Canadian Journal of Health Technologies

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

August 2025 Volume 5 Issue 8

Drugs Health Technologies Health Systems

Reimbursement Recommendation

Dupilumab (Dupixent)

Indication: 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. Dupixent can be used with or without topical corticosteroids.

Sponsor: Sanofi-Aventis Canada Inc.

Final Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Dupixent?

Canada's Drug Agency (CDA-AMC) recommends that Dupixent 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?

Dupixent should only be covered to treat adult patients with moderate-to-severe PN who have been diagnosed by a dermatologist, have severe itching (based on a Worst Itch Numeric Rating Scale score of 7 or higher), have at least 20 PN lesions on both sides of the body, and have tried topical prescription therapies and had an inadequate response.

What Are the Conditions for Reimbursement?

Dupixent should only be reimbursed if the patient is under the care of a dermatologist who has expertise in the management of PN, and if the cost of Dupixent is reduced. When first prescribed, Dupixent should only be reimbursed for 6 months. Dupixent should not be used in combination with other systemic therapies for PN.

Why Did CDA-AMC Make This Recommendation?

- In 2 clinical trials that enrolled patients with moderate-to-severe PN whose disease was inadequately controlled on topical prescription therapies or for whom those therapies were not advisable, Dupixent improved itching, reduced the number of PN lesions, and improved health-related quality of life compared with placebo.
- Dupixent may meet some needs that are important to patients, including improving itch control and health-related quality of life and offering a subcutaneous treatment option that can be administered in a patient's home.
- Based on the CDA-AMC assessment of the health economic evidence, Dupixent 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, Dupixent is estimated to cost the public drug plans approximately $187 million over the next 3 years.

Summary

Additional Information

What Is PN?

PN is a rare condition that affects the skin, causing raised, red nodules that are extremely itchy. Constant scratching causes the nodules to become crusted and bleed, which can make the itching worse. Severe PN can be debilitating and disrupt sleep, work, and school, and negatively impact mental health. The prevalence is estimated to be 83 per 100,000 people.

Unmet Needs in PN

There is no cure for PN, and existing treatments are often unable to adequately control itch. There is a need for safe and effective therapies that address the underlying causes of PN and that are easy to administer.

How Much Does Dupixent Cost?

Treatment with Dupixent is expected to cost approximately $26,425 per patient in the first year and $25,446 per patient in subsequent years of treatment.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that dupilumab be reimbursed 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, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two phase III, double-blind, placebo-controlled trials (LIBERTY-PN PRIME [PRIME], N = 151; and LIBERTY-PN PRIME2 [PRIME2], N = 160) demonstrated that dupilumab resulted in added clinical benefit in patients with PN whose disease was inadequately controlled on topical prescription therapies or when those therapies were not advisable. The PRIME and PRIME2 trials showed that, compared to placebo, dupilumab resulted in statistically significant and clinically meaningful improvements in pruritus control — measured by a Worst Itch Numeric Rating Scale (WI-NRS) improvement of at least 4 points — and in the number of PN lesions — assessed by an Investigator's Global Assessment PN-Stage score (IGA PN-S) of 0 or 1. The treatment difference in the proportions of patients with a WI-NRS improvement from baseline to week 24 was 42.7% (95% confidence interval [CI], 27.8 to 57.7) and 42.6% (95% CI, 29.1 to 56.1) in the PRIME and PRIME2 studies, respectively. The treatment difference in the proportions of patients with an IGA PN-S score of 0 or 1 from baseline to week 24 was 28.3% (95% CI, 13.4 to 43.2) and 30.8% (95% CI, 16.4 to 45.2) in the PRIME and PRIME2 studies, respectively. These results were supported by statistically significant and clinically meaningful improvements in health-related quality of life (HRQoL) — assessed as change from baseline to week 24 in the Dermatology Life Quality Index (DLQI) score (least square mean difference = −6.19 [95% CI, −8.34 to −4.05] and −6.39 [95% CI, −8.42 to −4.36], in the PRIME and PRIME2 studies, respectively).

There was no evidence comparing dupilumab with currently available off-label systemic therapies, phototherapy, or high- to super–high-potency steroid treatment. Therefore, the comparative efficacy and safety of dupilumab versus these alternative treatments remain unknown.

Patients expressed a need for treatments that provide effective and sustained itch relief with minimal adverse effects, improve HRQoL (allowing patients to resume personal, professional, and social activities), and offer a convenient route of administration. CDEC concluded that, compared with placebo, dupilumab met some of the needs identified by patients by improving itch control and HRQoL and offering a subcutaneous treatment option that can be administered in a patient’s home; however, the impact of dupilumab relative to other comparators remains unknown. CDEC noted that dupilumab’s safety profile in patients with PN was consistent with that seen in its other indications and appeared manageable; however, uncertainty remained in the absence of long-term safety data.

Using the sponsor-submitted price for dupilumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for dupilumab and best supportive care (BSC) was $138,915 per quality-adjusted life-year (QALY) compared with BSC alone. At this incremental cost-effectiveness ratio, dupilumab

is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for the treatment of adult patients with moderate-to-severe PN whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. A price reduction is required for dupilumab to be considered cost-effective at a $50,000 per QALY threshold. The cost-effectiveness compared to off-label systemic therapies is unknown.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients (aged ≥ 18 years) must have a confirmed diagnosis of moderate-to-severe PN with the following criteria: 1.1. PN diagnosis by a dermatologist 1.2. WI-NRS score ≥ 7 points 1.3. IGA PN-S score of 3 or greater (i.e., a minimum of 20 PN lesions distributed bilaterally) 1.4. history of inadequate response to an appropriate course of topical prescription therapy.	Evidence from 2 phase III RCTs (PRIME and PRIME2) demonstrated that dupilumab resulted in a clinically meaningful improvement in pruritus control, the number of PN lesions, and the DLQI score in patients with these characteristics.	Clinical experts noted that an appropriate course of topical prescription therapy includes 6 to 8 weeks of a high- to super–high-potency TCS or, in patients in whom a TCS is not advisable, 6 to 8 weeks of TCIs. The PRIME and PRIME2 studies included patients in whom topical prescription therapies for PN were medically inadvisable because of intolerance or contraindications to these therapies.
2. The maximum duration of initial authorization is 6 months.	PRIME and PRIME2 trials assessed initial treatment response at 24 weeks. Clinical experts noted that an initial authorization period of 6 months would be reasonable to assess the treatment response.	In jurisdictions with limited access to dermatologists, a duration of 12 months for initial authorization could be considered.
Renewal		
3. Reimbursement of dupilumab treatment should be continued after the initial 6 months of treatment, if there is a documented change of at least 1 of the following: 3.1. reduction in itch indicated by a decrease in the WI-NRS score of 4 points or greater 3.2. decrease in the total count of lesions to 5 or fewer indicated by an IGA PN-S score of 0 or 1.	The PRIME and PRIME2 trials used at least a 4-point reduction in the WI-NRS as a threshold for clinically meaningful improvement in pruritus, which is supported by the clinical experts. In the PRIME and PRIME2 trials, IGA PN-S success was defined as achieving an IGA PN-S score of 0 (no nodules) or 1 (5 or fewer nodules), which was considered a clinically meaningful outcome by the clinical experts.	Clinical experts noted that for patients with a good response to treatment after the initial 6 months of treatment, assessments for renewal should occur every year. Dupilumab could be renewed similarly to other biologics currently reimbursed for the treatment of PN as per the reimbursement criteria for each public drug plan.
4. For subsequent renewal, the treating clinician must verify that the initial response observed after the first 6 months of dupilumab therapy has been sustained in at least 1 of the following: the WI-NRS score or IGA PN-S score.	This is to ensure patients are maintaining their response to treatment with dupilumab.	—

Reimbursement condition	Reason	Implementation guidance
Prescribing		
5. Dupilumab should be prescribed by a dermatologist with expertise in the management of PN.	This is to ensure that dupilumab is prescribed for appropriate patients and that adverse effects are managed in an optimal and timely manner.	—
6. Dupilumab should not be administered in combination with systemic therapies for PN.	There was no evidence submitted to CDEC to support the use of dupilumab in combination with other systemic treatments for PN.	Dupilumab was approved by Health Canada for use with or without TCSs. Based on clinical expert input, dupilumab may be used in combination with TCSs, TCIs, intralesional corticosteroid injections, and/or phototherapy.
Pricing		
7. A reduction in price is required.	The ICER for dupilumab plus BSC is $138,915 when compared with BSC alone. A price reduction of at least 61% would be required for dupilumab to achieve an ICER of $50,000 per QALY compared to BSC alone. Due to uncertainty in the clinical evidence, a higher price reduction may be needed.	—
Feasibility of adoption		
8. The economic feasibility of adoption of dupilumab must be addressed.	At the submitted price, the incremental budget impact of dupilumab is expected to be greater than $40 million in year 2 and year 3.	—

BSC = best supportive care; CDEC = Canadian Drug Expert Committee; DLQI = Dermatology Life Quality Index; ICER = incremental cost-effectiveness ratio; IGA PN-S = Investigator's Global Assessment Prurigo Nodularis-Stage; PN = prurigo nodularis; PRIME = LIBERTY-PN PRIME; PRIME2 = LIBERTY-PN PRIME2; QALY = quality-adjusted life-year; RCT = randomized controlled trial; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid; WI-NRS = Worst Itch Numerical Rating Scale.

