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CADTH Reimbursement Recommendation

Mepolizumab (Nucala)

Indication: Severe chronic rhinosinusitis with nasal polyps

Sponsor: GlaxoSmithKline Inc.

Final recommendation: Reimburse with conditions

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Nucala?

CADTH recommends that Nucala should be reimbursed by public drug plans for the treatment of patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Nucala should only be covered to treat adult patients with severe CRSwNP who have polyps on both sides of the nose, have already had at least 1 surgery to treat their nasal polyps or cannot have this type of surgery, and still have symptoms despite corticosteroid treatment for at least 3 months. When Nucala is first prescribed, physicians must submit a baseline Sino-nasal Outcome Test-22 (SNOT-22) score or endoscopic nasal polyp score so that response to treatment can be measured.

What Are the Conditions for Reimbursement?

Nucala should only be reimbursed in patients whose nasal polyps are responding to treatment with Nucala and if it is prescribed by a physician with expertise in managing severe CRSwNP. The cost of Nucala must be lowered to be cost-effective and affordable.

Why Did CADTH Make This Recommendation?

- Results from 1 clinical trial showed that treatment with Nucala improved nasal polyps (as measured by endoscopy) and relieved nasal obstruction in patients with severe CRSwNP who were also taking corticosteroids. Nucala also improved CRSwNP symptoms.
- In addition, Nucala improved health-related quality of life, delayed nasal polyp surgery, and reduced the need for treatment with corticosteroids, all of which were needs patients identified as important.
- Based on CADTH's assessment of the health economic evidence, Nucala does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on the public list price, Nucala is estimated to cost the public drug plans approximately $104 million over the next 3 years.

Additional Information

What Is Chronic Rhinosinusitis With Nasal Polyps?

CRSwNP is a combination of nasal and sinus inflammation with benign growths in the nasal passage, called polyps. Nasal obstruction, severe nasal congestion, loss of smell and/or taste, and constant runny nose are all associated with CRSwNP. Currently, Canadian data on prevalence and incidence of CRSwNP are not available. In the US, the prevalence of CRSwNP is between 1% and 4% of the general population and between 25% and 30% of patients with chronic rhinosinusitis.

Unmet Needs in Chronic Rhinosinusitis With Nasal Polyps

Not all patients with CRSwNP respond to available treatments; even when patients do respond, the nasal polyps often recur. There is a need for more treatments targeted toward nasal polyps for these patients.

How Much Does Nucala Cost?

Treatment with Nucala is expected to cost approximately $27,308 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that mepolizumab be reimbursed as add-on maintenance treatment with intranasal corticosteroids in adult patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP) inadequately controlled by intranasal corticosteroids alone only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One multicentre, double-blind, placebo-controlled, randomized, phase III clinical trial (SYNAPSE, N = 414) showed that treatment with 100 mg/mL of mepolizumab once every 4 weeks resulted in statistically significant and clinically meaningful endoscopic improvement and relief of nasal obstruction in patients with severe recurrent CRSwNP who are treated with inhaled nasal corticosteroids. At the end of the 52-week treatment period, the adjusted median difference in change from baseline for total endoscopic nasal polyp score (NPS) was statistically significant in favour of mepolizumab compared with placebo (mean difference = −0.73; 95% confidence interval [CI], −1.22 to −0.34; P < 0.001). For the nasal obstruction visual analogue scale (VAS) score, the adjusted median difference in change from baseline to week 52 was statistically significant in favour of mepolizumab compared with placebo (mean difference = −3.14; 95% CI, −4.09 to −2.18; P < 0.001). Mepolizumab also was found to be efficacious in improving CRSwNP symptoms as measured by the VAS (adjusted mean difference at week 52 = −2.68; 95% CI, −3.44 to −1.91; P = 0.020), improving health-related quality of life (HRQoL) as measured by the Sino-nasal Outcome Test-22 (SNOT-22) (adjusted mean difference at week 52 = −16.49; 95% CI, −23.57 to −9.42; P = 0.003), prolonging time to nasal surgery (hazard ratio = 0.43; 95% CI, −0.25 to 0.76; P = 0.003), and reducing the probability of needing systemic corticosteroids for nasal polyps (odds ratio = 0.58; 95% CI, 0.36 to 0.92; P = 0.02).

