported AEs included infections and infestations (54.3%); skin and subcutaneous tissue disorders (36.8%); musculoskeletal and connective tissue disorders (26.0%); respiratory, thoracic, and mediastinal disorders (17.0%); and nervous system disorders (15.4%). SAEs were reported in 54 patients (10.6%). SAEs experienced by more than 1 patient were neurodermatitis (4; 0.8%), myocardial infarction (3; 0.6%), and angina pectoris, congestive cardiac failure, cholelithiasis, pneumonia, osteoarthritis, and carotid artery stenosis (2 [0.4%] patients each). A total of 35 patients (6.9%) had an AE leading to withdrawal from the study. AESIs occurred among 319 (62.8%) patients. The most commonly reported AESIs were infections (54.5%) and injection-related reactions (31.7%). Newly diagnosed asthma or worsening of asthma was reported in 5.7% of patients. Two (0.4%) patients experienced an AE leading to death. The causes of death were myocardial infarction and end-stage renal disease; however, both patients had medical history of comorbidities and neither death was considered related to the study drug.

Critical Appraisal

The OLYMPIA LTE was a phase III, prospective, single-arm, multicentre, open-label study. The single-arm design of the study limits the ability to draw conclusions on the long-term efficacy of nemolizumab. The open-label nature of the study may increase the risk of bias in the evaluation of subjective outcomes. The accumulative exposure to study treatment and treatment compliance were not summarized by each group (i.e., continuous nemolizumab, re-treatment or placebo to nemolizumab), and this further compromised the ability to make a judgment on the potential different patterns of correlations between treatment exposure and outcome over the long term. Patients received treatment in the LTE study based on their previous enrolment in nemolizumab studies; the impact of these differing dosing regimens on efficacy results is unknown.

Data from patients contributing to analyses steadily decreased over time as they discontinued treatment (approximately 30% at interim analysis 2). Those patients who discontinued from the LTE study (17.9% and 14.9% in the continuous nemolizumab and placebo-to-nemolizumab groups, respectively) could be systematically different from those who remained in the study. Therefore, the trend of relative stable treatment effect over time could be biased because of survival or attrition bias. The sample size in the re-treatment group was small, which limits the ability to draw any conclusions regarding efficacy results. The majority of patients received at least 1 concomitant therapy during the treatment period, and the effect of these on efficacy outcomes cannot be determined. The harms data aligned with the evidence from the pivotal studies.

Indirect Comparisons

Description of Studies

Due to the lack of direct evidence comparing nemolizumab with other existing relevant therapies for treatment of patients with PN, the sponsor submitted 1 ITC: an NMA comparing nemolizumab with dupilumab, vixarelimab, nalbuphine, and placebo. The outcomes assessed in the NMA included PP NRS score change from baseline, PP NRS response, IGA success, composite PP NRS and IGA responders, DLQI score, and AEs at various time points ranging from week 4 to week 24. This ITC summary focuses on the comparison of nemolizumab with dupilumab because vixarelimab and nalbuphine are not relevant in settings in Canada.

Efficacy Results

The NMA demonstrated a favourable benefit of nemolizumab when compared with dupilumab. However, the favourable effect was not consistent and was influenced by the outcomes measured (e.g., PP NRS score change from baseline, PP NRS response, IGA success, composite PP NRS and IGA responders, and DLQI score change from baseline), the time points assessed, as well as the choice of the model fit (fixed-effect model analysis versus random-effect model analysis). Although the findings of the NMA are subject to considerable limitations due to the significant heterogeneity between trials included in the analyses, the clinical experts consulted for this review indicated that, overall, the results aligned with their expectation that the effects of nemolizumab would be comparable to that of dupilumab in clinical practice.

Sensitivity analyses were conducted based on no-topical corticosteroid and/or no-topical calcineurin inhibitor population. Based on the fixed-effect model analysis, for PP NRS response at week 12, a favourable effect of nemolizumab was reported. No favourable effect of nemolizumab was reported for other outcomes. Based on the random-effect model analysis, a favourable effect for nemolizumab was observed for PP NRS response at week 12, whereas no favourable effect for nemolizumab was observed for other outcomes (e.g., composite PP NRS and IGA response at week 24).

Harms Result

Based on both fixed-effect and random-effect model analysis, the NMA did not show a favourable safety profile for nemolizumab when compared with dupilumab.

Critical Appraisal

Overall, the NMA was conducted according to accepted methodological guidance. The potential limitations of the NMA are discussed subsequently.