Discussion Points

- **Significant unmet need**: CDEC deliberated on dupilumab, considering the criteria for significant unmet need that are described in the Procedures for Reimbursement Reviews. Input from patient groups and clinicians highlighted that PN is a rare, chronic, and debilitating skin condition characterized by persistent, severe itching that disrupts overall well-being, daily and social activities, and sleep. Currently, no established treatments exist for patients with moderate-to-severe PN whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. CDEC heard from clinical experts that available therapies are used off-label, have limited efficacy, have significant adverse effects, and have access challenges. Given that the PRIME and PRIME2 trials compared dupilumab only to placebo, the committee weighed the absence of active comparators against the significant unmet need in this patient population. Based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment

indicating “high” to “moderate” certainty in clinically meaningful efficacy outcomes and considering the lack of established and effective alternative treatments, the committee concluded that the available evidence supports the use of dupilumab in the requested patient population.

- **Efficacy:** The committee noted that compared to placebo, dupilumab results in statistically significant and clinically meaningful improvements in pruritus control, number of PN lesions, and HRQoL; this evidence was associated with “high” to “moderate” levels of certainty per the GRADE assessment. CDEC discussed the fact that longer-term efficacy data on dupilumab compared with placebo were not available in the PRIME and PRIME2 trials even though PN is a chronic condition and there may be a need to continue dupilumab for a lifetime. Weighing the absence of long-term data against the significant unmet need, CDEC concluded that the available evidence meets patient needs, based on clinically meaningful improvements in key efficacy outcomes — in pruritus control, number of PN lesions, and HRQoL — after 6 months of treatment with dupilumab.
- **Adverse events (AEs):** CDEC discussed patients’ desire for treatments with minimal adverse effects. Although the PRIME and PRIME2 trials did not provide direct comparative evidence regarding the adverse effects of dupilumab versus available off-label systemic therapies, CDEC noted that overall treatment-emergent AEs (TEAEs) occurred at similar rates in patients receiving dupilumab and placebo. Overall, CDEC agreed that dupilumab’s safety profile in patients with PN was consistent with that seen in its other indications.
- **Comparators:** CDEC deliberated on the lack of evidence comparing dupilumab to alternative treatment options in the Canadian clinical practice setting. CDEC heard from the clinical experts that available off-label systemic therapies offer limited relief, are associated with significant adverse effects, and are supported by low-quality evidence. These medicines may not be suitable for some patients because of other comorbidities. Phototherapy may be another treatment option for patients. The clinical experts noted that it requires several clinic visits each week, and access remains limited due to a shortage of equipment. Additionally, its benefits tend to be short-lived, according to the experts. The sponsor conducted a feasibility assessment of indirect treatment comparisons between dupilumab and alternative treatments for PN. This assessment concluded that performing an indirect treatment comparison was unlikely to produce robust effect estimates based on limitations identified in the evidence for off-label systemic treatments and phototherapy (small sample sizes, lack of standardized outcome measures, and heterogeneity across studies). The comparative efficacy and safety of dupilumab versus these alternative treatments remain unknown.
- **Generalizability:** In the PRIME and PRIME2 studies, patients using high- or super–high-potency topical corticosteroids (TCSs) had to switch to medium-potency TCSs to enter the studies. While patients were allowed to use higher-potency TCSs as rescue therapy, this study requirement may affect the generalizability of the study findings to patients who, in real-world clinical settings, would continue on high- or super–high-potency steroids.
- **Long-term data:** CDEC discussed the longer-term retrospective observational studies submitted by the sponsor. CDEC noted that due to the lack of a control group, other biases associated with

nonrandomized studies, and small sample sizes, these studies were unable to address the longer-term safety or efficacy of dupilumab in patients with PN.

- **Cost-effectiveness against some comparators is unknown:** Given the clinical efficacy of dupilumab plus BSC (consisting of low-to-medium TCSs and topical calcineurin inhibitors) compared with phototherapy, high- to super–high-potency steroid treatment, and off-label systemic therapies for moderate-to-severe PN is unknown, the cost-effectiveness of dupilumab plus BSC relative to these alternative treatments is also unknown.

Background

PN is a chronic and rare inflammatory skin disease characterized by numerous symmetrically distributed, pruritic, hyperkeratotic nodules, papules, and plaques. PN is associated with a neuronal sensitization to itch (pruritus), which leads to the development of an itch-scratch cycle. The continuous intense pruritus and scratching in PN culminate in the formation of crusted or excoriated, hyperkeratotic, light to bright red nodules or plaques with hyperpigmented margins that may number from a few to hundreds of lesions. The burden of disease is significant because patients experience debilitating signs and symptoms that negatively affect their HRQoL, sleep, and mental health. While the exact prevalence and incidence rates of PN are not known, the prevalence rates reported in the literature range from 5.82 cases per 100,000 individuals to 70 per 100,000 individuals, based on estimates from Poland, the UK, and the US.

The clinical experts consulted by CDA-AMC noted that PN is 1 of the most challenging dermatologic conditions to manage due to its severe, chronic pruritus. The existing topical and off-label systemic treatments are often unable to control the disease and/or may be associated with significant toxicity. The initial treatment of PN includes medium- to high-potency TCSs to reduce inflammation and alleviate pruritus. Intralesional corticosteroid injections may also be used, as well as other symptomatic therapies, such as topical calcineurin inhibitors (TCIs), topical anesthetics, and oral antihistamines. For patients with moderate-to-severe PN, topical therapies often do not adequately control symptoms of PN and are associated with adverse effects such as skin thinning and systemic corticosteroid absorption. Phototherapy may be effective for some patients; however, it requires multiple clinic visits each week and is inaccessible to the majority of patients due to the shortage of phototherapy equipment in many jurisdictions. Off-label systemic immunosuppressant therapies that are used for patients with severe or refractory PN (e.g., methotrexate, cyclosporine) have limited evidence of efficacy, are not suitable for many patients who are older or have comorbidities, and have safety concerns when used longer-term. The clinical experts we consulted expressed the need for highly effective, disease-modifying systemic PN therapies that provide sustained relief, are safe for long-term use, and are convenient and accessible.

Dupilumab was approved by Health Canada for the treatment of adult patients with moderate-to-severe PN whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab can be used with or without TCSs. It is available as a 300 mg per 2 mL prefilled

syringe or pen for subcutaneous injection. The product monograph recommends an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every 2 weeks.

Sources of Information Used by the Committee

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

- a review of 2 double-blind, randomized controlled trials (RCTs) in patients with moderate-to-severe PN; and 5 observational studies included in the Studies Addressing Gaps in the Evidence From the Systematic Review Evidence section
- 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
- 2 clinical specialists with expertise in diagnosing and treating patients with PN
- a review of the pharmacoeconomic model and report submitted by the sponsor.
- No clinician groups submitted input to CDA-AMC for this recommendation.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Group Input

This section was prepared by the review team based on the input provided by patient groups.

CDA-AMC received input from CSPA for this submission. CSPA is a national charity organization that improves the health and well-being of people across Canada affected by skin, hair, and nail conditions through collaboration, advocacy, and education. Information for this submission was gathered via an online survey that was conducted from September 12, 2024, to November 29, 2024. The survey had 9 respondents (8 patients and 1 caregiver), and 2 of the respondents had experience with the drug under review.

Based on the patient group input, most of the respondents (5 of 9) were from Ontario. Five respondents provided their age, and all were older than 35 years, with more than half older than 55 years. Five respondents who answered the disease history question indicated that they had PN for less than 5 years. Three respondents reported having severe PN, and 1 respondent rated their PN as being of moderate severity. No respondent reported their PN as mild.

