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: Add-on maintenance treatment with intranasal corticosteroids in adult patients with severe chronic rhinosinusitis with nasal polyposis inadequately controlled by systemic corticosteroids and/or surgery

Sponsor: Sanofi-Aventis Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the CDA-AMC Reimbursement Recommendation for Dupixent?

Canada's Drug Agency (CDA-AMC) recommends that Dupixent be reimbursed by public drug plans for the treatment of severe chronic rhinosinusitis with nasal polyposis (CRSwNP) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Dupixent should only be covered to treat adults with severe CRSwNP whose bilateral nasal polyps are confirmed endoscopically or by CT scan, who are tolerant and able to continue the use of an intranasal corticosteroid (INCS) but have refractory symptoms despite use of an optimized INCS for at least 3 months, and who have persistent symptoms despite adequate recent treatment with a systemic corticosteroid (SCS) and/or nasal polyp surgery.

What Are the Conditions for Reimbursement?

Dupixent should only be reimbursed if the patient is under the care of a physician with expertise in managing severe CRSwNP. When Dupixent is first prescribed, the physician must submit a baseline 22-item Sino-Nasal Outcome Test (SNOT-22) score or endoscopic Nasal Polyp Score (NPS) so that response to treatment can be measured. The cost of Dupixent should be reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that Dupixent reduced the severity of nasal polyps and improved nasal congestion and/or obstruction and health-related quality of life (HRQoL) at 24 weeks with sustained improvements at 52 weeks, as well as improved overall symptom and disease severity.
- Dupixent met several patient-identified needs, including reducing the severity of nasal polyps, improving sense of smell and HRQoL, and likely reducing the severity of nasal congestion and/or obstruction and the need for SCSs and/or surgery.
- 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 $46 million over the next 3 years. However, the actual budget impact is uncertain.

Summary

Additional Information

What Is Severe CRSwNP?

CRSwNP is a long-term inflammatory condition of the nose and sinuses that causes symptoms such as nasal congestion and/or blockage, facial pressure, loss of smell, and poor sleep, which can significantly affect HRQoL. In Canada, CRSwNP affects about 25% to 30% of people with chronic rhinosinusitis, with an overall chronic rhinosinusitis prevalence of 18.8 to 23.3 per 1,000 people.

Unmet Needs in CRSwNP

Not all patients' CRSwNP responds to available treatments and even when a patient's disease responds, nasal polyps often recur. Treatments that provide long-term symptom control, reduce recurrence after surgery, target the underlying type 2 inflammation, and improve sense of smell and overall quality of life are needed.

How Much Does Dupixent Cost?

Treatment with Dupixent is expected to cost approximately $25,534 per patient per year.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that dupilumab be reimbursed as an add-on maintenance treatment with INCSs in adults with CRSwNP inadequately controlled by an SCS and/or surgery, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 2 multicentre, randomized, double-blind, placebo-controlled, parallel-group studies (the LIBERTY NP SINUS-24 [SINUS-24] study [N = 276] and the LIBERTY NP SINUS-52 [SINUS-52] study [N = 448]) demonstrated that treatment with dupilumab as an add-on to an INCS resulted in clinical benefit for adults with severe chronic CRSwNP inadequately controlled by an SCS and/or surgery when compared to placebo. In the SINUS-24 and SINUS-52 studies, treatment with dupilumab 300 mg once every 2 weeks for 24 weeks resulted in a reduction in the severity of nasal polyps based on the NPS and an improvement in HRQoL based on SNOT-22 score, and sustained meaningful improvements at 52 weeks when compared to placebo. Additionally, both trials showed that dupilumab likely improved the nasal congestion and/or obstruction score (NC score) at 24 weeks with sustained, meaningful benefits at 52 weeks compared to placebo. Although the overall pattern of benefit was similar to that observed for NPS, the evidence of the reduction in NC score was assessed to be of moderate certainty because the between-group difference in change from baseline included the possibility of no clinically meaningful benefit. Both trials suggest that treatment with dupilumab is associated with relevant improvements in disease symptoms and severity based on the change from baseline in total symptom score and decreased or loss of smell. Dupilumab was well tolerated and no new safety concerns other than known adverse events (AEs) were identified. In the absence of a head-to-head trial with mepolizumab, a key comparator, an indirect treatment comparison (ITC) results suggested that dupilumab is likely as effective and provides similar clinical benefit when compared to mepolizumab.

Input from the clinical experts indicated that patients' disease often becomes refractory to current treatment options, particularly INCS and surgery, and available treatments cannot reverse the course of the disease or modify the underlying pathophysiology of CRSwNP. Input from patients and clinicians indicated that the most important treatment goals for patients with severe CRSwNP are to reduce the severity of nasal polyps and nasal congestion and need for surgery, and improve a patient's sense of smell, HRQoL, and reliance on oral corticosteroids. CDEC concluded that dupilumab met some of the needs identified by patients, including a reduction in the severity of nasal polyps and an improvement in patients' sense of smell and HRQoL. Additionally, CDEC concluded that dupilumab likely meets some of the needs identified by patients, including a reduction in the severity of nasal congestion and the need for oral corticosteroids and/or surgery.

Using the sponsor-submitted price for dupilumab as an add-on to best supportive care (BSC) and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for dupilumab as an add-on to BSC was $106,988 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 adults with severe CRSwNP inadequately controlled by systemic corticosteroids and/or surgery. A price reduction is required for dupilumab to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients must have all of the following: 1.1. have severe CRSwNP, confirmed endoscopically or by CT, with documented bilateral nasal polyps 1.2. be tolerant and able to continue use of an INCS but have refractory symptoms despite use of an optimized INCS for at least 3 months 1.3. have persistent symptoms despite adequate recent treatment with systemic corticosteroids (within past 2 years) and/or nasal polyp surgery.	Evidence from both trials suggested that treatment with dupilumab as an add-on to an INCS resulted in clinical benefit for adults with severe CRSwNP inadequately controlled by SCS and/or surgery.	Condition 1.1: In the trial, severe CRSwNP is defined as patients with bilateral sinonasal polyposis that persisted despite prior treatment with an SCS within the past 2 years; and/or had a medical contraindication to SCSs; and/or had prior sinonasal surgery for nasal polyps, and had baseline endoscopic bilateral NPS of at least 5 out of a maximum score of 8 (at least a score of 2 in each nostril) and had 1 of the following: • ongoing symptoms of nasal congestion and/or blockage with moderate or severe severity (NC score of at least 2 on a scale of 0 to 3) and a weekly average severity of at least 1 • another symptom such as loss of smell or rhinorrhea (anterior and/or posterior) for at least 8 weeks. The guidelines suggest that diagnosis of severe CRSwNP can be confirmed by CT documentation of bilateral nasal polyps along with the previously identified clinical symptoms, as an alternative to endoscopic bilateral NPS. Condition 1.2: In the setting in Canada, the optimized INCS option is mometasone furoate nasal spray, two 50 mcg sprays in each nostril twice daily or equivalent, where tolerated. Condition 1.3: Lack of response to nasal polyp surgery is demonstrated within 3 months of surgery; hence, treatment with dupilumab should not be initiated if the patient has undergone nasal polyp surgery within the past 3 months.
2. The prescribing clinician must submit a baseline score for SNOT-22 or endoscopic NPS.	Evidence from the SINUS trials suggested that treatment with dupilumab resulted in clinically relevant improvements in SNOT-22 score and NPS.	Jurisdictions may consider criteria for dupilumab that aligns with the criteria for mepolizumab used by each of the public drug plans.