Patients identified a need for new treatments that delay time to surgical intervention, improve HRQoL, and reduce the need for oral corticosteroids. Based on the evidence, mepolizumab appears to meet these needs.

Using the sponsor-submitted price for mepolizumab, the incremental cost-effectiveness ratio (ICER) for mepolizumab in combination with standard of care (SOC) was $380,251 per quality-adjusted life-year (QALY) compared with SOC alone. At this ICER, mepolizumab is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold for adults with severe CRSwNP inadequately controlled by intranasal corticosteroids alone. A price reduction is required for mepolizumab 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. endoscopically or CT--	Evidence from the SYNAPSE study demonstrated that treatment with mepolizumab resulted in a clinical benefit	CDEC acknowledged that treatment with mepolizumab may also benefit patients who have a contraindication to nasal polyp

Reimbursement condition	Reason	Implementation guidance
documented bilateral nasal polyps 1.2. have undergone at least 1 prior surgical intervention for nasal polyps or have a contraindication to surgery 1.3. be tolerant and able to continue use of inhaled nasal corticosteroids but have refractory symptoms despite use of inhaled corticosteroids for 3 months at maximally tolerated doses.	in patients with these characteristics. Prior to enrolment in the SYNAPSE trial, patients were required to be on maximal tolerated doses of inhaled nasal corticosteroids for 8 weeks. However, clinical experts indicated that patients should be on maximally tolerated daily intranasal corticosteroids for at least 3 months to determine its full effect.	surgery, although such patients were not included in the SYNAPSE trial.
2. Prescribing clinician must submit a baseline SNOT-22 or endoscopic NPS.	In the SYNAPSE study, mepolizumab resulted in improvements on the clinically relevant measures of the SNOT-22 and NPS (see renewal criteria).	—
Renewal		
3. Patients must exhibit a clinically meaningful response on the Sino-nasal Outcome Test (SNOT-22) or endoscopic NPS relative to their baseline score. 3.1. Response to treatment should be assessed after every 52 weeks.	In the SYNAPSE trial, the treatment effect of mepolizumab was demonstrated after 52 weeks, which is consistent with what would occur in clinical practice.	• A clinically meaningful response on the SNOT-22 is a decrease in score from baseline of 8.9 points or greater. • A clinically meaningful response for NPS is a decrease in score from baseline of 1 point or greater.
Prescribing		
4. Mepolizumab should be prescribed by physicians with expertise in managing severe CRSwNP (e.g., otolaryngologists, allergists, respirologists).	Accurate diagnosis and management of patients with CRSwNP is important to ensure that mepolizumab is prescribed to appropriate patients.	According to the clinical expert consulted, ears, nose, and throat specialists or allergists should be required to diagnose, treat, and monitor patients who may receive mepolizumab.
Pricing		
5. A reduction in price.	The ICER for mepolizumab is $380,251 compared with SOC. A price reduction of at least 86% would be required for mepolizumab to be able to achieve an ICER of $50,000 per QALY compared with SOC.	—

CDEC = CADTH Canadian Drug Expert Committee; CRSwNP = chronic rhinosinusitis with nasal polyps; ICER = incremental cost-effectiveness ratio; NPS = nasal polyp score; SNOT-22 = Sino-nasal Outcome Test-22; SOC = standard of care; QALY = quality-adjusted life-year.