CSPA highlighted that PN is far more than a skin condition; it impacts patients' psychological well-being, social interactions, day-to-day functioning, sleep, and body image. Persistent and severe itching (pruritus) is the predominant symptom, which significantly disrupts daily activities and sleep. The visible nodules and scars may lead to embarrassment and reduced self-esteem. The chronic nature of PN can result in emotional distress, anxiety, and depression. According to the CSPA survey, all patients reported itchy skin, itchy bumps (nodules), burning or stinging skin, scratching, pain, and hyperpigmentation (dark spots). Three

patients (75%) reported skin symptoms of scarring because of PN. One patient (25%) reported experiencing adverse effects of flares and hypopigmentation (light spots).

Regarding the aspects of life impacted by a PN diagnosis, survey respondents reported that family relationships, intimate relationships, sex life, work life, mental health, social life, daily activities, sleep, self-esteem, and finances were all effected. Regarding impact on daily activities, 25% of respondents reported missing work 5 to 10 times monthly due to PN, 25% reported missing work 1 to 5 times monthly, and 50% reported not missing work due to PN.

CSPA explained that caregivers are also impacted, often witnessing their loved ones endure emotional pain, insecurity, and social withdrawal. The psychological burden on caregivers was reported as being potentially immense because they provide ongoing emotional support and encouragement while often feeling helpless themselves.

According to the CSPA, many patients reported limited success with existing therapies, highlighting the need for new and more effective treatments. CSPA noted that the survey respondents indicated that they tried multiple treatments to manage their PN, such as TCSs, TCIs, topical capsaicin, oral antihistamines and methotrexate, phototherapy, and medical cannabis. CSPA explained that the respondents emphasized the limited efficacy of these treatments. CSPA added that 2 patients reported trying dupilumab in the past, but both patients found there to be “no change” in their condition. CSPA noted the small sample size of survey respondents with experience with dupilumab and resulting challenges on which to draw conclusions on dupilumab’s efficacy. Many respondents expressed frustration and emotional distress from trying multiple therapies that resulted in little to no improvement. CSPA explained that when asked what aspects of a new PN treatment were most important to patients, survey respondents reported that these were effectiveness, affordability, and lack of adverse effects. Other less important aspects reported were that the treatment is easy to take or apply and is convenient in terms of the patient’s schedule. According to the patient group input, in addition to managing itch, psychological and social relief are the motivations underlying these desired outcomes. With a treatment that offers tangible improvement and restores a sense of normalcy, patients anticipate a significant enhancement in quality of life, self-confidence, and social participation.

Regarding the adverse effects of current treatments, CSPA noted that respondents reported experiencing a racing heart, skin irritation, nausea, vomiting, hypopigmentation, and hyperpigmentation. Only 1 respondent shared that they stopped treatment for PN because of adverse effects, and 3 respondents shared that they stopped treatment because of a lack of efficacy. CSPA highlighted that 4 of 5 respondents strongly agreed that they would be interested in a new a treatment for PN and that they wish there was a better PN treatment option for them.

Based on the input, respondents also shared that they have experienced financial challenges that have affected their access to PN treatments, and the caregiver who responded to the survey disclosed that the cost of medication is the most important aspect of a new treatment for them. Currently, there are no treatments indicated for PN that are funded by public drug plans in Canada.

Clinician Input

Input From Clinical Experts Consulted for This Review

All CDA-AMC review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of PN.

Unmet Needs

The clinical experts we consulted identified a need for safe and effective therapies to treat PN that do not have a significant treatment burden. One critical gap is for highly effective systemic agents that directly address the underlying immune dysregulation and neuronal sensitization driving PN, rather than just providing generalized immunosuppression or some symptomatic management. There is currently no available treatment that can permanently cure or halt the progression of the disease. While many therapies can temporarily alleviate symptoms, relapses are common after the cessation of treatment, leading to a cyclical pattern of flare-ups. This underscores the need for more durable therapeutic solutions that can sustain disease remission and prevent the recurrence of new nodules. In addition, treatment resistance can develop over time, leading to the disease becoming refractory, meaning that patients who initially show improvement later experience recurrent symptoms or worsening disease. This necessitates a constant adjustment of therapy and highlights the limitations of current treatment options in achieving long-term disease control. Moreover, the existing treatments do not effectively address the HRQoL concerns of patients, particularly with respect to the emotional and psychological toll of chronic pruritus and disfiguring lesions.

The clinical experts stated there is a need for treatments that are safe for both short- and long-term use, ensuring sustained relief without accumulating risks. This includes treatments that are suitable for all age groups, particularly older adults, who represent a significant portion of the PN population and are more vulnerable to treatment adverse effects. The clinical experts noted that existing off-label systemic immunosuppressants are often not viable options for patients with common comorbidities, including chronic liver disease, chronic kidney disease, HIV, and hepatitis; therefore, the treatments available for these patients are limited. In addition, there is a need for treatments that are safe for pregnant patients, allowing those with PN to receive effective therapy without risk to the fetus or the pregnant person. Lastly, there is an unmet need for convenient treatment options that do not require regular monitoring or frequent clinic visits, reducing the burden on patients. Rather than topical therapies that can be messy and cumbersome to apply, oral therapies that require frequent dosing, or phototherapy that requires multiple appointments per week, there is a growing need for long-acting formulations or alternative delivery systems that could simplify treatment regimens and improve overall adherence.

The experts stated that, at present, there are no Health Canada–approved treatments that fully meet these needs. The lack of targeted, safe, and accessible therapies leaves many patients with chronic, debilitating symptoms and few viable options, highlighting the urgent need for novel treatments that can address the immune-mediated, neurogenic, and quality of life aspects of PN, while ensuring safety across diverse patient populations.

Place in Therapy

According to the clinical experts we consulted, dupilumab (and other biologics) are expected to redefine the treatment approach for PN, potentially becoming a first-line systemic treatment for moderate-to-severe PN in eligible patients. The availability of dupilumab may allow for earlier escalation to disease-modifying systemic therapy. Dupilumab directly targets IL-4 and IL-13 — key cytokines involved in type 2 inflammation, which plays a major role in PN pathogenesis. The clinical experts noted that the targeted mechanism allows dupilumab to be used without the risks associated with broad immunosuppression. Dupilumab may be used as monotherapy for many patients, or it can be combined with TCSs, intralesional corticosteroid injections, phototherapy (if available), and other symptomatic treatments such as antihistamines. The clinical experts stated that, in their experience, methotrexate may be used as a short-term bridging therapy in patients with severe PN at the start of dupilumab treatment and is tapered and discontinued once dupilumab takes effect.

The clinical experts stated that it would be appropriate for patients to first try traditional therapies, such as TCSs, with or without intralesional corticosteroid injections, to manage mild-to-moderate cases of PN. However, for patients with more severe, chronic, or refractory PN, the use of dupilumab would be justified when these standard therapies fail to provide adequate relief. Many patients with PN have contraindications to the off-label systemic immunosuppressants, warranting dupilumab as a reasonable first-line systemic treatment in this cohort. Given the poor efficacy and safety concerns with off-label systemic immunosuppressants, the clinical experts did not recommend that all patients be required to try these therapies before initiating dupilumab.

Patient Population

According to the clinical experts we consulted, dupilumab is most suitable for patients with moderate-severe or refractory PN, particularly those with persistent pruritus that significantly impacts HRQoL and who have chronic or widespread nodules that have not responded to conventional treatments. Dupilumab would be suitable for patients with comorbidities (e.g., kidney disease, liver disease, hepatitis, or HIV) for whom other systemic agents are contraindicated. It may also benefit patients with a history of type 2 inflammatory diseases, such as atopic dermatitis or asthma.

The clinical experts indicated that dupilumab is not suitable for patients with mild PN or those with mild symptoms who can manage with conventional treatments. The primary method of identifying suitable patients is clinical judgment, based on the number of lesions, and focusing on symptom severity (itching severity) and HRQoL.

The clinical experts emphasized that diagnosis of PN should be made by a dermatologist who has the expertise to distinguish PN from other pruritic conditions (e.g., eczema, psoriasis). Diagnosis is made through a thorough clinical evaluation. Skin biopsy is not required for an accurate diagnosis.