Reimbursement condition	Reason	Implementation guidance
Renewal		
3. Patients must exhibit a clinically meaningful response on the SNOT-22 or endoscopic NPS relative to their baseline score. 3.1. Response to treatment should be assessed after every 52 weeks.	Evidence from both trials suggested that treatment with dupilumab resulted in a greater proportion of patients who had at least an 8.9-point decrease in SNOT-22 score and a 1-point decrease in NPS compared to placebo. In the SINUS studies, the treatment effect of dupilumab was demonstrated after 24 weeks; however, renewal criterion based on 52 weeks of treatment was used to allow flexibility and to align with clinical practice.	Jurisdictions may consider renewal criteria for dupilumab that aligns with the criteria for mepolizumab used by each of the public drug plans. A clinically meaningful response on the SNOT-22 is a decrease in score from baseline of at least 8.9 points or greater. A clinically meaningful response for NPS is a decrease in score from baseline of at least 1 point or greater.
Prescribing		
4. Dupilumab should be prescribed by physicians with expertise in managing severe CRSwNP (e.g., otolaryngologists, allergists, respirologists).	This is meant to ensure the accurate diagnosis and management of patients with CRSwNP and that dupilumab is prescribed for appropriate patients.	Jurisdictions may consider prescribing criteria for dupilumab that aligns with the criteria for mepolizumab used by each of the public drug plans.
Pricing		
5. A reduction in price	The ICER for dupilumab is $106,988 when compared with BSC. A price reduction of 50% would be required for dupilumab to achieve an ICER of $50,000 per QALY compared to BSC.	—
Feasibility of adoption		
6. The feasibility of adoption of dupilumab must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate.	—

BSC = best supportive care; CDA-AMC = Canada's Drug Agency; CRSwNP = chronic rhinosinusitis with nasal polyposis; ICER = incremental cost-effectiveness ratio; INCS = intranasal corticosteroid; NC = nasal congestion and/or obstruction; NPS = Nasal Polyp Score; QALY = quality-adjusted life-year; SCS = systemic corticosteroid; SNOT-22 = 22-item Sino-Nasal Outcome Test.

Discussion Points

- **Current treatment options and patient needs**: CDEC discussed the currently available treatment options for patients with severe CRSwNP, which include the chronic use of an INCS, short courses of an SCS when symptoms worsen, and sinonasal surgery. Mepolizumab is also reimbursed for patients who have undergone at least 1 prior surgical intervention for nasal polyps or have a contraindication to surgery. CDEC noted input provided by patient groups, which indicated that currently available treatments lack efficacy and are associated with poor symptom control. Further, patients described

living with severe CRSwNP as having a significant impact on daily activities such as sleep, overall well-being, and HRQoL. CDEC also noted input from clinical experts that highlighted that the current treatment options, with the exception of mepolizumab, for severe CRSwNP do not address the underlying chronic type 2 inflammation pathology and lead to a cycle of high morbidity, poor symptom control, loss of smell and/or taste, and poor HRQoL. Based on this input, CDEC recognized the need for an additional treatment option for patients with severe CRSwNP.

- **Continuation of the use of an INCS**: In the SINUS trials, all patients continued INCS use throughout the study period, reflecting current clinical guidelines that recommend ongoing use of an INCS as standard of care. The clinical experts noted that discontinuing an INCS during treatment with dupilumab may compromise disease control and confound assessment of continued effectiveness. CDEC emphasized that dupilumab should be used as an add-on maintenance treatment with INCS, unless an INCS is contraindicated or otherwise not justified clinically.
- **Certainty of evidence:** CDEC discussed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of selected outcomes from the SINUS trials and noted that the certainty of the outcomes for the severity of nasal polyps and HRQoL as measured by the change from baseline in NPS and SNOT-22 score were considered "high," while the certainty of evidence for the severity of nasal congestion was considered to be "moderate." Additionally, the certainty of safety outcomes ranged from "low" (proportion of patients with myalgia and eosinophilia) to "moderate" (proportion of patients with nasopharyngitis and headache).
- **Comparative evidence:** Evidence comparing dupilumab to mepolizumab, another biologic for the treatment of severe CRSwNP, was limited to indirect evidence submitted by the sponsor. The sponsor-submitted indirect evidence suggested that dupilumab is likely as effective, and potentially more effective, than mepolizumab when assessed using the NPS and NC score end points. However, CDEC noted that there is uncertainty related to superiority due to methodological limitations and population differences across the included studies, and that the magnitude of difference between treatment groups was not clinically meaningful. In the absence of direct comparative evidence and considering the limitations of the indirect evidence, CDEC concluded that the clinical benefit of dupilumab is comparable to mepolizumab and therefore represents another treatment option for patients with severe CRSwNP. Furthermore, the clinical experts expressed that nasal polyp surgery is the gold standard for severe CRSwNP. However, evidence directly or indirectly comparing dupilumab to nasal polyp surgery was not submitted by the sponsor. Thus, CDEC concluded that the clinical benefit of dupilumab compared to surgery, particularly in those who have persistent symptoms despite adequate treatment with systemic corticosteroids, is uncertain.
- **Gap in evidence of long-term efficacy and safety:** CDEC discussed that there was no evidence of efficacy and safety of dupilumab beyond 52 weeks based on the SINUS trials, although the clinical experts consulted for this review considered the duration of the trials to be sufficient to assess response to treatment with dupilumab. The experts also indicated that in their experience, all patients demonstrate a treatment response to dupilumab within 1 year and some within 6 months. Of the 5 additional studies submitted by the sponsor to address this gap, CDEC discussed 1 observational

single-centre study; however, they concluded it was not relevant to this review because the majority of patients were receiving dupilumab at intervals greater than 2 weeks at 48 weeks and beyond, which is not aligned with the dosing approved by Health Canada. As such, there remains a gap in the long-term evidence beyond 52 weeks.

- **Uncertain economic evidence:** CDEC noted that there is remaining uncertainty in the economic evidence regarding the impact of severe asthma on patients with CRSwNP and the time point of response assessment used in clinical practice. Additionally, the cost-effectiveness of dupilumab versus mepolizumab remains uncertain due to limitations in the sponsor-submitted indirect evidence and the confidential prices paid by plans for both comparators.

Background

Chronic rhinosinusitis is a heterogeneous disease characterized by inflammation of the nose and paranasal sinuses, tissue edema, nasal obstruction, and increased mucus production. Chronic rhinosinusitis presents with symptoms such as NC and rhinorrhea that persist for at least 12 weeks. Current medical consensus categorizes chronic rhinosinusitis into 2 major phenotypes based on the presence or absence of nasal polyps. These 2 categories are CRSwNP and chronic rhinosinusitis without nasal polyposis. Nasal polyps in CRSwNP occur bilaterally and are noncancerous, edematous inflammatory lesions that usually originate from the mucosa of the ethmoid, maxillary, and sphenoidal sinuses. A retrospective study in Alberta (2004 to 2014) estimated the prevalence of chronic rhinosinusitis to range from 18.8 to 23.3 per 1,000 population. Among all patients with chronic rhinosinusitis, between 25% and 30% have CRSwNP. The peak incidence of CRSwNP generally occurs in working adults between the ages of 45 to 60 years. Patients with CRSwNP suffer with a high symptom burden, including nasal congestion, loss of sense of smell, facial pain or pressure, discoloured sinonasal discharge, breathing impairment, sleep disorders, fatigue, and increased risk of infection. Among these, the symptoms with the greatest impact on patients' HRQoL are sinonasal congestion, loss of smell, and sleep impairment. CRSwNP is diagnosed based on the presence of 2 or more symptoms of rhinosinusitis (NC, rhinorrhea, loss of smell, facial pain and/or headache), presence of nasal polyps in nasal endoscopy, and evidence of sinus inflammation on CT scan. In addition, the assessment of CRSwNP also takes into consideration the severity of the disease, which is often categorized using a visual analogue scale and the duration of symptoms.

International guidelines recommend a stepwise disease severity treatment approach for the treatment and management of CRSwNP. In this context, CRSwNP treatment is limited to the chronic use of INCS, short courses of SCS when symptoms worsen, and sinonasal surgery when medical therapy fails. In clinical settings in Canada, the INCS for initial treatment for CRSwNP is mometasone furoate nasal spray. An SCS is typically more effective than an INCS in reducing polyp size and nasal symptoms; however, long-term SCS use for severe CRSwNP has been associated with increased AEs, including infections, gastrointestinal events, pneumonia, retinopathy, and long-term diseases such as diabetes, hypertension, kidney disease, peptic ulcer disease, and osteoporosis and/or osteopenia. In patients whose disease does not respond to medical therapy, surgical management may be required to provide symptom relief and to

remove inflammatory tissue, but the recurrence of CRSwNP symptoms after surgery is common and multiple surgeries may be needed to address recurrent symptoms. The current stepwise approach to CRSwNP treatment does not address the underlying chronic type 2 inflammation pathology and leads to a cycle of high morbidity, poor symptom control, loss of smell and/or taste, and poor HRQoL. The Canadian Rhinology Working Group recommends the use of biologic therapies for patients with CRSwNP to address the gaps in treatment. Biologic therapies that are currently available in Canada include dupilumab, omalizumab, and mepolizumab (Nucala). Although omalizumab (Xolair) is approved by Health Canada for use in CRSwNP, it is not publicly reimbursed in Canada. Not all patients have disease that responds to mepolizumab.