Discussion Points

- CDEC recognized the need for an additional treatment for patients with severe CRSwNP as there is currently no treatment available for patients who do not respond to SOC (which includes nasal corticosteroids) alone. CDEC acknowledged that these patients are difficult to treat and that mepolizumab represents an additional treatment option for patients with severe CRSwNP who are not adequately controlled with SOC treatment.
- CDEC acknowledged that the clinical experts indicated that the need for prednisone or surgery would represent a loss of response to treatment. However, for patients who require surgical intervention despite treatment with mepolizumab there may be a role for continuing treatment to prevent recurrence. This is reflective of the patient population enrolled in the SYNAPSE study.
- CRSwNP is a chronic condition, and it is unknown whether the treatment effect observed in the SYNAPSE study would persist beyond 52-weeks due to the lack of long-term evidence supporting continued use of mepolizumab.

Background

Chronic rhinosinusitis is a chronic inflammatory disease of the nasal passage linings and/or sinuses that can occur with or without nasal polyps. Nasal polyps are outgrowths of sinonasal tissues; those that accompany chronic rhinosinusitis are benign and typically develop bilaterally in the sinonasal cavity. The prevalence of CRSwNP is estimated to be between 1% and 4% of the US general population and between 25% and 30% of patients with chronic rhinosinusitis. Currently, Canadian data on prevalence and incidence of CRSwNP are not available. CRSwNP is more common in men and older individuals. Nasal obstruction and hyposmia or anosmia, as well as rhinorrhea, severe nasal congestion, and loss of smell and/or taste are key symptoms associated with CRSwNP. The long-term symptoms associated with CRSwNP negatively affect physical and mental HRQoL. Disease burden is particularly high among patients who require repeated treatment with systemic corticosteroids and/or sinonasal surgeries to alleviate uncontrolled symptoms.

The goal of therapy for CRSwNP is to reduce symptoms and complications by minimizing inflammation and controlling secondary infection that may occur. In clinical practice in Canada, initial treatment for CRSwNP generally starts with an intranasal corticosteroid with mometasone furoate (MF) nasal spray (2 sprays each nostril twice daily or an equivalent). Endoscopic sinus surgery is reserved for patients whose CRSwNP is not responsive to medical treatment.

Mepolizumab is a targeted anti-interleukin-5 (IL-5) immunoglobulin G1 (IgG1) kappa monoclonal antibody that is approved by Health Canada as an add-on maintenance treatment with intranasal corticosteroids in adult patients with severe CRSwNP inadequately controlled by intranasal corticosteroids alone. The Health Canada recommended dosing is 100 mg/mL once every 4 weeks via subcutaneous injection.

Sources of Information Used by the Committee

To make their recommendation, CDEC considered the following information:

- a review of 1 clinical study (SYNAPSE) in adults with recurrent CRSwNP
- patients' perspectives gathered by patient groups, including input from Asthma Canada and the Patient Lung Groups of the British Columbia Lung Association (BCLA)
- input from public drug plans that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with CRSwNP
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Patient input was provided by 2 groups: Asthma Canada and the Patient Lung Groups of the BCLA. Asthma Canada gathered patient perspectives using an online survey for which there were 17 responses.

Survey respondents indicated that CRSwNP symptoms have a direct negative impact on their daily lives, including decreased quality of life (90%), sleep disturbances (66%), missed time from work or school (30%), financial difficulties (20%), and hospital visits because of CRSwNP (20%). Among the survey respondents who identified as caregivers, 66% reported an impact on sleep because of nighttime symptoms and being burdened by managing frequent appointments (44%) and multiple medications (33%) for the patient they care for. The patient group also described patients experiencing fatigue and having less energy to work and exercise. The symptoms and consequent activity limitations were reported to make social connections and activity more difficult.