Assessing the Response to Treatment

In clinical practice, the experts indicated that response to treatment is assessed based on a reduction in disease severity, itch intensity, and HRQoL. Disease severity is often assessed by lesion count and scoring systems like the IGA PN-S, with a clinically meaningful response being a reduction in IGA PN-S score to 0 or 1 (i.e., 5 or fewer lesions). Itch intensity may be assessed by patients' subjective reporting of improvement (e.g., "good to excellent" improvement in itch) or measured by a numeric rating scale NRS (e.g., WI-NRS, with a reduction of at least 4 points considered clinically important). Additionally, improvements in quality of life (e.g., DLQI) are important indicators, particularly because PN severely impacts sleep and social well-being.

Treatment response is typically assessed at regular intervals, with follow-up every 3 to 6 months when active and up to 1 year if the disease is controlled (with or without therapy). The experts indicated that the initial treatment response for a biologic would usually be assessed after 6 months. While clinical outcomes in practice may overlap with those used in clinical trials, practical application focuses more on symptom relief and functional improvements. A clinically meaningful response would include a reduction in lesions and/or a substantial reduction in pruritus and improvement in daily life, with variations among physicians in how these outcomes are prioritized.

Discontinuing Treatment

When deciding to discontinue treatment with dupilumab, the clinical experts would evaluate whether the patient had achieved the desired clinical outcomes within a 6-month time frame. Specifically, a clinically important response would be a decrease in the lesion count from 20 or more at the start of therapy to 5 or fewer, or if the WI-NRS severity decreased by at least 4 points out of 10 on the NRS. The experts emphasized that some patients may not meet these specific parameters, but if they had experienced some improvement and wished to continue, then therapy would not be stopped. In patients with a partial response to therapy, decisions to stop treatment would include consideration of whether any other effective treatment options were available. Moreover, there is a component of patient-centred approach and patient-reported "happiness" that is considered when deciding whether to continue therapy. The experts also noted that pruritus may improve before lesions or vice versa, and both may not always show simultaneous improvement. If neither outcome is achieved, discontinuation due to lack of improvement would be considered. Additional factors for discontinuation may include serious AEs or the emergence of comorbidities requiring other treatments, but the primary focus should be on achieving clinical milestones related to disease severity and symptom control.

Prescribing Considerations

Both clinical experts agreed that due to the complexity of diagnosing PN, it is essential that treatment with dupilumab be initiated by a dermatology specialist. PN is both underdiagnosed and overdiagnosed by nondermatology providers. PN has a broad differential that requires the clinician to rule out other potential

causes. Patients with PN can also have other underlying diagnoses. As such, treatment with dupilumab for PN should only be initiated by a dermatologist. PN is a clinical diagnosis that cannot be reliably diagnosed through biopsy alone, and dermatopathologists rely on clinical correlation for pathologic diagnosis; many conditions appear similar under histology. The clinical experts stated that dermatologists are best equipped to maximize dupilumab treatment outcomes by optimizing the use of concurrent conventional therapies, and they noted that academic (hospital) and community dermatologists are qualified to diagnose PN and prescribe dupilumab.

Clinician Group Input

No clinician groups submitted input to CDA-AMC.

Drug Program Input

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Before dupilumab, there were no Health Canada–approved targeted systemic therapies, only off-label therapies. The comparators used in the clinical studies are "best supportive care," which includes: • TCSs: full benefit in most jurisdictions • TCIs: special access in most jurisdictions and may not be funded for patients with PN. **Question:** Are there other drugs (including off-label) with similar clinical effects to dupilumab in the treatment of PN that should be included as relevant comparators?	The clinical experts agreed that emollients and TCSs with intralesional corticosteroid injections are currently the best supportive care for patients with PN. Although the experts stated that off-label immunosuppressants are used in clinical practice, they lack evidence to support their use and are often ineffective. In addition, the short- and longer-term safety concerns with methotrexate or cyclosporin limit their use, especially considering that PN is more common in older patients who often have comorbidities. CDEC acknowledged that the clinical experts noted the lack of high-quality evidence to support the use of currently available off-label systemic immunosuppressant therapies.
Question: Nemolizumab is also being reviewed for PN. Should dupilumab and nemolizumab be considered in the same line of therapy for PN?	CDEC acknowledged feedback from the clinical experts that dupilumab and nemolizumab would be considered in the same line of therapy for patients with PN.
Considerations for initiation of therapy	
According to the sponsor, a "diagnosis of PN is clinically determined and is largely one of exclusion. A PN diagnosis is typically based on the presence of core symptoms." "The workup may include history of comorbidities, possible skin biopsy, laboratory investigations, or radiological investigations." **Question:** When should a biopsy be required to confirm a diagnosis of PN?	The clinical experts noted that PN is a clinical diagnosis, and if PN is diagnosed by a dermatologist, a biopsy is not required. On biopsy, PN can be similar to other chronic pruritic or excoriating disorders, and biopsy results are not entirely specific to PN. CDEC acknowledged the clinical experts' feedback.

Implementation issues	Response
The PRIME and PRIME2 trials inclusion criteria required: • PN diagnosis by a dermatologist for at least 3 months • WI-NRS ≥ 7 on average • Minimum of 20 PN lesions on both legs, and/or both arms, and/or trunk • History of failing a 2-week course of medium- to super–high-potency TCSs (unless medically unadvisable) **Question:** Should patients have to meet all the aforementioned inclusion criteria to be eligible for dupilumab?	The experts agreed that the inclusion criteria listed were reasonable initiation criteria for reimbursement of dupilumab. Diagnosis of PN by a dermatologist is important because PN may be misdiagnosed or underdiagnosed by other practitioners. The clinical experts commented that, at the time of determining patient eligibility, having a specific itch score requirement may not be necessary, given that patients with moderate-to-severe PN would be experiencing severe itch. However, clinical experts acknowledged that documenting a WI-NRS score at baseline may be useful to allow for quantitative follow-up in determining clinical improvement in pruritus. The number of lesions and WI-NRS criteria were consistent with moderate-to-severe PN. The experts stated that all patients should have tried topical therapies before starting dupilumab or nemolizumab, especially considering that TCSs would likely be prescribed by family physicians before patients were able to access a dermatologist. Clinical experts noted that an adequate course of topical prescription therapy typically includes 6 to 8 weeks of high- to super–high-potency TCSs. CDEC agreed with the clinical experts' feedback.
Question: Is the WI-NRS score commonly used in practice?	The clinical experts indicated that patients' subjective reporting of the severity of pruritus is usually used to assess itch intensity. The WI-NRS, while not routinely used, could be incorporated into practice. They stated the WI-NRS would have value as part of reimbursement initiation and renewal criteria because it provides a numerical measure of pruritus intensity. CDEC acknowledged the clinical experts' feedback.

The sponsor suggested the following reimbursement criteria.
Initiation condition:
• For the treatment of adult patients with moderate-to-severe PN whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable, defined as:
  ◦ A total of ≥ 20 nodular lesions
  ◦ Pruritus for at least 6 weeks with a history and/or signs of repeated scratching, picking, or rubbing
  ◦ Inadequate response, intolerance, or contraindications to topical therapies for PN.
Renewal condition:
• The patient must exhibit reduced pruritus from baseline, reduced lesion count, and improved overall HRQoL as reported by the patient (e.g., sleep disturbance, emotional status).
Prescribing conditions:
• Dupilumab should be prescribed by physicians experienced in the treatment of PN.
• The initiation conditions requested by the sponsor do not
	CDEC agreed with the clinical experts that a baseline WI-NRS score of 7 and an IGA PN-S score of at least 3 (i.e., ≥ 20 PN lesions) were reasonable criteria for the initiation of dupilumab therapy.