The potential key limitations of the NMA were the considerable heterogeneity across the included studies in terms of the study and patient characteristics (e.g., eligibility criteria, population, trial duration). For example, the dupilumab trials required patients to have a history of failure of a 2-week course of medium- to super-high–potency topical corticosteroids or not be medically advisable for them to use TCS, this was not required in the nemolizumab trials. Therefore, the NMA results may be potentially biased in favour of nemolizumab because patients with a history of being refractory to treatment (in dupilumab trial) may have a relatively poorer response during the trial compared with patients without prior treatment-refractory history. These

significant differences in patient and trial characteristics across included studies may threaten the transitivity assumption for the NMA analysis.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps in the systematic review evidence were submitted by the sponsor.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Short-term decision tree (16 weeks) followed by long-term Markov model
Target population	Adults with moderate to severe PN (defined as an IGA score of 3 or 4, a PP NRS score of at least 7, and at least 20 pruriginous lesions)
Treatment	Nemolizumab plus BSC BSC consists of antihistamines, emollients, topical corticosteroids, topical calcineurin inhibitors, systemic corticosteroids, and immunosuppressants
Dose regimen	• For patients weighing < 90 kg, nemolizumab is recommended to be administered at an initial dose of 60 mg, through two 30 mg injections, followed by 30 mg administered every 4 weeks. • For patients weighing ≥ 90 kg, nemolizumab is recommended to be administered at an initial dose of 60 mg, through two 30 mg injections, followed by 60 mg every 4 weeks.
Submitted price	Nemolizumab: $2,995.00 per 30 mg prefilled syringe
Submitted treatment cost	First year for patients weighing < 90 kg: $42,064 Subsequent years for patients weighing < 90 kg: $39,069 First year and subsequent years for patients weighing ≥ 90 kg: $78,137
Comparators	• Dupilumab plus BSC • BSC alone
Perspective	Publicly funded health care payer in Canada
Outcomes	QALYs, life-years
Time horizon	Lifetime (45 years)
Key data sources	OLYMPIA 1 and OLYMPIA 2 trials and long-term extension study Indirect treatment comparison between nemolizumab plus BSC and dupilumab plus BSC
Submitted results	Nemolizumab is expected to generate more QALYs and fewer costs than dupilumab plus BSC and BSC alone; therefore, it dominates both treatment options.
Key limitations	• The sponsor used an estimate of treatment efficacy that introduces a bias that favours nemolizumab. The submitted model used a composite marker of treatment response that was derived from an NMA comparing nemolizumab to dupilumab and BSC alone at different observation dates for nemolizumab and dupilumab (16 weeks vs. 12 weeks). When the same composite measure was evaluated at 24 weeks for both treatments, the results no longer

Component	Description
	suggested a statistically significant difference. Clinical experts consulted by CDA-AMC for this review suggested that they would expect nemolizumab and dupilumab to be equivalent in terms of efficacy and that the differences between them at week 24 were not clinically meaningful. • The decision model does not accurately reflect the decision problem. In the submitted economic model, patients who discontinue dupilumab could go on to receive nemolizumab. As a consequence, nemolizumab is present in both the treatment and comparator. Therefore, the model does not address the question if nemolizumab is cost-effective for the treatment of PN. Additionally, there was no clinical evidence in the OLYMPIA trials to inform the efficacy of nemolizumab for patients who were previously treated with dupilumab. • The sponsor derived utility estimates from the OYMPIA trial. Beyond week 52, the sponsor assumed higher health state utility for patients receiving nemolizumab compared to other treatments, despite experiencing the same health state. CDA-AMC guidelines specify that treatment-specific utility estimates should not be used because utility estimates should be based on a simulated patient's state of health.
CDA-AMC reanalysis results	• The CDA-AMC base case was derived by removing subsequent biologic treatments, using the 24-week estimate from the sponsor's NMA to estimate relative efficacy for dupilumab vs. nemolizumab, and removing treatment-specific utilities. • In the CDA-AMC base case, nemolizumab plus BSC was associated with more costs and more QALYs than dupilumab plus BSC or BSC alone. The sequential ICER of nemolizumab plus BSC was $1,124,092 per QALY gained when compared to dupilumab plus BSC (incremental costs = $73,066; incremental QALYs = 0.07). • The pairwise ICER for nemolizumab plus BSC compared to BSC alone was $248,002 per QALY gained. A price reduction of 71% is required for nemolizumab (from $2,995 to $869 per prefilled pen or prefilled syringe) plus BSC to be considered cost-effective compared to BSC alone at a willingness-to-pay threshold of $50,000 per QALY. • Given the implication of the 24-week comparative efficacy estimates in the sponsor's NMA, the evidence is insufficiently robust to conclude any difference in effectiveness between nemolizumab and dupilumab. Therefore, a price premium is not supported for nemolizumab over dupilumab.

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; IGA = Investigator's Global Assessment; LY = life-year; NMA = network meta-analysis; PN = prurigo nodularis; PP NRS = Peak Pruritus Numeric Rating Scale; QALY = quality-adjusted life-year.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis. The eligible population sizes are uncertain and were likely underestimated by the sponsor. The comparators are also uncertain. The sponsor included dupilumab as a comparator, which is not currently reimbursed for PN in Canada. The comparators included in BSC did not differ as the reimbursement population changed from the broader Health Canada indication to the sponsor's narrower reimbursement request population. The CDA-AMC reanalyses increased the sizes of the populations eligible for nemolizumab to align with the Health Canada indication and the sponsor's reimbursement request population. Based on the CDA-AMC reanalyses, the 3-year incremental budgetary cost of reimbursing nemolizumab for patients with moderate to severe PN whose disease is not adequately treated by topicals (the place in therapy covered by the Health Canada indication) is expected to be $186,009,877 (year 1: $52,537,538; year 2: $63,652,592; year 3: $69,819,742).

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. Ran Goldman; Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: May 29, 2025

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

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

ISSN: 2563-6596

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