The Asthma Canada submission described the "cornerstones" of CRSwNP management as nasal corticosteroid spray to help shrink polyps and reduce irritation, oral corticosteroids to reduce the size of polyps, and endoscopic surgery to remove the polyps and "fix" the sinuses to help prevent more polyps. Of the survey respondents, 39% reported using nasal sprays to manage their CRSwNP, 28% reported having surgery, 17% reported using oral corticosteroids, and 17% reported using a biologic (e.g., dupilumab or omalizumab) to treat their nasal polyps. Experience with treatment side effects was also an issue for patients. Side effects most commonly reported included altered sense of smell (63%), allergic reactions (36%), mental or mood changes (27%), increased risk of sinus infection (27%), headaches or dizziness (18%), and ineffectiveness (18%). Furthermore, both Asthma Canada and BCLA expressed concern with the short- and long-term side effects associated with oral corticosteroids in patients who have failed to achieve adequate control with previous lines of therapy, such as weight gain, cataracts, osteoporosis, increased risk of infection, and high blood glucose.

Patients and caregivers reported the following outcomes as important for new treatment options: easier management of symptoms (63%), decreased anxiety about nasal polyps (45%), decreased reliance on oral corticosteroids and/or steroids (36%), reduced need for surgery (36%), and improved process for taking medication (27%). Of note, 63% of survey

respondents indicated that any potential side effects of mepolizumab would be worth tolerating in exchange for a measurable improvement in CRSwNP management. The patient input highlighted the need for new and additional therapeutic options for CRSwNP that can be effective in controlling disease symptoms because some patients have disease that remains uncontrolled with standard treatment.

Clinician Input

Input From Clinical Experts Consulted by CADTH

One clinical expert was consulted for this review. According to the clinical expert consulted by CADTH, not all patients are responsive to current treatments for the management for CRSwNP. Due to the chronic and recurring nature of CRSwNP, there is a medical need for targeted treatment of nasal polyps. Recurrence of nasal polyps is most likely to occur with high levels of local IL-5 and IgE, which drives eosinophilic inflammation. The anti-IL-5 mechanism of mepolizumab would prevent the inflammation most associated with nasal polyp recurrence. The clinical expert noted that mepolizumab would be most appropriate for use in patients who fail or cannot tolerate topical steroid treatment.

According to the clinical expert consulted, patients with eosinophilic polyps are most likely to respond to anti-IL-5 treatments. Eosinophilic polyps can be identified via pathology at the time of polyp removal. Those polyps identified as being neutrophilic are less likely to respond to anti-IL-5 treatments. The clinical expert also noted that biologic treatments would likely be unnecessary among patients who respond to topical steroids. The clinical expert noted that response to treatment is determined by severity of nasal congestion. Response to treatment should typically occur within 6 months of initiating therapy. The clinical expert noted that the need for prednisone or surgery could indicate a loss of response to treatment. Of note, for those patients who require surgery, continued treatment with mepolizumab may be considered to prevent recurrence of nasal polyps.

Clinician Group Input

No input was received from any clinician groups for this submission.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for mepolizumab. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs (Table 2).

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Consideration for initiation of therapy	
Are VAS scores and endoscopic bilateral nasal polyp score routinely used in clinical practice?	VAS scores are not routinely used in clinical practice. CDEC defers to the expertise of the clinical expert.