Dupilumab is approved by Health Canada as an add-on maintenance treatment with an INCS in adults with severe CRSwNP inadequately controlled by an SCS and/or surgery. Dupilumab is available as a 300 mg single-use prefilled syringe or pen administered by subcutaneous injection and the dosage recommended in the product monograph is 300 mg every other week.

Sources of Information Used by the Committee

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

- a review of 2 phase III double-blind, placebo-controlled, multicentre studies in adults (aged 18 years and older) with severe CRSwNP inadequately controlled by an SCS and/or surgery; 1 ITC; and 1 real-life, prospective observational cohort study addressing long-term evidence of efficacy and safety
- patients' perspectives gathered by 1 patient group, Asthma Canada (AC)
- input from the public drug plans that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with severe CRSwNP
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

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

Patient Input

One patient group input submission from AC was received for this review. AC is a national charitable patient-driven organization that advocates for improved health and quality of life for people living with asthma and respiratory allergies through effective collaboration with policy-makers, researchers, and health care providers. AC gathered information for this submission through an online survey involving people in Canada living with or caring for patients with nasal polyps between October 30, 2024, to November 28, 2024. The survey received 8 responses from adults living with nasal polyps, including 3 people in British Columbia, 1 in

Manitoba, and 4 in Ontario. Of the 8 respondents, 1 was chosen at random for a one-to-one interview to gain an in-depth knowledge of the impacts of nasal polyps on the quality of life of people living with the condition.

When asked about their disease experience, respondents indicated that nasal congestion, trouble breathing, frequent sneezing, and loss of sense of smell and taste are the most common symptoms associated with nasal polyps. Overall, respondents highlighted that the most challenging aspects of living with nasal polyps include breathing difficulties, persistent nasal congestion, navigating the health care system, the risk of requiring surgery, and associated pain. These physical discomforts interfere with daily activities, sleep, and overall well-being. According to respondents, frequent medical appointments, financial difficulty, and an increase in missed work and/or school days are among the several challenges that family and caregivers face while caring for an individual with nasal polyps.

The respondents indicated that currently available treatment options for nasal polyps include INCS sprays, over-the-counter nasal sprays, nasal irrigation or saline rinses, and biologics such as mepolizumab and omalizumab. Based on these available treatment options, 4 respondents noted that their current treatments are largely ineffective and have poor symptom control. Six respondents expressed concerns such as frequent sinus infection, allergic reactions, and headaches and/or dizziness as side effects of available medications, especially oral corticosteroids. The patient who participated in the one-on-one interview indicated that they struggled finding effective treatment, including 2 surgeries and a short trial with Xolair (omalizumab), which eventually became ineffective.

Overall, respondents expressed a need for new effective symptom relief for day-to-day symptoms, emphasizing the need for new therapies that can provide longer-lasting benefits and reduce recurrence, the need for surgery, and reliance on oral corticosteroids. These preferences underline the desire for treatments that do not only alleviate immediate symptoms but also provide sustainable relief and minimize the physical and emotional burdens associated with managing the condition. Although none of the respondents had direct experience with dupilumab, 4 respondents indicated that the advantages of dupilumab, including easier management of disease symptoms and better long-term results, outweigh the potential side effects compared to other treatment options.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts consulted for this review indicated that the most important treatment goals for patients with CRSwNP include reducing symptom severity, preventing disease progression, minimizing complications, improving HRQoL, and reducing the risk of surgery. The clinical experts noted that the current standard of care for patients with CRSwNP in Canada starts with a standard or high dose (as tolerated) INCS and when this fails to control disease severity, which is often the case, oral steroids and surgical options are pursued. Oral corticosteroids only provide temporary improvement in severe symptoms and have significant side effects when used frequently. Although surgical intervention leads to symptom relief, nasal polyps often recur, requiring repeat procedures. The clinical experts indicated that patients often become refractory to current treatment options, particularly INCS and even surgery, and available treatments cannot reverse the course of

the disease or modify the underlying pathophysiology of CRSwNP. Therefore, new therapies that are better tolerated, are more effective, and can improve HRQoL relative to current standard of care are needed.

The clinical experts noted that dupilumab has a unique mechanism of action that is more targeted to the underlying inflammation driving CRSwNP. The clinical experts indicated that, based on their clinical experience, dupilumab is more effective than INCS, oral corticosteroids, and surgery because it particularly targets the underlying type-2 inflammation in the pathogenesis of CRSwNP. This is because dupilumab's mechanism of action makes it a disease-modifying treatment, distinguishing it from traditional therapies that only manage symptoms without altering the disease process. Compared to available treatment options in the current landscape in Canada, the clinical experts noted that dupilumab will not be a first-line therapy but rather a second-line therapy after failed INCSs and/or surgery. The experts also noted that it would be appropriate to consider use in combination with other treatments such as nasal corticosteroids or surgery.

According to the clinical experts, patients best suited for dupilumab include those with severe, uncontrolled symptoms, particularly those whose disease has not responded to, or who are intolerant of, traditional therapies like an INCS, oral steroids, and/or surgery. Based on their experience, the clinical experts consulted for this review suggested that patients with eosinophilic-driven inflammation and significant nasal polyp burden may be best suited for dupilumab, whereas patients with mild disease or noneosinophilic CRSwNP may be least suited for dupilumab. The clinical experts indicated that there are no issues related to CRSwNP diagnosis, and no companion diagnostic test is needed.

The clinical experts noted that response to dupilumab should be assessed based on clinical symptoms (e.g., nasal obstruction, loss of smell), change in SNOT-22 scores, anterior rhinoscopy, and, when available, in-office nasal endoscopy, which is commonly performed to objectively assess nasal polyp size and severity. According to the clinical experts, treatment response to dupilumab should be assessed at 6 months and 1 year after treatment initiation. According to the clinical experts, outcomes used in clinical practice align closely with those used in the SINUS clinical trials.

According to the clinical experts, dupilumab should be discontinued if patients' disease does not respond to treatment by 1 year or if they develop AEs such as eosinophilia that is clinically significant, blepharitis and/or conjunctivitis that cannot be managed, or myalgias that are intolerable to the patient. This should be determined based on persistence and severity of symptoms and, when relevant, imaging. The clinical experts indicated that dupilumab is typically prescribed in specialty settings such as outpatient clinics or specialty clinics with access to comprehensive diagnostic and monitoring tools. In addition, dupilumab should only be prescribed by a specialist (i.e., allergist; respirologist; or ear, nose, and throat specialist).

Clinician Group Input

No clinician group input was received for this submission.

Drug Program Input

Input was obtained from the drug programs that participate in our reimbursement review process. Refer to Table 2 for further information. The following were identified as key factors that could potentially impact the implementation of dupilumab:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for prescribing of therapy
- generalizability
- system and economic issues.