Implementation issues	Response
include any baseline scoring; however, renewal conditions include reduced pruritus from baseline, reduced lesion count, and improved HRQoL as reported by the patient (e.g., sleep disturbance, emotional status). **Question:** Should a baseline score for 1 or both of pruritus (WI-NRS or other) and HRQoL be required?	
Both the Health Canada approval and the sponsor's reimbursement request for dupilumab were limited to adults with PN. Dupilumab is indicated in pediatric individuals with other medical conditions (asthma, atopic dermatitis, and eosinophilic esophagitis). **Question:** Would you anticipate dupilumab being used in pediatric individuals with PN? **Question:** Should pediatric individuals be excluded from dupilumab funding for the treatment of PN?	The experts stated that PN is rare in pediatric patients. At present, there are no phase III studies in pediatric patients, and until these data are available, dupilumab should not be approved or reimbursed for these patients. CDEC agreed with the clinical experts that there is currently insufficient evidence to guide a recommendation for dupilumab for pediatric patients.
Question: Should individuals be required to have an inadequate response to off-label oral immunosuppressant therapies (such as methotrexate) before becoming eligible for dupilumab?	The experts emphasized that off-label systemic immunosuppressants have low efficacy and significant toxicity, which limits their long-term use. As most patients with PN are older adults and have other comorbidities and polypharmacy, methotrexate and cyclosporin are often not suitable treatments. Dupilumab offers targeted immunosuppression that addresses the underlying disease process and is generally safe for older patients. A requirement to use off-label systemic immunosuppressants before dupilumab would delay many patients from receiving an effective therapy. CDEC acknowledged and agreed with the clinical experts' feedback.
Question: Is phototherapy an appropriate alternative for the treatment of PN? **Question:** Is phototherapy readily available in all areas of Canada? **Question:** If CDEC feels phototherapy is an appropriate alternative for the treatment of PN, should individuals be required to have an inadequate response to phototherapy (if accessible) before being eligible for dupilumab?	The experts noted that there are significant barriers to accessing phototherapy and that wait lists to access this treatment can be substantial. They also noted that the treatment burden is high given that phototherapy requires patients to visit the clinic 3 times a week, which is not feasible for most patients. While it may be effective for some patients, long-term efficacy is limited. The experts stated that patients should not be required to try phototherapy before being eligible for dupilumab. CDEC acknowledged and agreed with the clinical experts' feedback.
The PRIME and PRIME2 studies excluded individuals with PN secondary to medications or medical conditions. **Question:** Should individuals with secondary PN be excluded from funding?	The experts stated that patients with chronic pruritus associated with medications or other comorbid conditions, but who did not meet the criteria for PN, would not be eligible for dupilumab. Only patients with idiopathic PN or PN related to renal failure, atopic dermatitis, or other underlying conditions would be treated with dupilumab. CDEC agreed with the clinical experts' feedback.
With regard to consistency of initiation criteria with other drugs, the drug programs noted that nemolizumab is currently under review by CDA-AMC for the treatment of moderate-to-severe PN.	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
Considerations for continuation or renewal of therapy	
The requested renewal conditions include reduced pruritus from baseline, reduced lesion count, and improved HRQoL as reported by the patient (e.g., sleep disturbance, emotional status). **Question:** Should patients be required to experience an improvement in all 3 areas (pruritus, lesion count, and HRQoL), or would improvement in 1 of the 3 areas (pruritus, lesion count, or HRQoL) be sufficient to determine response? **Question:** Should response to therapy be based on the patient's subjective response (i.e., improvement in HRQoL and/or itch), or should an objective measure (scoring tool) be used to determine response?	The clinical experts stated that improvement in pruritus symptoms and the number of lesions are the key considerations for continuation of therapy. The experts considered an itch response to be at least a 4-point improvement in WI-NRS from baseline. One expert indicated that an IGA PN-S score of 0 or 1 (≤ 5 lesions) could be used as a criterion for improvement in the number of lesions, but the other expert stated either an IGA PN-S score of 0 or 1, or a 2-point improvement from baseline, would be appropriate. While both pruritus and lesion count outcomes are important, the experts agreed that patients should not be required to fulfill both criteria for continuation of treatment. Patients with a partial response should not be prohibited from receiving dupilumab, given there may be no other treatment options available, and even an incomplete response to 1 or both criteria may be considered important by patients. The clinical experts commented that assessment for treatment renewal (i.e., response to treatment) should occur after 4 to 6 months of therapy. They noted that improvement in lesions may be delayed, relative to relief of pruritus, and that at least 6 months may be needed for patients to show full treatment effects. Typically, in practice, patients are assessed in the first 6 months of therapy and then annually afterwards. The clinical experts agreed that, for patients who do not maintain a good response to therapy (as previously outlined), treatment with dupilumab should be discontinued. CDEC acknowledged and agreed with the clinical experts' feedback.
The primary end point measured in the PRIME and PRIME2 trials was the proportion of patients with at least a 4-point reduction in WI-NRS from baseline at week 24. **Question:** If an objective measure should be used to determine response, and WI-NRS is commonly used in clinical practice, would a reduction in 4 or more points in WI-NRS be an appropriate renewal parameter?	CDEC agreed with the experts that a 4-point improvement in WI-NRS from baseline would be a reasonable renewal criterion for dupilumab.
The key secondary end point of the PRIME and PRIME2 trials was an IGA PN-S of 0 to 1 at 24 weeks, with other end points including change from baseline in DLQI, Skin Pain NRS, HADS, and Sleep NRS. **Question:** Would IGA PN-S, DLQI, Skin Pain NRS, HADS, or Sleep NRS be more appropriate tools than WI-NRS to determine response to therapy?	The clinical experts stated that improvement in pruritus symptoms and the number of lesions are the key considerations for continuation of therapy. CDEC agreed with the clinical experts' feedback.
Question: Once the initial response to dupilumab is determined, how often would patients likely be assessed for ongoing response? **Question:** Should the improvements initially noted in the first 24 weeks of dupilumab be maintained indefinitely?	Patients who start on dupilumab will typically be seen by the dermatologist for the first assessment of response to treatment after 4 to 6 months, preferably 6 months. For those with a good response to treatment at that assessment, the next scheduled assessment would be about 1 year later. Dupilumab has been shown to have good longer-term efficacy in

Implementation issues	Response
	other dermatologic conditions, but for patients with PN, the trial data are limited to 24 weeks in duration.
With regard to the consistency of renewal criteria with other drugs, the drug programs note that nemolizumab is currently under review by CDA-AMC for the treatment of moderate-to-severe PN.	Comment from the drug programs to inform CDEC deliberations.
Considerations for prescribing of therapy	
The sponsor's reimbursement request states that "dupilumab should be prescribed by physicians experienced in the treatment of PN." **Question:** What types of specialists may be "experienced in the treatment of PN"? **Question:** Would all dermatologists be considered "experienced in the treatment of PN"? **Question:** If a patient is unable to access a physician experienced in the treatment of PN, are there other practitioners who could manage this condition?	Both clinical experts agreed that due to the complexity of diagnosing PN, it is essential that treatment with dupilumab be initiated by a dermatology specialist. PN has a broad differential that requires the clinician to rule out other potential causes. As such, treatment with dupilumab for PN should be limited to dermatologists because these specialists are best equipped to maximize dupilumab treatment outcomes by optimizing the use of concurrent conventional therapies. Academic (hospital) and community dermatologists are well equipped to diagnose PN and prescribe dupilumab. CDEC agreed with the clinical experts' feedback.
Question: Should individuals be eligible for the use of dupilumab in combination with other treatments for PN (i.e., off-label methotrexate or nemolizumab)?	The experts stated dupilumab would not be used in combination with nemolizumab or cyclosporin but may be used with methotrexate in patients with severe PN, particularly in the first few months of dupilumab therapy. Dupilumab would be used concurrently with emollients, TCSs, intralesional corticosteroid injections, and potentially phototherapy (if accessible). CDEC noted that there is insufficient evidence to guide a recommendation on combining dupilumab with systemic therapies such as nemolizumab or methotrexate. CDEC agreed that dupilumab could be used concurrently with emollients, TCSs, TCIs, intralesional corticosteroid injections, and potentially phototherapy (if accessible).
Dupilumab is indicated (and funded in many jurisdictions) for atopic dermatitis and asthma. Additionally, dupilumab is currently under review for nasal polyps. **Question:** If an individual has multiple medical conditions that may be treated with dupilumab (and it is funded by the drug plans for these conditions — that is, for atopic dermatitis or asthma), should reimbursement of multiple biologics be considered for the individual? Alternatively, should the individual be provided funding for only 1 biologic that treats both conditions? For instance, if the patient is being treated for PN with dupilumab and another product (e.g., mepolizumab) for asthma, should they be eligible for funding of both, or should the individual be provided funding for only 1 product that is indicated for the treatment of both conditions?	CDEC agreed with the clinical experts that dupilumab would not be used in combination with other biologics. If a patient had multiple conditions, clinicians would try to find 1 biologic that could be used to manage both conditions.
With regard to the consistency of prescribing criteria with other drugs, the drug programs note that nemolizumab is currently under review by CDA-AMC for the treatment of moderate-to-severe PN.	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
Generalizability	
Is the efficacy and safety of dupilumab as observed in the adult clinical trials generalizable to pediatric patients?	The clinical experts stated that PN is rare in children. Based on their clinical practice, they had no comments on the use of dupilumab in pediatric patients with PN. CDEC agreed with the clinical experts that there is currently insufficient evidence to guide a recommendation for dupilumab for pediatric patients.
System and economic issues	
The budget impact may be more substantial if off-label oral immunotherapies (e.g., methotrexate) are not required to be trialled before initiation of dupilumab for PN.	Comment from the drug programs to inform CDEC deliberations.
Dupilumab has successfully gone through price negotiations for asthma and atopic dermatitis.	Comment from the drug programs to inform CDEC deliberations.

CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; DLQI = Dermatology Life Quality Index; HADS = hospital anxiety and depression scale; HRQoL = health-related quality of life; IGA PN-S = Investigator Global Assessment Prurigo Nodularis-Stage; NRS = numerical rating scale; PN = prurigo nodularis; PRIME = LIBERTY-PN PRIME; PRIME2 = LIBERTY-PN PRIME2; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid; WI-NRS = Worst Itch Numerical Rating Scale.

Clinical Evidence

Systematic Review

Description of Studies

Two randomized, double-blind, placebo-controlled, multicentre, parallel-group phase III studies were included in the systematic review. The PRIME and PRIME2 trials evaluated the efficacy and safety of dupilumab in adult patients (aged 18 to 80 years) with PN who were inadequately controlled on topical prescription therapies or when those therapies were not advisable. Patients were required to have at least 20 PN lesions in total on both legs and/or both arms and/or trunk at the screening visit and on day 1 (randomization), have a history of a 2-week course of a medium- to super–high-potency TCS failing or for whom TCSs were not medically advisable, and have an average WI-NRS score of at least 7 points in the 7 days before randomization.

In the PRIME and PRIME2 studies, 151 and 160 patients, respectively, were randomized (1:1) to receive either dupilumab 300 mg every 2 weeks (with a 600 mg loading dose), or matching placebo, by subcutaneous injection for 24 weeks. Concurrent use of low- to medium-potency TCSs or TCIs was allowed if patients were receiving these treatments before the study.

The primary outcome in both studies was the proportion of patients with an improvement (reduction) in the WI-NRS by at least 4 points from baseline to 24 weeks in the PRIME study and from baseline to 12 weeks in the PRIME2 study. The WI-NRS is a patient-reported outcome comprised of a single item rated on a scale from 0 ("no itch") to 10 ("worst imaginable itch"). The analysis was based on the 7-day average of daily WI-NRS scores over the previous week. Key secondary end points included the proportion of patients with Investigator Global Assessment Prurigo Nodularis-Stage (IGA PN-S) score of 0 or 1 at week 24 (for

both studies). The IGA PN-S is a clinician-reported assessment of the stage of the disease using a 5-point scale as follows: 0 (clear; no nodules); 1 (almost clear; ≤ 5 nodules), 2 (mild; 6 to 19 nodules), 3 (moderate; 20 to 99 nodules) to 4 (severe; ≥ 100 nodules). Another secondary outcome was the change from baseline to week 24 in the DLQI total score. The DLQI is a patient-reported outcome that assesses the impact of skin disease on patients' HRQoL over the previous week. It includes 10 items that cover symptoms, leisure activities, work, school or holiday time, personal relationships (including intimate relationships), the adverse effects of treatment, and emotional reactions to having a skin disease. Overall scoring ranges from 0 to 30, with a high score indicative of a poor HRQoL.

The patients enrolled in the 2 trials had similar characteristics, with a mean age per treatment group ranging from 46.7 years (standard deviation [SD] = 15.2) to 51.1 years (SD = 15.8). Most patients were female (62.2% to 69.3%), and the minority were male (30.7% to 37.8%). The mean duration of PN was between 5.4 years (SD = 6.9) and 6.0 years (SD = 7.6), and less than half of the patients enrolled had a history of atopy (36.8% to 48.8%). A majority of patients were on stable doses of TCSs or TCIs (56.1% to 62.7%) at baseline, and all but 1 patient had used topical therapies in the past. Most patients had also received systemic therapies for PN, of which antihistamines (46.2% to 60.0%), corticosteroids (11.5% to 22.7%), and nonsteroidal immunosuppressant drugs (13.2% to 25.6%) were most common. A minority of patients had previously received intralesional corticosteroid injections, phototherapy, or cryotherapy to treat their PN (9.2% to 17.9%). Based on the IGA PN-S score, more patients had moderate PN (60.5% to 72.0%) than severe PN (28.0% to 39.5%), and the mean WI-NRS score at baseline ranged from 8.3 (SD = 1.1) to 8.6 (SD = 0.9).

Efficacy Results

In the PRIME study, 60.0% versus 18.4% of patients in the dupilumab and placebo group, respectively, reported at least a 4-point reduction in WI-NRS score from baseline to week 24. The between-group difference was 42.7% (95% CI, 27.8 to 57.7) favouring dupilumab versus placebo (P < 0.0001) (Table 3). At week 24, the results of the PRIME2 study also favoured dupilumab with 57.7% versus 19.5% of patients meeting the WI-NRS response criteria (difference 42.6%; 95% CI, 29.1 to 56.1; P < 0.0001 for dupilumab versus placebo). At week 12, the between-group differences in the proportion of patients with at least a 4-point reduction in WI-NRS score was 29.2% (95% CI, 14.5 to 43.8; P = 0.0003 [not controlled for multiple comparisons]), and 16.8% (95% CI, 2.3 to 31.2; P = 0.0216) in the PRIME and PRIME2 studies, respectively.

The proportion of patients with an IGA PN-S score of 0 (clear) or 1 (almost clear) at week 24 was reported for 48.0% of patients in dupilumab group and 18.4% of patients in the placebo group in the PRIME study, with a between-group difference of 28.3% (95% CI, 13.4 to 43.2; P = 0.0004) favouring dupilumab. The results were similar in the PRIME2 study, in which 44.9% and 15.9% of patients met the IGA PN-S response criteria in the dupilumab and placebo groups, respectively. The between-group difference was 30.8% (95% CI, 16.4 to 45.2; P < 0.0001).

The change from baseline in DLQI total score to week 24 favoured the dupilumab group versus the placebo group in both studies. In the PRIME study, a least squares mean difference of −6.2 points (95% CI, −8.3 to −4.1; P < 0.0001) was reported, and in the PRIME2 study, a least squares mean difference of

−6.4 points (95% CI, −8.4 to −4.4 was reported; P < 0.0001) for dupilumab versus placebo. In patients with PN, a 4.0-point change in DLQI (range 3.5 to 6.5) was estimated to represent a meaningful between-group change.[11]

Harms Results

Based on the pooled data from the PRIME and PRIME2 studies [redacted] patients ([redacted]) who received dupilumab and [redacted] patients ([redacted]) who received placebo, reported at least 1 TEAE over the 24-week treatment period. The most common events were [redacted], headache (5.3% versus 5.7%), nasopharyngitis (3.9% versus 1.9%), and neurodermatitis ([redacted] versus [redacted]) in the dupilumab versus placebo groups, respectively.

Seven patients (4.6%) in the dupilumab group experienced a serious AE compared with 12 patients (7.6%) in the placebo group. No patients died during the trials and none of the patients who received dupilumab stopped treatment due to TEAEs, whereas in the placebo group, 4 (2.5%) patients discontinued therapy for this reason.

Conjunctivitis was identified as an important AE, and the product monograph contains a warning for these AEs. In the PRIME study, [redacted] of patients in each group experienced 1 or more TEAE related to conjunctivitis, whereas in the PRIME2 study, [redacted] of patients in the dupilumab group and [redacted] of patients in the placebo group, had 1 of these AEs. No severe conjunctivitis AEs were reported in either trial. The evidence was too uncertain to draw conclusions on the impact of dupilumab on the frequency of conjunctivitis-related AEs.

Critical Appraisal

The CDA-AMC review team did not identify any concerns with the methods used to randomize patients, conceal allocation, or maintain blinding in either study. There were some minor demographic differences between groups at baseline, but clinical experts consulted by CDA-AMC agreed that any baseline discrepancies were unlikely to bias the findings. However, more patients in the placebo group dropped out or stopped the study drug than in dupilumab group; thus, it is unclear if the treatment groups remained balanced throughout the study.