Drug program implementation questions	Clinical expert response
Is nasal endoscopy typically done by a specialist other than ENT (i.e., allergists, respirologists) or would these specialists refer to an ENT for the procedures?	Endoscopic bilateral nasal polyp surgery is performed by an ENT doctor and some allergists. CDEC defers to the expertise of the clinical expert.
When would nasal polyp surgery be contraindicated?	Nasal polyp surgery is considered contraindicated in patients who cannot undergo general anesthetic. CDEC defers to the expertise of the clinical expert.
Would patients who had not had prior nasal polyp surgery or do not have bilateral disease still qualify for coverage?	Patients who do not have bilateral disease should first undergo biopsy. If biopsy reveals benign eosinophilic polyps anti-IL-5 may be considered beneficial. If the patient has bilateral nasal polyps and cannot tolerate surgery, anti-IL-5 could be considered. CDEC noted that the SYNAPSE trial only included participants with evidence of bilateral nasal polyps.
Can nasal polyps occur unilaterally?	Nasal polyps may occur unilaterally. In these cases, malignancy must be ruled out. However, eosinophilic polyps rarely occur unilaterally. Such patients were not enrolled into the SYNAPSE trial. CDEC agrees with the input provided by the clinical expert.
Would LTRAs be trialled before mepolizumab in "appropriate patients"? Who would qualify as an "appropriate patient"?	Although LTRAs target eosinophilic inflammation, the evidence regarding the efficacy of LTRAs in nasal polyps is weak and not as strong as intranasal corticosteroids. CDEC defers to the expertise of the clinical expert.
Should the criteria/implementation advice specify use of intranasal steroids at the Health Canada–approved dose for nasal polyps for at least 8 weeks?	Biologics would be considered unnecessary among patients who respond to topical steroids. CDEC agrees with the input provided by the clinical expert and acknowledges that the expert also indicated that up to 3 months of treatment with an INCS may be required for a benefit to be observed.
Considerations for continuation or renewal of therapy	
Would nasal endoscopy be used in clinical practice to assess response to treatment?	Nasal endoscopy is performed in clinical practice by an ENT doctor or allergist who is trained to perform nasal endoscopy. CDEC expressed concern that the access to nasal endoscopy may differ across Canada.
Is 1 year an appropriate time frame for the initial assessment of therapeutic response vs. 6 months initially and annually thereafter?	Although it is acceptable to change therapy if patients have not responded to treatment by 6 months, it may be best to assess initial response to therapy at 8 to 12 months because 6 months is required to reach a steady state. CDEC noted that the input provided by the clinical expert differs from the data reviewed by CADTH and that, in the SYNAPSE study, end points were assessed at 52 weeks.
How would response to treatment be defined in terms of improvement in the various scores (i.e., VAS, NPS, SNOT-22)?	An improved response to treatment as assessed by NPS and SNOT-22 may be defined by the established MID for the assessment tool. For the NPS, response to treatment is defined by an improvement (decrease in score) of at least 1 point, whereas for the SNOT-22, response is defined by an improvement (decrease in score) of greater than 8.9 points. Response to treatment as assessed by VAS has not been definitively established. Generally, an improvement (decrease in score) between 2 points and 5 points indicates response to treatment when assessed by

Drug program implementation questions	Clinical expert response
	VAS. CDEC agrees with the input provided by the clinical expert.
Consideration for discontinuation of therapy	
How would loss of response or disease progression be defined?	The need for prednisone or surgery would indicate a loss of response to treatment. Of note, for those patients who require surgery, continued treatment with mepolizumab may be considered to prevent recurrence. CDEC noted that the input provided by the clinical expert is not reflective of the data reviewed by CADTH and that based on the information available for this review, it is unclear when patients should be required to discontinue treatment with mepolizumab.
Consideration for prescribing of therapy	
Is there potential for dose escalation for the CRSwNP indication?	Current studies have not been able to demonstrate a clinical difference of mepolizumab at higher doses but there are not many studies published that assessed this. CDEC cannot comment because only doses recommended by Health Canada were considered within this review.
Would use of mepolizumab be a lifelong treatment?	Although it is possible that treatment may be gradually withdrawn or even stopped in the case of clinical remission, treatment may be lifelong for patients with large polyps that recur post-surgery. CDEC defers to the expertise of the clinical expert.

CDEC = CADTH Canadian Drug Expert Committee; ENT = ears, nose, and throat; LTRA = leukotriene receptor antagonist; MID = minimal important difference; NPS = nasal polyp score; SNOT-22 = Sino-nasal Outcome Test Questionnaire-22; VAS = visual analogue scale.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