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

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Considerations for initiation of therapy	
Should severe CRSwNP be defined and if so, what criteria are used to diagnose severe CRSwNP?	According to the clinical experts, the criteria for diagnosing severe CRSwNP include CRSwNP that is refractory to high-dose INCS sprays and that the patient has required an SCS or surgery to manage their condition (or have contraindications to SCSs or surgery). Patients who have CRSwNP that has had a significant impact on their HRQoL fall under the criteria for severe CRSwNP. In addition, the Health Canada definitions for severe CRSwNP are referenced in practice. CDEC agreed with the clinical experts and noted that the consideration for initiation of dupilumab should align with mepolizumab reimbursement recommendation.
Dupilumab is used in pediatric populations for other indications, is there a place in therapy for dupilumab in children with CRSwNP?	The 2 clinical experts noted that CRSwNP is very uncommon in individuals younger than 18 years and rare in adolescents. The experts also indicated that safety of dupilumab for indications other than CRSwNP in pediatric populations has been shown. CDEC noted that the dupilumab indication for CRSwNP is for adults and it has not been approved for use in pediatric populations.
What dose, duration, and timeline of therapy for an SCS would be considered for the criterion of “previous use”? What would constitute a “medical contraindication” to SCS use? If SCS use is for temporary symptom relief and not a long-term treatment, should its use be required at all?	The clinical experts indicated that any requirement for SCS use, such as history of 1 course of prednisone in the past, is enough criterion for previous use. According to the clinical experts, contraindications to SCS use include poorly controlled diabetes, hypertension, kidney disease, peptic ulcer disease, retinopathy, cataracts, glaucoma, active infections, latent infections (e.g., untreated tuberculosis), peptic ulcer disease, history of upper gastrointestinal bleed, osteoporosis and/or osteopenia, and first trimester pregnancy. The 2 clinical experts suggested that experience with an SCS should not be a requirement for treatment with dupilumab as

Drug program implementation questions	Clinical expert response
	the need for an SCS is more of a criterion for defining severe disease. CDEC agreed with the clinical experts.
Referring to the indication, should the type of surgery required be specified, or is any reference to surgery within the past 10 years sufficient?	According to the clinical experts, the type of surgery should be sinus surgery. However, previous surgery should not be a barrier to accessing dupilumab. The experts indicated that disease severity should be considered more important than prior surgery when determining a patient's eligibility for dupilumab. The experts also noted that wait times to see an ENT specialist followed by wait times for surgery can delay access to effective treatment for CRSwNP when prior surgery is an eligibility criterion for treatments like dupilumab. CDEC agreed with the clinical experts.
Are there scenarios in which a patient eligible for surgery would replace surgery with SCS use? If a patient is ineligible for surgery, should they be required to use an SCS? Are there scenarios in which the patient is ineligible for both surgery and an SCS?	The 2 clinical experts noted that an SCS should not be used to replace surgery; however, patients who are on a waitlist for surgery should be eligible for an SCS. The clinical experts noted that this will depend on the observation of an ENT specialist. Patients ineligible for surgery can use an SCS if there is no contraindication to an SCS. According to the clinical experts, patients are ineligible for surgery if they have uncontrolled medical conditions like poorly managed diabetes or hypertension, infections such as active sinus or systemic infections, bleeding disorders such as hemophilia or use of anticoagulants, untreated dental issues or periodontal disease, or other concerns as indicated by the ENT caring for the patient. CDEC agreed with the clinical experts.
In the setting in Canada, the optimized INCS option is mometasone furoate nasal spray, two 50 mcg sprays in each nostril twice daily, where tolerated. Are there any equivalent nasal sprays in Canada and is there any reliable equivalency between INCS options in practice?	According to the clinical experts, apart from mometasone furoate nasal spray, other equivalents used are fluticasone propionate, two 50 mcg twice daily; fluticasone furoate, two 25 mcg twice daily; ciclesonide, two 50 mcg twice daily; and budesonide, two 64 mcg twice daily. The clinical experts noted that, apart from mometasone, all the listed equivalent nasal sprays are used off-label in these higher concentrations. The clinical experts further noted that there is reliable equivalency between these INCS options. CDEC agreed with the clinical experts.
Considerations for continuation or renewal of therapy	
If a patient's disease does not meet the criterion for showing "clinically meaningful response" and they are denied renewal, should they be eligible for re-treatment in the future? Are there any scenarios to consider as "extenuating circumstances" for renewal consideration for a patient not reaching the required clinically meaningful response beyond 52 weeks?	The clinical experts indicated that they had no experience with patients whose disease did not respond to dupilumab yet. Although they noted that a patient who had previously been denied renewal should not impact eligibility for re-treatment in the future. The clinical experts indicated that unexpected treatment interruptions, such as pregnancy or other reasons beyond the control of patient, are some of the scenarios to consider as

Drug program implementation questions	Clinical expert response
	"extenuating circumstances" for renewal consideration. CDEC agreed with the clinical experts.
Considerations for prescribing of therapy	
Is there potential for dose escalation for this indication?	The clinical experts indicated that, based on their clinical experience, there is no need for potential dose escalation for this indication. CDEC agreed with the clinical experts.
Should tapering be considered after 24 weeks, 52 weeks, or specific to clinical needs for this indication?	The clinical experts indicated that off-label use should not be considered. The currently approved Health Canada dosing recommendation for dupilumab for CRSwNP does not include tapering. CDEC agreed with the clinical experts.
Generalizability	
It is appropriate to consider switching a patient to dupilumab from another product, such as mepolizumab? If so, should different initiation criteria be used for patients who would like to switch between products? And would achieving a clinically meaningful response be a factor when switching? Can baseline values before comparator therapy be used for initial assessment?	According to the clinical experts, given the different mechanism of action of dupilumab, switching patients from another biologic (e.g., mepolizumab) to dupilumab could be considered. The clinical experts indicated that patients who are eligible for mepolizumab should be eligible for dupilumab. The experts noted that initiation criteria for switching products should include evidence of minimal improvement in symptoms despite 4 to 6 months of treatment. According to the clinical experts, baseline values should be considered for initial assessment before comparator therapy. CDEC noted that there is no evidence to support switching of patients from another biologic therapy (mepolizumab) to dupilumab.
System and economic issues	
Should the reimbursement of multiple biologics be considered for differing indications?	The clinical experts indicated that the reimbursement of multiple biologics can be considered for different indications but not for the same indication. They also indicated that multiple biologics should not be used concurrently for the same indication. The CDA-AMC review team noted that there is no evidence to support the use of dupilumab for the treatment of CRSwNP in combination with other biologics. CDEC agreed with the clinical experts.
Should patients be eligible for both mepolizumab and dupilumab at the same time for treatment of CRSwNP, considering they have different mechanisms of action?	The 2 clinical experts indicated that dupilumab and mepolizumab should not be used concurrently. CDEC noted that there is no evidence that dupilumab and mepolizumab should not be used concurrently.

CDA-AMC = Canada's Drug Agency; CDEC= Canadian Drug Expert Committee; CRSwNP = chronic rhinosinusitis with nasal polyposis; ENT = ear, nose, and throat; HRQoL = health-related quality of life; NPS = Nasal Polyp Score; INCS = intranasal corticosteroid; SCS = systemic corticosteroid.

Note: Reference to SCS includes both IV and oral SCS, although IV SCS is rarely used in practice.

Clinical Evidence

Systematic Review

Description of Studies

Two studies met the inclusion criteria of the sponsor-submitted systematic literature review: the SINUS-24 and SINUS-52 studies.

The SINUS-24 and SINUS-52 studies were 2 multinational, multicentre, randomized, double-blind, placebo-controlled, parallel-group studies that assessed the efficacy and safety of dupilumab in adults with severe CRSwNP. The SINUS-24 study was conducted in 67 centres in 13 countries while the SINUS-52 study was conducted in 117 centres in 14 countries. There were no sites in Canada in the SINUS-24 study; however, there were 8 sites in Canada in SINUS-52. Both trials are completed, and the data presented in this report corresponds with a data cut-off date of July 5, 2018, for the SINUS-24 study and August 29, 2018, for the SINUS-52 study.

In the SINUS-24 study, 276 patients were randomized 1:1 to receive dupilumab 300 mg (N = 133) or a matching placebo (N = 143) every 2 weeks for 24 weeks. In the SINUS-52 study, 448 patients were randomly assigned (1:1:1) to dupilumab 300 mg every 2 weeks for 52 weeks (arm A) (N = 150), the same schedule for the first 24 weeks followed by dupilumab 300 mg every 4 weeks for an additional 28 weeks (arm B) (N = 145), or placebo (arm C) (N = 153). Randomization was stratified by the presence of comorbid asthma and/or nonsteroidal anti-inflammatory drug (NSAID)–exacerbated respiratory disease, prior nasal polyp surgery (yes or no), and country.