Based on the patient and clinician input received, the outcomes assessed were clinically relevant. No major limitations were identified in the statistical analysis of the WI-NRS or IGA PN-S data; however, there were missing data for the DLQI data that may impact the change from baseline results. In the PRIME study, 24-week DLQI data were missing for [redacted] and [redacted] and were imputed for [redacted] and [redacted] of patients in the dupilumab and placebo groups, respectively. For the PRIME2 trial, [redacted] and [redacted] of patients had missing DLQI data at week 24, and [redacted] and [redacted] of patients had data imputed in the dupilumab and placebo groups, respectively. DLQI data after patients received rescue treatment, or missing data after treatment discontinuation due to lack of efficacy, were imputed by worst observation carried forward. Missing data due to other reasons were imputed using multiple imputation methods. Given the magnitude and differential nature of the missing and imputed data in the dupilumab and placebo groups, the potential for bias cannot be

ruled out. No supplementary analyses were available to test other missing data imputation strategies, which may have improved confidence in the DLQI findings.

Of the key efficacy outcomes included in this report, only 1 was not part of the hierarchical statistical testing procedure to control for multiple comparisons. In the PRIME study, the proportion of patients with at least a 4-point improvement in WI-NRS at 12 weeks was not controlled for multiple comparisons and, thus, no statistical inferences can be drawn from these findings and they should be viewed as supportive data.

The clinical experts we consulted agreed that the patients enrolled were generally consistent with patients with moderate-to-severe PN living in Canada who would be eligible for dupilumab. As background therapy, 61% and 56% of patients in the PRIME and PRIME2 studies, respectively, were on stable doses of TCSs or TCIs at the start of the trial. All but 1 of the patients enrolled had previously received topical therapies, and most patients (71% and 63% in the PRIME and PRIME2 studies, respectively) had received prior systemic therapies to manage their PN. Prior systemic therapies included nonsteroidal immunosuppressants (e.g., cyclosporine, methotrexate, or thalidomide) in 17% and 24% of patients in the PRIME and PRIME2 studies, respectively. The clinical experts consulted by CDA-AMC felt it would be reasonable to generalize the trial results to anticipated clinical practice (i.e., first-line systemic therapy for patients with moderate-to-severe PN whose disease was not adequately controlled with topical prescription therapies or when those therapies were not advisable). Given the poor efficacy and safety concerns with off-label systemic immunosuppressants, the clinical experts consulted by CDA-AMC did not recommend that patients be required to try these therapies before initiating dupilumab.

The clinical experts noted that PN is most prevalent in older patients, who often have comorbidities; however, the trials excluded patients with comorbid conditions such as neuropathy or psychiatric conditions, renal disease, immunodeficiency, history of malignancy, substance use disorder, or infection. Thus, the safety and efficacy of dupilumab in these patients are unclear. The trials were 24 weeks in duration, which the clinical experts we consulted agreed was a reasonable time frame to show initial treatment response. However, longer-term efficacy and safety are uncertain.

Based on clinical expert feedback, off-label systemic therapies may be used to manage patients with PN whose disease is not adequately controlled with topical therapies. Based on the results of a sponsor-conducted feasibility assessment, the sponsor concluded that an indirect treatment comparison was likely to provide biased treatment effect estimates for the comparison of dupilumab versus other systemic therapies due to the low quality of the evidence available. Therefore, it remains unknown how dupilumab compares to other systemic therapies. Nemolizumab is currently under review by CDA-AMC for moderate-to-severe PN. At the time of this review, CDA-AMC has not issued a final recommendation for nemolizumab and, therefore, based on CDA-AMC procedures, it was not considered to be a relevant comparator for the present review of dupilumab.

GRADE Summary of Findings and Certainty of the Evidence

For the RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform 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 refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence 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 thresholds used for the presence or absence of an important effect were based on clinical expert opinion for the WI-NRS and IGA PN-S end points and based on the literature for the DLQI end point. For conjunctivitis, the presence or absence of any non-null effect was used.

For the GRADE assessments, findings from the PRIME and PRIME2 studies were considered together and summarized narratively per outcome because these studies were similar in population, interventions, design, and outcome measures. 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 the patient group and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: proportion of patients with at least a 4-point improvement in WI-NRS; proportion of patients with an IGA PN-S score of 0 or 1; the change from baseline in the DLQI total score; and conjunctivitis-related AEs (Table 3).

Table 3: Summary of Findings for Dupilumab Versus Placebo for Patients With Moderate-to-Severe PN

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Pruritus NRS ≥ 4-point reduction				
Proportion of patients with ≥ 4-point reduction from baseline in WI-NRS[a] Follow-up: 24 weeks	251 (2 RCTs)	PRIME study DUP: 600 per 1,000 PBO: 184 per 1,000 aRD (95% CI): [redacted] PRIME2 study: DUP: 577 per 1,000 PBO:195 per 1,000 aRD (95% CI): [redacted]	High	Dupilumab results in a clinically important increase in the proportion of patients with at least a 4-point improvement in WI-NRS score at 24 weeks compared with placebo.
Proportion of patients with ≥ 4-point reduction from baseline in WI-NRS[a] Follow-up: 12 weeks	251 (2 RCTs)	PRIME study DUP: 440 per 1,000 PBO: 158 per 1,000 aRD (95% CI): [redacted] PRIME2 study:	Moderate[b]	Dupilumab likely results in a clinically important increase in the proportion of patients with at least a 4-point improvement in WI-NRS score at 12

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		DUP: 372 per 1,000 PBO: 220 per 1,000 aRD (95% CI): [redacted]		weeks compared with placebo.
IGA PN-S score of 0 or 1				
Proportion of patients with IGA PN-S score of 0 or 1[c] Follow-up: 24 weeks	251 (2 RCTs)	PRIME study DUP: 480 per 1,000 PBO: 184 per 1,000 aRD (95% CI): [redacted] PRIME2 study DUP: 449 per 1,000 PBO: 159 per 1,000 aRD (95% CI): [redacted]	High	Dupilumab results in a clinically important increase in the proportion of patients with an IGA PN-S score of 0 or 1 compared with placebo.
Change in DLQI total score				
DLQI score (0 [best] to 30 [worst]) LS mean change from baseline[d] Follow-up: 24 weeks	296 (2 RCTs)	PRIME study DUP (SE): [redacted] PBO (SE): [redacted] Difference (95% CI): [redacted] PRIME2 study DUP (SE): [redacted] PBO (SE): [redacted] Difference (95% CI): [redacted]	Moderate[e]	Dupilumab likely results in a clinically important improvement in the change in the DLQI total score compared with placebo.
Harms				
Proportion of patients with conjunctivitis-related AEs[f] Follow-up: 24 weeks	N (2 RCTs)	PRIME study DUP: [redacted] PBO: [redacted] RD (95% CI): [redacted] PRIME2 study DUP: [redacted] PBO: [redacted] RD (95% CI): [redacted]	Very low[g]	The evidence is very uncertain about the effect of dupilumab on the proportion of patients with 1 or more conjunctivitis-related AEs compared with placebo.

AE = adverse event; aRD = adjusted risk difference; CDA-AMC = Canada's Drug Agency; CI = confidence interval; DLQI = Dermatology Life Quality Index; DUP = dupilumab; HRQoL = health-related quality of life; IGA PN-S = Investigator's Global Assessment Prurigo Nodularis - Stage; LS = least squares; NE = not estimable; NR = not reported; NRS = numeric rating scale; PBO = placebo; PN = prurigo nodularis; PRIME = LIBERTY-PN PRIME; PRIME2 = LIBERTY-PN PRIME2; RCT = randomized controlled trial; RD = risk difference; SAE = serious adverse event; SE = standard error; TCS = topical corticosteroid; WI-NRS = Worst Itch Numerical Rating Scale.

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 WI-NRS is a patient-reported, single-item, daily, 11-point scale. The scale is used by patients to rate their worst itch severity over the past 24 hours, with 0 indicating "no itch" and 10 indicating "worst itch imaginable." Based on clinical expert input, the threshold for a clinically important between-group difference was 20% (200 per 1,000) for the proportion of patients with at least a 4-point reduction from baseline.

[b]The WI-NRS end point at 12 weeks was rated down 1 level because of serious limitations due to imprecision, given that the lower bound of the 95% CIs for the between-group differences of both studies includes the possibility of no clinically important difference. Although the point estimate of the PRIME2 study is less than the clinically relevant threshold of 20%, had the 2 studies been pooled, the overall effect estimate would likely exceed the threshold. Thus, the CDA-AMC review team did not rate down due to inconsistency. Note that the 12-week time point in the PRIME study was not controlled for type I error rate for multiple comparisons and should be interpreted as supportive data.