One study was included in this systematic review. SYNAPSE was a randomized, double-blind, placebo-controlled, parallel group, phase III study that assessed the clinical efficacy and safety of mepolizumab as an add-on maintenance treatment in adults with recurrent CRSwNP. A total of 414 adults were randomized at 86 sites across 11 countries, including 34 people (8.2%) across 8 sites in Canada. The study comprised a 4-week run-in period followed by a 52-week treatment period in which patients were randomized to receive either mepolizumab (n = 207) or matching placebo (n = 207). During the treatment period, patients received either mepolizumab 100 mg every 4 weeks (a total of 13 does) or placebo delivered by subcutaneous injection. The final dose of the study treatment was administered at week 48. All patients remained on SOC treatment for CRSwNP throughout the study. SOC included daily MF nasal spray and, if required, saline nasal douching and an occasional short course of high-dose oral corticosteroids and/or antibiotics. Changes in the MF dosing regimen between screening and end of the study were not permitted.

The co-primary efficacy end points were change from baseline in endoscopic NPS at week 52 and change from baseline in nasal obstruction VAS symptom score during the 4 weeks

before week 52. The key secondary end point was time to first actual surgery for nasal polyps by week 52. Other secondary end points included change from baseline in the overall VAS symptom score, change from baseline in the SNOT-22 score, the proportion of patients requiring systemic steroids for nasal polyps, change from baseline in the composite VAS symptom score (combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat, and loss of smell), and change from baseline in the loss of smell VAS score. Multiplicity was controlled using a hierarchical closed testing approach in making inferences for the secondary end points. Analyses were adjusted for the following covariates: country region, blood eosinophil count, baseline endoscopic nasal score, number of previous surgeries, and number of courses of oral corticosteroids for nasal polyps in the previous 12 months.

The randomized patients were middle-aged (mean = 48.8 years; standard deviation [SD] = 13.01 years) and generally overweight (mean body mass index = 28.16 kg/m^2; SD = 5.36 kg/m^2). The mean time since onset of nasal polyps at baseline was 11.41 years (SD = 8.39 years). Patients presented with severe CRSwNP as indicated by baseline total endoscopic NPS (centrally read) (mean = 5.5; SD = 1.29), nasal obstruction VAS score (mean = 8.97; SD = 0.83), SNOT-22 total score (mean = 64.1; SD = 18.32), and a history of at least 1 surgery for nasal polyps in the past 10 years. Although the majority of all patients had a history of 1 or 2 surgeries (70%), a greater proportion of patients in the placebo group than the mepolizumab group had more than 1 surgery (60% versus 48%).

Efficacy Results

Severity of Nasal Polyps

At the end of the 52-week treatment period, the mean change in total endoscopic NPS from baseline was −0.1 (SD = 1.46) and −0.9 (SD = 1.90) in the placebo and mepolizumab groups, respectively. The median changes from baseline in the placebo and mepolizumab groups were 0 (interquartile range [IQR], −1.0 to 1.0) and −1.0 (IQR, −2.0 to 0.0), respectively. The adjusted median difference in change from baseline was statistically significant in favour of mepolizumab compared with placebo (adjusted median difference = −0.73; 95% CI, −1.22 to −0.34; P < 0.001). In total, 28.4% and 50.5% of patients in the placebo and mepolizumab groups, respectively, demonstrated the minimal important difference (MID) of at least 1 point improvement in their total endoscopic NPS. According to the clinical expert consulted by CADTH for this review, the response to treatment as defined by the total endoscopic NPS is indictive of a treatment response in the clinical setting.

Exploratory subgroup analyses in patients with or without asthma and in patients with or without prior surgery for nasal polyps were conducted; however, no formal hypothesis testing was done. Therefore, the effect of mepolizumab compared with these subgroups is unknown.

Nasal Obstruction

For the 4-week recall period from week 49 to week 52, the mean change in total nasal obstruction VAS score from baseline was −2.45 (SD = 3.15) and −4.24 (SD = 3.42) in the placebo and mepolizumab groups, respectively. The median changes from baseline to week 52 in the placebo and mepolizumab groups were −0.82 (IQR, −4.84 to 0.0) and −4.41 (IQR, −7.27 to −0.36), respectively. The adjusted median difference in change from baseline to week 52 was statistically significant in favour of mepolizumab compared with placebo (adjusted median difference = −3.14; 95% CI, −4.09 to −2.18; P < 0.001). Of note, 23% and 44% of patients in the placebo and mepolizumab groups, respectively, demonstrated an improvement greater than 5 points (suggested MID) in their nasal obstruction VAS score.