In both trials, patients were included if they were diagnosed with CRSwNP and had a bilateral sinonasal polyposis and chronic symptoms of nasal congestion and another symptom such as loss of smell or rhinorrhea despite background treatment with an INCS and maximum standard of care therapy, including SCSs and/or surgery for nasal polyposis in the past and signed a written informed consent. Patients with persistent signs and symptoms or disease relapse after short courses of an SCS or after surgery were permitted in the trials. Key exclusion criteria included patients using a systemic immunosuppressant to treat inflammatory disease or autoimmune disease, patients receiving anti-immunoglobulin E therapy (e.g., omalizumab) 130 days or more before baseline, or those who had received intranasal and/or sinonasal surgery (including polypectomy) less than or equal to 6 months before baseline or sinonasal surgery that changed the lateral wall structure of the nose making the evaluation of NPS impossible.

The coprimary objectives of both the SINUS-24 and SINUS-52 studies were to evaluate the efficacy of dupilumab compared to placebo based on the change from baseline in nasal congestion severity and nasal polyp size at week 24 in both trials. In the SINUS-52 study, outcomes were also assessed at week 52. Key secondary objectives of both trials were to evaluate the efficacy and safety of dupilumab in improving total symptom score (TSS), HRQoL (SNOT-22 score), sense of smell, the proportion of patents who received an SCS or planned to undergo sinonasal surgery. A prespecified hierarchical testing procedure was used to control the overall type I error rate for both NPS and NC score as well as selected secondary end points, including SNOT-22 score, TSS, and decreased or loss of smell. Safety outcomes included AEs; serious

adverse events (SAEs); adverse events of special interest (AESIs); deaths; and notable harms, including myalgia, eosinophilia, nasopharyngitis, and headaches.

In the SINUS-24 study, the median age of patients was 51 years (range = [redacted]) and most were male (N = 158; 57.2%), whereas in the SINUS-52 study, the median age of patients was 52 years (range = [redacted]). The number of patients with at least 1 type 2 inflammation-mediated condition, including asthma and/or NSAID-exacerbated respiratory disease, was 75.3% and 82.3% in the SINUS-24 and SINUS-52 studies, respectively. In the SINUS-24 study, 71.7% of patients had prior nasal polyp surgery while 58.2% of patients included in the SINUS-52 study had prior nasal polyp surgery. The mean time since first diagnosis of CRSwNP in the overall study population of the SINUS-24 study was 11.11 years (range = 0.2 years to 42.5 years) and 10.94 years (range = 0.1 years to 61.3 years) in the SINUS-52 study. In both trials, nearly all patients had chronic symptoms with nasal polyposis (i.e., nasal congestion, rhinorrhea, or loss of smell) and the majority of patients presented with at least 2 symptoms 8 weeks before screening. The mean time since asthma onset was 15.51 years (range = [redacted]) in the SINUS-24 study and 17.72 years (range = [redacted]) in the SINUS-52 study. There were 208 patients (75.4%) in the SINUS-24 study and 369 patients (82.4%) in the SINUS-52 study who had a medical history of at least 1 type 2 inflammation-mediated condition.

Efficacy Results

For the SINUS-52 study, we reported results for dupilumab 300 mg every 2 weeks and the placebo group. The results for the group receiving dupilumab 300 mg every 2 weeks to every 4 weeks are not reported because they do not match the indication for this review. For week 24 results, the 2 dupilumab arms were pooled so results are for 295 patients and comparisons are for the pooled dupilumab arms versus placebo.

Severity of Nasal Polyps and Nasal Obstruction

Nasal Polyp Score

NPS was a coprimary outcome and was assessed based on centrally read video recordings of nasal endoscopy by 2 physicians. In the SINUS-24 study, the least squares (LS) mean change from baseline in NPS at week 24 was –1.89 for the 300 mg every 2 weeks dupilumab group and 0.17 for the placebo group, with a mean difference versus placebo of –2.06 (95% confidence interval [CI], –2.43 to –1.69; P < 0.0001). In the SINUS-52 study, the LS mean change in NPS at week 24 was lower in the dupilumab group (–1.72; SD = 1.77) compared to the placebo group (0.12; SD = 0.95). The LS mean difference at week 24 was –1.80 (95% CI, –2.10 to –1.51; P < 0.0001) in favour of the dupilumab treatment group. At week 52, the LS mean difference between the dupilumab and placebo groups was –2.40 (95% CI, –2.77 to –2.02; P < 0.0001).

In both trials, the responder analysis of the change from baseline in NPS at week 24 was conducted as supportive analysis to determine the proportion of patients with improvement in at least 1 point in NPS based on the minimal important difference (MID) identified in the literature. In the SINUS-52 study, a responder analysis was also conducted for the change from baseline to week 52. In the SINUS-24 study, the proportion of patients with at least a 1-point decrease in NPS was 65.0% in the dupilumab group compared to 17.3% in the placebo group. In the SINUS-52 study, the proportion of patients with at least a 1-point decrease in NPS

in the dupilumab compared to placebo group at week 24 and 52 were 62.0% and [redacted] versus 10.5% and [redacted] respectively.

NC Score

The change from baseline in NC score was a coprimary outcome in both trials. Nasal congestion was a patient-reported outcome that assessed the severity of nasal congestion on a daily basis and scores were calculated based on a weekly average of the daily scores. In the SINUS-24 study, the LS mean change from baseline in NC scores at week 24 was –1.34 for the dupilumab every 2 weeks group and –0.45 for the placebo group. The LS mean difference in change from baseline in NC scores at week 24 between dupilumab and placebo was –0.89 (95% CI, –1.07 to –0.71; P < 0.0001) in favour of the dupilumab group. In the SINUS-52 study, the LS mean change in NC scores from baseline to week 24 was –1.25 for the dupilumab group and –0.38 for the placebo group, with a mean difference of –0.87 (95% CI, –1.03 to –0.71; P < 0.0001) in favour of the placebo group. At week 52, the LS mean difference in change from baseline in NC scores was –0.98 (95% CI, –1.17 to –0.79; P < 0.0001).

[redacted]

Health-Related Quality of Life

Sino-Nasal Outcome Test

SNOT-22 score was a patient-reported outcome used to assess the impact of CRSwNP on HRQoL in the preceding 2 weeks. The SNOT-22 is a 22-item validated questionnaire in which each item is scored on a scale from 0 (no impact of CRSwNP on HRQoL) to 5 (impact of CRSwNP on HRQoL). The sum of the response to each of the 22 questions informed the global score. The change from baseline in SNOT-22 score was included as a key secondary outcome. In the SINUS-24 study, the LS mean change from baseline to week 24 was –30.43 (SD = 1.54) for the dupilumab group and –9.31 (SD = 1.62) for the placebo group. The LS mean difference in change from baseline in SNOT-22 scores was –21.12 (95% CI, –25.17 to –17.06; P < 0.0001) in favour of dupilumab. In the SINUS-52 study, the LS mean difference in change from baseline in SNOT-22 scores at both week 24 and week 52 were –17.36 (95% CI, –20.87 to –13.85; P < 0.0001) and –20.96 (95% CI, –25.03 to –16.89; P < 0.0001).

[redacted]

[redacted].

Disease Symptoms and Severity

Total Symptom Score

TSS was assessed as a composite score (ranging from 0 and 9) based on the sum of the following symptoms: nasal congestion or obstruction, decreased or loss of sense of smell, rhinorrhea (average of anterior and/or posterior nasal discharge). The symptom scores were calculated using the same approach as for NC scores (a weekly average based on daily scores). The change from baseline in TSS was included as a key secondary outcome in both trials. In the SINUS-24 study, the LS mean change from baseline in TSS at week 24 to 3.69 (SD = 2.04) for the dupilumab group and –1.26 (SD = 1.71) for the placebo group. The LS mean difference in change from baseline to TSS between dupilumab and placebo was –2.61 (95% CI, –3.04 to –2.17; P < 0.0001). In the SINUS-52 study, the LS change from baseline in TSS at week 24 was –3.54 (SD = 2.47) for the dupilumab every 2 weeks group and –1.03 (SD =1.66) for the placebo group. The LS mean difference in the change from baseline in TSS was –2.44 (95% CI, –2.87 to –2.02; P < 0.0001) compared to the placebo. At week 52, the LS mean difference in the change from baseline TSS was [redacted] also in favour of dupilumab group.