[c]The IGA PN-S measures the investigator's global assessment of the patient's stage of PN using a 5-point scale as follows: 0 (clear; no nodules); 1 (almost clear; ≤ 5 nodules), 2 (mild; 6 to 19 nodules), 3 (moderate; 20 to 99 nodules) to 4 (severe; ≥ 100 nodules). Based on clinical expert input, the threshold for a clinically important between-group difference was 15% (150 per 1,000) for the proportion of patients with an IGA PN-S score of 0 or 1. The CDA-AMC review team noted that the lower bound of the 95% CI for the PRIME study included the possibility of no clinically important difference between treatments. However, the CDA-AMC review team did not rate down the outcome for imprecision, considering that the GRADE guidance states that the threshold should be "appreciably crossed" to warrant down-grading and that pooling results across the 2 trials may have shifted the lower bound of the 95% CI closer to the threshold of clinical importance.

[d]The DLQI is a patient-reported, 10-item HRQoL questionnaire that covers 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment) over the "last week." The total score ranges from 0 (no impact of skin disease on quality of life) to 30 (maximum impact on quality of life). The minimally important difference of 4 points for the DLQI was selected as the threshold for a clinically important between-group difference based on the literature and clinical expert input.

[e]The change from baseline in DLQI was rated down 1 level due to serious study limitations due to missing data.

[f]Conjunctivitis-related AEs included the following events: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, atopic keratoconjunctivitis, blepharitis, dry eye, eye irritation, eye pruritus, lacrimation increased, eye discharge, foreign body sensation in eyes, photophobia, xerophthalmia, ocular hyperaemia, and conjunctival hyperaemia.

[g]Conjunctivitis AEs were rated down 2 levels due to serious imprecision because the CIs for the between-group differences include the possibility of no difference, benefit (fewer harms), or more harms. Conjunctivitis AEs were rated down 1 level due to indirectness, given that the sample size and duration of treatment were insufficient to detect uncommon AEs. In addition, the clinical experts we consulted stated that dermatologists may not have sufficient expertise to distinguish between eye disorders with a similar presentation; thus, the reported conjunctivitis-related AEs may be flawed.

Source: Clinical Study Report for PRIME study, Clinical Study Report for PRIME2 study. Additional data supplied by the sponsor.

Long-Term Extension Studies

No long-term extension studies were submitted.

Indirect Comparisons

No indirect comparisons were submitted.

Studies Addressing Gaps in the Evidence From the Systematic Review

The sponsor submitted 5 studies to address sponsor-identified gaps in the pivotal evidence. These included 4 retrospective observational studies by Paganini et al. (2024), Richter et al. (2023), Selvaraj et al. (2023), and Chiricozzi et al. (2024) to address the lack of long-term data from the PRIME and PRIME2 trials, and 1 retrospective cohort study by Georgakopoulous et al. (2021), to address the lack of long-term data for patients living in Canada. Full-text publications were available for 2 studies only.

The study by Paganini et al. (2024) was a retrospective, cross-sectional, observational, chart review of 16 patients with PN and with moderate-to-severe atopic dermatitis who received dupilumab at a single centre in Rome, Italy. The proportion of patients with an IGA PN score of 0 or 1 was 77% by week 16, 83% by week 52, and 100% by week 84. The proportion of patients with at least a 4-point improvement in the Itch NRS was 91% by week 6, 100% by week 16, 83% by week 52, and 100% by week 84. The proportion of patients with at least a 4-point improvement in the DLQI was 92% by week 16, 83% by week 52, and 67% by week 84.

The study by Richter et al. (2023) was a retrospective, single-centre case series of 10 patients with chronic PN who received dupilumab at a single centre in Zurich, Switzerland. The average and maximum Itch NRS both showed a 54% decrease, and the DLQI score demonstrated a 42% reduction, over 1 year.

In both studies, the observational and retrospective nature of the studies limits the ability to draw inferences on the effects of dupilumab. The patients were aware they were receiving active treatment; thus, their expectations of treatment may have influenced the reporting of subjective outcomes. Given the small sample sizes, the results may not be broadly generalizable.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evidence

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree followed by Markov model
Target population	Adult patients with moderate-to-severe PN, aligned with the PRIME and PRIME2 clinical trials
Treatment	Dupilumab plus BSC
Dose regimen	Initial dose of 600 mg, followed by 300 mg every other week
Submitted price	Dupilumab: $978.70 per prefilled syringe
Submitted treatment cost	First year: $26,425 per patient Subsequent years: $25,446 per patient
Comparator	BSC is defined as a basket of therapies, consisting of low- to medium-potency topical corticosteroids and calcineurin inhibitors.
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (50 years)
Key data sources	PRIME and PRIME2 clinical trials
Key limitations	• Long-term efficacy of dupilumab is uncertain. The CDA-AMC clinical review found that no definitive conclusions could be made about the duration of treatment response beyond the trial follow-up period (i.e., 24-week randomized, double-blinded period). The sponsor's submitted model suggests that patients will continue to experience a treatment effect for more than 50 years. The lack of evidence to support this long-term benefit adds uncertainty to estimated incremental effectiveness. • The sponsor modelled higher utility for patients whose PN did not respond to dupilumab compared to BSC based on sponsor-sought expert input. The sponsor's approach to modelling higher utility than baseline for patients whose PN did not respond to dupilumab lacks face validity. The sponsor's assumed benefit from discontinuing dupilumab post treatment also lacks justification and empirical support. The sponsor's modelled utility assumptions for patients whose PN did not respond to dupilumab overestimated the QALYs

Component	Description
	associated with dupilumab plus BSC, resulting in a lower ICER that favours dupilumab. • Based on clinical expert feedback, immunosuppressants such as methotrexate and cyclosporine may be used to manage patients with PN whose disease is not adequately controlled with topical therapies, which would make them relevant comparators to dupilumab. Because this was not considered by the sponsor, the cost-effectiveness of dupilumab plus BSC compared with immunosuppressants is unknown. • The sponsor's assumption that patients with PN in the "no response" health state experience 1 hospitalization per year lacks face validity based on clinical expert feedback received for this review. The sponsor's assumption overestimated disease management costs for PN that did not respond to dupilumab and the cost savings associated with dupilumab. • The use of adherence to adjust drug cost for dupilumab is inappropriate and introduces a bias that reduces the treatment cost and total cost of dupilumab. • The sponsor adopted poor modelling practices such as extensive use of IFERROR statements, which made it difficult to perform a thorough validation of the sponsor's model.
CDA-AMC reanalysis results	• CDA-AMC undertook reanalyses that addressed some of the identified limitations, including setting utilities for PN that did not respond to dupilumab at week 24 to be identical to baseline utilities and utilities for patients who discontinued treatment with dupilumab to be identical to baseline after 6 months, assuming no hospitalization for patients whose PN did not respond to dupilumab, and assuming 100% adherence to dupilumab. • In the CDA-AMC base case, dupilumab plus BSC is associated with an ICER of $138,915 per QALY gained compared with BSC alone (incremental costs = $122,220; incremental QALYs = 0.88). A price reduction of approximately 61% is required for dupilumab (from $979 to $384 per 300 mg single-use prefilled syringe) to be considered cost-effective compared to BSC alone at a WTP threshold of $50,000 per QALY gained.

BSC = best supportive care; CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; LY = life-year; PN = prurigo nodularis; PRIME = LIBERTY-PN PRIME; PRIME2 = LIBERTY-PN PRIME2; QALY = quality-adjusted life-year; WTP = willingness-to-pay.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis. The prevalence of PN is uncertain and was underestimated. The criteria used to restrict eligibility did not align with clinical expert input received for this review, which noted that all patients with moderate-to-severe PN and uncontrolled on topical therapy would be eligible for treatment with dupilumab. The proportion of patients eligible for coverage by public drug plans was also uncertain. The market uptake of dupilumab may have been underestimated. Moreover, the market capture of dupilumab was uncertain because new treatments are emerging in the treatment landscape for PN. The CDA-AMC reanalysis included adopting a prevalence of 8.3 per 10,000 persons and restricting eligibility criteria to those with moderate-to-severe disease and uncontrolled on topical therapy. Based on the CDA-AMC base case, the 3-year budget impact was expected to be $186,941,572 (year 1 = $34,257,697; year 2 = $67,915,552; year 3 = $84,768,323) if the public drug plans reimburse dupilumab for the treatment of adult patients with moderate-to-severe PN whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The 3-year total budgetary impact was sensitive to the prevalence of PN.

CDEC Information

Members of the Committee

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

Meeting date: May 28, 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

Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

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