Exploratory subgroup analyses in patients with or without concurrent asthma and in patients with or without prior surgery for nasal polyps were conducted; however, no formal hypothesis testing was done. Therefore, the effect of mepolizumab compared with these subgroups is unknown.

The magnitude of the treatment effect for nasal obstruction VAS score was modest, yet indicative of a treatment response in the clinical setting according to the clinical expert consulted by CADTH for this review. According to the clinical expert, an increase in score between 20% and 50% of the baseline VAS score is considered acceptable in clinical practice. In the SYNAPSE trial, the mean change from baseline across the VAS end points fell within this range.

Symptoms

In the 4-week recall period from week 49 to week 52, the mean changes in nasal symptom composite VAS score from baseline were −2.19 (SD = 2.82) and −3.81 (SD = 3.19) in the placebo and mepolizumab groups, respectively. The median changes from baseline in the placebo and mepolizumab groups were −0.89 (IQR, −4.06 to 0.0) and −3.96 (IQR, −6.68 to −0.32), respectively. The adjusted median difference in change from baseline was statistically significant in favour of mepolizumab compared with placebo (adjusted median difference = −2.68; 95% CI, −3.44 to −1.91; P = 0.020). In total, 20% and 37% of patients in the placebo and mepolizumab groups, respectively, demonstrated an improvement greater than 5 points in their nasal symptom composite VAS score.

In the 4-week recall period from week 49 to week 52, the mean changes in nasal symptom and facial pain composite VAS score from baseline were −2.24 (SD = 2.88) and −3.80 (SD = 3.18) in the placebo and mepolizumab groups, respectively. The median changes from baseline in the placebo and mepolizumab groups were −0.99 (IQR, −4.29 to 0.0) and −3.88 (IQR, −6.45 to −0.25), respectively. The adjusted median difference in change from baseline favoured the mepolizumab group compared with the placebo group (adjusted median difference = −2.50; 95% CI, −3.33 to −1.67). In total, 21% and 38% of patients in the placebo and mepolizumab groups, respectively, demonstrated an improvement greater than 5 points in their nasal symptoms and facial pain composite VAS score.

In the 4-week recall period from week 49 to week 52, the mean changes in loss of smell VAS score from baseline were −1.38 (SD = 2.65) and −2.83 (SD = 3.61) in the placebo and mepolizumab groups, respectively. The median changes from baseline in the placebo and mepolizumab group were 0 (IQR, −1.28 to 0.0) and −0.53 (IQR, −5.60 to 0.0), respectively. The adjusted median difference in change from baseline was statistically significant in favour of mepolizumab compared with placebo (adjusted median difference = −0.37; 95% CI, −0.65 to −0.08; P = 0.020). In total, 13% and 30% of patients in the placebo and mepolizumab groups, respectively, demonstrated an improvement of at least a 5 points in their loss of smell VAS score.

The magnitude of the treatment effect for the compositive VAS scores were indicative of an acceptable treatment response in the clinical setting according to the clinical expert consulted by CADTH for this review. For loss of smell, however, the magnitude of the treatment effect was considered small. According to the clinical expert, it is difficult to regain loss of smell once lost.

Nasal Congestion

At week 52, the mean change from baseline in peak nasal inspiratory flow was greater in the mepolizumab group (mean change = 32.5; SD = 57.98) than in the placebo group (mean change = 11.2; SD = 65.78). The median changes from baseline in the placebo and mepolizumab groups were 0 (IQR, −20.0 to 50.0) and 30 (IQR, 0.0 to 60.0), respectively. The improvement in the mepolizumab group was in excess of the established 20 L/min MID.