Decreased or Loss of Smell

Decreased or loss of smell was a patient-reported outcome that assessed the severity of CRSwNP symptoms daily during the trials and scores were calculated using a 0 to 3 categorical scale (where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms). The symptom scores were calculated using the same approach as for NC scores where a weekly average of daily scores was calculated. The change from baseline in decreased or loss of smell was included as a key secondary outcome. In the SINUS-24 study, the LS mean difference in the change from baseline in decreased or loss of smell at week 24 was –1.12 (95% CI, –1.31 to –0.93) in favour of the dupilumab treatment group. In the SINUS-52 trial, the LS mean difference in the change from baseline in decreased or loss of smell at week 24 and week 52 were –0.98 (95% CI, –1.15 to –0.81; P < 0.0001) and [redacted] respectively.

Rescue Therapy

Proportion of Patients Who Received SCS Rescue or Surgery for Nasal Polyposis (Actual or Planned)

The proportion of patients who received an SCS or sinonasal surgery (actual or planned) was used as rescue therapy for CRSwNP in both trials. The proportion of patients who received an SCS or planned surgery for NP was included as a secondary outcome. In the SINUS-24 study, the number of patients who received an SCS as rescue therapy in the dupilumab group was 6.3% compared to 18.8% in the placebo group. Nine patients (6.8%) in the placebo group and 3 patients (2.1%) in the dupilumab group had surgery for nasal polyposis (actual or planned). Compared to the placebo, the proportion of patients who received an SCS as rescue therapy during the treatment period in the SINUS-52 study was lower in the dupilumab group

(14.7%; N = 22) than the placebo group (41.2%; N = 63). Additionally, 13 patients (8.5%) in the placebo group and 2 patients (1.3%) in the dupilumab group had surgery for nasal polyposis (actual or planned).

Harms Results

Adverse Events

In the SINUS-24 study, 65.0% of patients in the dupilumab group experienced treatment-emergent adverse events (TEAEs) during the entire treatment period compared to 70.5% of patients in the placebo group. In the SINUS-52 study, the proportion of patients with at least 1 TEAE during the entire treatment period was lower in the dupilumab treatment group (83.2%) than in the placebo group (90.7%).

Serious Adverse Events

In the SINUS-24 study, the incidence of treatment-emergent SAEs was lower in the dupilumab group, with 4.2% in the dupilumab group versus 14.4% in the placebo group. In the SINUS-52 study, a total of 15 patients (10.0%) in the placebo group compared to 8 patients (5.4%) in the dupilumab 300 mg every 2 weeks treatment group experienced a treatment-emergent SAE.

Withdrawals Due to Adverse Events

The discontinuation rate due to TEAEs in the SINUS-24 study was 3.5% in the dupilumab group compared to 2.3% in the placebo group. The most frequently reported TEAE that led to permanent treatment discontinuation was nasal polyps and this occurred in 2 patients (1.4%) in the dupilumab treatment group and 1 patient (0.8%) in the placebo group. In the SINUS-52 study, 11.3% of patients in the placebo group and 4.0% in the dupilumab group discontinued treatment due to a TEAE.

Mortality

In the SINUS-24 study, 1 patient in the placebo group died during the post-treatment period due to myocardial infarction, though it was assessed as unrelated to the study drug. In the SINUS-52 study, 1 patient died during the follow-up period due to a traumatic intracranial hemorrhage arising from an accidental fall from a bike, which was assessed as unrelated to the study drug by the investigator.

Notable Harms

Notable harms included in this review were the proportion of patients who had myalgia, eosinophilia, nasopharyngitis, and headaches during the treatment period. In the SINUS-24 study, no patients experienced myalgia in the dupilumab group compared to 1 patient in the placebo group. More patients in the dupilumab group had eosinophilia (1.4% versus 0.8%) and headache (4.95 versus 8.3%) compared to the placebo group while the incidence of nasopharyngitis (13.3% versus 15.2%) was lower in the dupilumab group. There were 9 patients (6.8%) in the placebo group and 6 patients (4.2%) in the dupilumab group who experienced an AESI. In the SINUS-52 study, fewer patients in the dupilumab group experienced myalgia (1.3% versus 3.3%), nasopharyngitis (20.1% versus 24.0%), and headache (10.8% versus 12.0%) compared to the placebo group. The incidence of eosinophilia was higher in the dupilumab group than in the placebo group (1.3% versus 0.7%). There were 13 patients (8.7%) in the placebo group and 8 patients (5.4%) in the dupilumab group who experienced an AESI.

Critical Appraisal

The SINUS-24 and SINUS-52 studies were randomized, double-blind, placebo-controlled studies. Both studies employed appropriate methods for blinding and treatment allocation, and randomization was stratified based on presence of comorbid asthma and/or NSAID-exacerbated respiratory disease, prior polyposis surgery, and country. Although the trials were powered to detect differences in the coprimary outcomes, they were not powered to detect differences in subgroups of patients with or without prior nasal polyp surgery. However, a prespecified subgroup analysis demonstrated consistent treatment effect of dupilumab in patients with and without prior nasal polyp surgery. CDA-AMC noted that there were differences in concomitant medication use between treatment groups in both trials, which could signal differences in underlying morbidity; however, it is unclear whether this would result in an increased risk of bias in the results. Missing data ranged from 4% to 9% per treatment group for outcomes, including NPS, NC score, and SNOT-22 score, in both trials. Worst observation carried forward and multiple imputation methods were used to handle missing values. Multiple imputation methods can introduce bias because they depend on the assumption that data are missing at random, which is often not realistic. However, sensitivity analyses for approaches to missing data demonstrated similar results as the main analysis. The relatively short follow-up duration (24 to 52 weeks) and absence of long-term extension studies limit the assessment of sustained efficacy and long-term safety, which is particularly important for CRSwNP.

The study population was generally representative of patients with severe CRSwNP; however, the exclusion of patients with mild to moderate forms of CRSwNP, systemic immunosuppressant use, autoimmune diseases, or recent sinonasal surgery limits the generalizability of the findings to these populations. The lack of sites in Canada in the SINUS-24 study and the inclusion of few patients (and the fact that nearly all of them were white) from Canada in the SINUS-52 study raise concerns about the generalizability to the practice landscape in Canada, given the ethnic diversity of patients seen in clinical practice in Canada; however, the clinical experts consulted for the review indicated that they do not expect different results in Canadian populations. Both trials included NPS and NC scores as coprimary outcomes, which were also identified as important outcomes based on the inputs from patient groups and clinical experts consulted for this review. Notably, SNOT-22 score, which measures the impact of CRSwNP on HRQoL, was a key secondary outcome and was controlled for multiplicity. Of note, the pivotal trials were placebo controlled and no studies were submitted that evaluated a direct comparison to other biologics such as mepolizumab.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and randomized controlled trials identified in the sponsor's systematic review, the GRADE assessment 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 randomized controlled trials 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 target of the certainty of evidence assessment for the change from baseline in NPS and the change from baseline in NC score was informed by the literature and expert opinion (an MID of a decrease in score greater than or equal to 1).[27] The target of the certainty of evidence assessment for the change from baseline in SNOT-22 score was also informed by the literature and expert opinion (an MID of a decrease in score greater than or equal to 8.9).[28]

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 target of the certainty of evidence assessment for all other outcomes assessed by GRADE were informed by the clinical experts consulted for this review. The following list of outcomes was finalized in consultation with expert committee members:

- severity of nasal polyp (change from baseline in NPS)
- severity of nasal congestion and/or obstruction (change from baseline in NC score)
- HRQoL (change from baseline in SNOT-22 score)
- notable harms (myalgia, eosinophilia, nasopharyngitis, headaches).

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for dupilumab as an add-on maintenance treatment with an INCS in adults with severe CRSwNP inadequately controlled by an SCS and/or surgery.

- Dupilumab results in a reduction in NPS at 24 and 52 weeks of follow-up when compared with the placebo.
- Dupilumab likely results in a reduction in NC score at 24 and 52 weeks of follow-up when compared with the placebo (moderate certainty due to serious imprecision).
- Dupilumab results in a reduction in SNOT-22 score at 24 and 52 weeks of follow-up when compared with the placebo.
- Dupilumab may result in little to no difference in myalgia at 52 weeks of follow-up when compared with the placebo (low certainty due to very serious imprecision).
- Dupilumab may result in little to no difference in eosinophilia at 52 weeks of follow-up when compared with the placebo (low certainty due to very serious imprecision).
- Dupilumab likely results in little to no difference in nasopharyngitis at 52 weeks of follow-up when compared with the placebo (moderate certainty due to serious imprecision).
- Dupilumab likely results in little to no difference in headaches at 52 weeks of follow-up when compared with the placebo. (moderate certainty due to serious imprecision).

Table 3: Summary of Findings for the Efficacy and Safety of Dupilumab vs. Placebo in Adults With Severe CRSwNP Inadequately Controlled by Systemic Corticosteroids and/or Surgery

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Severity of nasal polyp				
Change from baseline in NPS (0 [no polyps] to 8 [large polyps causing complete obstruction]),[a] LS mean change from baseline, score (95% CI) Follow-up: Week 24	724 (2 RCTs)	**SINUS-24** Dupilumab: –1.89 [redacted] Placebo: 0.17 [redacted] Difference: –2.06 (–2.43 to –1.69) **SINUS-52** Dupilumab: –1.71 [redacted] Placebo: 0.10 [redacted] Difference: –1.80 (–2.10 to –1.51)	High[b]	Dupilumab results in a reduction in NPS when compared with the placebo.
Change from baseline in NPS (0 [no polyps] to 8 [large polyps causing complete obstruction]),[a] LS mean change from baseline, score (95% CI) Follow-up: Week 52	448 (1 RCT)	**SINUS-52** Dupilumab: –2.24 [redacted] Placebo: 0.15 [redacted] Difference: –2.40 (–2.77 to –2.02)	High[b]	Dupilumab results in a reduction in NPS when compared with the placebo.
Severity of nasal congestion and/or obstruction (NC score)				
Change from baseline in NC score (0 [no symptoms] to 6 [severe symptoms]),[c] LS mean change from baseline, score (95% CI) Follow-up: Week 24	724 (2 RCTs)	**SINUS-24** Dupilumab: –1.34 [redacted] Placebo: –0.45 [redacted] Difference: –0.89 (–1.07 to –0.71) **SINUS-52** Dupilumab: –1.25 [redacted] Placebo: –0.38 [redacted] Difference: –0.87 (–1.03 to –0.71)	Moderate[d]	Dupilumab likely results in a reduction in NC score when compared with the placebo.
Change from baseline in NC score (0 [no symptoms] to 6 [severe symptoms]),[c] LS mean change from baseline, score (95% CI) Follow-up: Week 52	448 (1 RCT)	**SINUS-52** Dupilumab: –1.35 [redacted] Placebo: –0.37 [redacted] Difference: –0.98 (–1.17 to –0.79)	Moderate[d]	Dupilumab likely results in a reduction in NC score when compared with the placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
HRQoL				
Change from baseline in SNOT-22 score (0 [less impact of CRSwNP on HRQoL] to 110 [most impact of CRSwNP on HRQoL]), LS mean change from baseline, score (95% CI) Follow-up: Week 24	724 (2 RCTs)	**SINUS-24** Dupilumab: –30.43 Placebo: –9.31 Difference: –21.12 (–25.17 to –17.06) **SINUS-52** Dupilumab: –27.77 Placebo: –10.40 Difference: –17.36 (–20.87 to –13.85)	High[e]	Dupilumab results in a reduction in SNOT-22 score when compared with the placebo.
Change from baseline in SNOT-22 score (0 [less impact of CRSwNP on HRQoL] to 110 [most impact of CRSwNP on HRQoL]), LS mean change from baseline, score (95% CI) Follow-up: Week 52	448 (1 RCT)	**SINUS-52** Dupilumab: –29.84 Placebo: –8.88 Difference: –20.96 (–25.03 to –16.89)	High[e]	Dupilumab results in a reduction in SNOT-22 score when compared with the placebo.
Harms				
Patients with myalgia, n (95% CI) Follow-up: Week 52	448 (1 RCT)	**SINUS-52** Dupilumab: Placebo: Difference:	Low[f]	Dupilumab may result in little to no difference in myalgia when compared with the placebo.
Patients with eosinophilia, n (95% CI) Follow-up: Week 52	448 (1 RCT)	**SINUS-52** Dupilumab: Placebo: Difference:	Low[g]	Dupilumab may result in little to no difference in eosinophilia when compared with the placebo.
Patients with nasopharyngitis, n (95% CI) Follow-up: Week 52	448 (1 RCT)	**SINUS-52** Dupilumab: 201 per 1,000 Placebo: 240 per 1,000 Difference: 39 less per 1,000	Moderate[h]	Dupilumab likely results in little to no difference in nasopharyngitis when compared with the placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Patients with headaches, n (95% CI) Follow-up: Week 52	448 (1 RCT)	**SINUS-52** Dupilumab: 94 per 1,000 [redacted] Placebo: 120 per 1,000 [redacted] Difference: 26 less per 1,000 [redacted]	Moderate[i]	Dupilumab likely results in little to no difference in headaches when compared with the placebo.

CI = confidence interval; CRSwNP = chronic rhinosinusitis with nasal polyposis; HRQoL = health-related quality of life; LS = least squares; MID = minimal important difference; RCT = randomized controlled trial; NPS = Nasal Polyp Score; NC = nasal congestion and/or obstruction; SNOT-22 = 22-item Sino-Nasal Outcome Test; 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.

[a]The score of NPS is 0 to 4 per each nostril; the overall score is a sum of the right and left nostril scores (range from 0 to 8).

[b]Based on a literature-based MID of 1 estimated for within-group effects; input from the clinical expert consulted by the review team considered that a between-group difference smaller than 1 point was not likely to be clinically important. A reduction in NPS corresponds to a reduction in the size of the nasal polyp.

[c]The score of NC is 0 to 3 per each nostril; the overall score is a sum of the right and left nostril scores (range from 0 to 6)

[d]Rated down 1 level for serious imprecision. A literature-based MID of 1 estimated for within-group effects was also considered clinically relevant for a between-group difference (i.e., a between-group difference smaller than 1 point was not likely to be clinically important) based on input from the clinical expert consulted by the review team. The 95% CIs for difference between groups include the possibility of no difference.

[e]Based on an MID of 8.9 from the literature for within-group effects; input from the clinical expert consulted by the review team considered that a between-group difference smaller than 8.9 points was not likely to be clinically important.

[f]The threshold for a clinically important difference was ≥ 10% (100 per 1,000), as informed by the clinical experts consulted for the review. Rated down 2 levels for very serious imprecision; the between-group effect was based on a very low number of events.

[g]The threshold for a clinically important difference was ≥ 3% (100 per 1,000), as informed by the clinical experts consulted for the review. Rated down 2 levels for very serious imprecision; the between-group effect was based on a very low number of events.

[h]The threshold for a clinically important difference was ≥ 20% (100 per 1,000), as informed by the clinical experts consulted for the review. Rated down 1 level for serious imprecision; the between-group effect was based on a low number of events.

[i]Rated down 1 level for serious imprecision. The lower bound of the CI shows potential for reduction in harm based on a threshold of ≥ 5% (100 per 1,000), as informed by the clinical experts consulted for the review.

Sources: SINUS-24 Clinical Study Report29; SINUS-52 Clinical Study Report.[30] The details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Comparisons

Description of Studies

In the absence of direct head-to-head evidence, the sponsor conducted ITCs to evaluate dupilumab versus mepolizumab for adults with uncontrolled CRSwNP. A Bucher method ITC was performed using placebo as the common comparator, and a matching-adjusted indirect comparison (MAIC) served as a supporting analysis to account for baseline differences across trials.

The ITCs drew results from 3 key randomized controlled trials: the SINUS-24, SINUS-52, and SYNAPSE trials. In the SINUS-24 and SINUS-52 studies, dupilumab was examined over 24 weeks and 52 weeks, respectively, in patients with severe CRSwNP who had a history of nasal polyp surgery or systemic corticosteroid use. SYNAPSE, by contrast, evaluated mepolizumab but required at least 1 nasal surgery in the past 10 years and a higher threshold for symptom severity on a visual analogue scale.

To address the substantial differences in eligibility criteria between the SINUS and SYNAPSE trials, the ITC restricted its comparative analyses to a “SYNAPSE-like” subgroup from the SINUS studies. This subgroup included only patients who met the more stringent SYNAPSE criteria, thereby helping to control for clinical heterogeneity and enabling a more consistent basis for indirect comparison. As a result, the final analyses of dupilumab versus mepolizumab reflect outcomes in this matched population.

Efficacy Results

Across both the Bucher ITC and the MAIC analyses, dupilumab demonstrated greater improvements than mepolizumab in key clinical outcomes — such as NPS, nasal congestion, and smell function — at 24 and 52 weeks. Dupilumab was also associated with numerically lower rates of nasal polyp surgery and a reduced need for an SCS compared to mepolizumab. While point estimates favoured dupilumab in most comparisons, the CI for the mean change in SNOT-22 score crossed the null in continuous analyses. However, other patient-reported outcomes presented in the ITC, such as the loss of smell score, visual analogue scale, and the SNOT-22 score responder analysis, showed improvements favouring dupilumab that excluded the null, despite some analyses having wider CIs, potentially reflecting variations like scale conversions or smaller effective sample sizes.

Harms Results

The submitted indirect comparisons did not assess harms.

Critical Appraisal

The ITCs offer useful insights into comparative efficacy when direct evidence is lacking; however, methodological constraints introduce limitations to the level of certainty and generalizability of the results. The reliance on fixed-effect models (potentially overstating precision for results close to the null, like NC score), the use of less than half the sample of the SINUS trials in the clinically similar analysis of the SYNAPSE-like population, the necessity to “downscale” outcome measures (e.g., nasal congestion) between trials, and the reduced effective sample sizes following MAIC reweighting introduce uncertainty. Notably, the comparison for NC score is subject to compounded uncertainty and the SNOT-22 score mean difference did not show a statistically significant advantage for dupilumab. Moreover, the SYNAPSE-like results limit generalizability beyond the most severe CRSwNP patient profile (i.e., those who have had prior surgery). Taken together, the consistent direction of effect favouring dupilumab is notable and dupilumab is likely as effective as, and might be more effective than, mepolizumab in patients who have had prior nasal polyp surgery, but residual heterogeneity and gaps in external validity are considered limitations in the analysis. There is no comparative evidence for patients with CRSwNP who did not have prior surgery. A head-to-head study of dupilumab and mepolizumab is expected to be completed in 2026 and has also limited its enrolment to patients with prior nasal polyp surgery.

Studies Addressing Gaps in the Evidence From the Systematic Review

One real-world observational cohort study conducted in a single tertiary referral centre was submitted by the sponsor to address the gaps in long-term efficacy and safety evidence from the systematic review. However, the observational study had patients increase the dosing interval over time, which was not consistent with

the approved Health Canada indication and recommended dose under review. At 48 weeks, 80% of patients were receiving dupilumab 300 mg at an interval of every 4 or every 6 weeks. Therefore, the efficacy and safety findings of this study were not considered relevant to this review.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree followed by Markov model
Target population	Adults with severe CRSwNP inadequately controlled by systemic corticosteroids and/or surgery
Treatment	Dupilumab as an add-on to BSC BSC consists of daily intranasal corticosteroids, occasional short courses of systemic steroids in case of worsening signs and/or symptoms requiring medical intervention, and/or systemic antibiotics in case of acute infection.
Dose regimen	300 mg given every other week
Submitted price	Dupilumab: $978.70 per 300 mg single-use syringe or pen
Submitted treatment cost	$25,534 per year, not including BSC
Comparators	• Mepolizumab as an add-on to BSC • BSC alone
Perspective	Publicly funded health care payer in Canada
Outcomes	QALYs, LYs
Time horizon	Lifetime (50 years)
Key data sources	Pooled data from the SINUS-24 and SINUS-52 trials, as well as a sponsor-conducted ITC
Key limitations	• The relative clinical efficacy of dupilumab compared to mepolizumab is uncertain due to differences between trial populations and limitations associated with the sponsor's ITC. The comparative efficacy of dupilumab for patients who have not previously had sinus surgery is unknown. • Response assessment in the model may not represent clinical practice in Canada. First, the sponsor modelled response based on NPS; however, NPS is typically not used to assess response in clinical practice. Second, the timing of the first response assessment (at 6 months) did not align with clinical practice or typical funding practices for mepolizumab, which is currently funded for 1 year before requiring response assessment. • The cost of mepolizumab may have been overestimated as a result of using Ontario's public list price, which is higher than it is in Saskatchewan. Mepolizumab has had successful negotiations with the pan-Canadian Pharmaceutical Alliance and it is likely that Saskatchewan's lower list price is a closer approximation of the potential confidential price. • The modelled benefits or nasal surgery were likely underestimated, including underestimation of the quality of life improvement likely to be seen after nasal surgery, and

Component	Description
	a potential overestimation of the annual proportion of patients experiencing recurrence after surgery. • Health care resource use for patients with uncontrolled severe CRSwNP was likely overestimated, particularly regarding the number of specialist visits and rhinoscopies (assumed to be 6 of each) patients are likely to receive each year. • The impacts of asthma were likely overestimated, including asthma-related health care resource use, mortality, and the disutility associated with asthma. • Poor modelling practices were employed, including numerous IFERROR statements precluding thorough validation of the submitted model, and an underestimation of the uncertainty inherent in some parameters.
CDA-AMC reanalysis results	• For the CDA-AMC base case, we assumed relative efficacy based on the SYNAPSE-like population analysis from the submitted ITC; used the Saskatchewan public list price for mepolizumab; modelled clinical response as an improvement in SNOT-22 score of ≥ 8.9 points; adjusted the utility gain following surgery and probability of recurrence after surgery; assumed the proportion of patients experiencing disutility due to uncontrolled asthma can only impact patients with asthma; and adjusted health care resource use in uncontrolled health states. • The CDA-AMC base case suggests that dupilumab plus BSC is associated with an ICER of $106,988 per QALY gained (incremental costs = $446,568; incremental QALYs = 4.17) when compared to BSC alone. Mepolizumab plus BSC remains extendedly dominated by a mix of dupilumab plus BSC and BSC alone. A price reduction of approximately 50% would be required for dupilumab to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained compared to BSC, consistent with a cost of $489 per 300 mg/2 mL prefilled syringe or pen.

BSC = best supportive care; CDA-AMC = Canada's Drug Agency; CRSwNP = chronic rhinosinusitis with nasal polyposis; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life-year; NPS = Nasal Polyp Score; QALY = quality-adjusted life-year; SNOT-22 = 22-item Sino-Nasal Outcome Test.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's budget impact analysis: the prevalence of chronic rhinosinusitis in Canada may be underestimated, as well as the proportion of patients with chronic rhinosinusitis who have nasal polyps; the cost of mepolizumab may be overestimated; the proportion of patients with severe CRSwNP who would be eligible for public funding is uncertain and likely underestimated; the proportion of dupilumab uptake that would displace mepolizumab is overestimated due to a narrower population being eligible for public funding of mepolizumab for CRSwNP than the population requested for dupilumab; the Non-Insured Health Benefits population was inappropriately calculated. CDA-AMC reanalyses assumed a higher prevalence of chronic rhinosinusitis, a lower unit cost of mepolizumab, and a lower proportion of dupilumab uptake coming from mepolizumab displacement. In the CDA-AMC base case, the budget impact of reimbursing dupilumab as an add-on maintenance treatment with INCSs in adults with severe CRSwNP inadequately controlled by systemic corticosteroids and/or surgery is expected to be $46,313,639 (year 1: $8,449,849; year 2: $16,063,660; year 3: $21,800,130).

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

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.