Peak nasal inspiratory flow is a measure of objective improvement in nasal congestion because it is affected by both polyp size and nasal mucosa inflammation. In the SYNAPSE trial, no analysis of treatment difference was conducted between the groups and the outcome was absent from the statistical testing hierarchy. As a result, conclusions cannot be made about the efficacy of mepolizumab to improve nasal congestion. This represents a missed opportunity to demonstrate an objective treatment effect on an outcome that is considered important in the clinical setting.

Response to Treatment

A total of 28% and 50% of patients in the placebo and mepolizumab groups, respectively, demonstrated an improvement of at least 1 point in their total endoscopic NPS at the end of the 52-week treatment period. The odds of being a responder in the mepolizumab compared with the odds of being a responder in the placebo group was 2.74 (95% CI, 1.80 to 4.18).

A total of 54% and 73% of patients in the placebo and mepolizumab groups, respectively, demonstrated an improvement of at least 8.9 points in their total SNOT-22 score at the end of the 52-week treatment period. The odds of being a responder in the mepolizumab compared with the odds of being a responder in the placebo group was 2.44 (95% CI, 1.60 to 3.73).

The SNOT-22 is used in the clinical practice setting to determine response to treatment. Approximately half the patients in the placebo group demonstrated a response to treatment as measured by the SNOT-22 score. The observed treatment effect in the placebo group is likely a result of the effectiveness of MF nasal spray treatment. According to the clinical expert consulted by CADTH for this review, the benefits derived from daily MF treatment may reflect improvement in sinusitis, nasal turbinate edema, and secretion, leading to symptomatic and objective improvement although the polyps are resistant to steroids.

Health-Related Quality of Life

At the end of the 52-week treatment period, the mean changes in total SNOT-22 score from baseline were −15.7 (SD = 23.93) and −29.4 (SD = 24.67) in the placebo and mepolizumab groups, respectively. The median changes from baseline to week 52 in the placebo and mepolizumab groups were −14.0 (IQR, −31.0 to 0.0) and −30.0 (IQR, −46.0 to −4.0), respectively. The adjusted median difference in change from baseline was statistically significant in favour of mepolizumab compared with placebo (adjusted median difference = −16.49; 95% CI, −23.57 to −9.42; P = 0.003).

At the end of the 52-week treatment period, the median changes from baseline for both the Physical Component Summary and Mental Component Summary of the Short Form (36) Health Survey (SF-36) were 0.0 (IQR, −1.75 to 4.61) and 0.0 (IQR, −3.75 to 5.76), respectively, for the placebo group. The median changes from baseline to week 52 for the PCS and MCS were 6.75 (IQR, 0.0 to 12.59) and 1.20 (IQR, −2.60 to 10.08), respectively, for the mepolizumab group.

Systemic Steroid Use for Nasal Polyps

Patient groups indicated a need for decreased reliance on oral corticosteroids or steroids.

Over the 52-week treatment period, 37% and 25% of patients in the placebo and mepolizumab groups, respectively, required at least 1 course of systemic steroid treatment for nasal polyps. By week 52, the probability of requiring an initial course of systemic steroid use for nasal polyps was 37.5% (95% CI, 31.1% to 44.6%) in the placebo group and 25.4% (95% CI, 20.0% to 32.1%) in the mepolizumab group.

Nasal Polyp Surgery

By week 52, 23% and 9% of patients in the placebo and mepolizumab groups, respectively, underwent nasal surgery. The estimated risk of having surgery before week 52 was 23.6% (95% CI, 18.3% to 30.0%) in the placebo group and 9.2% (95% CI, 5.9% to 13.2%) for patients in the mepolizumab group. The probability of undergoing nasal surgery at any time before week 52 was statistically significantly lower for the patients in the mepolizumab group compared with patients in the placebo group (hazard ratio, 0.43; 95% CI, −0.25 to 0.76; P = 0.003).

A reduced need for surgery was deemed to be important by patient groups. However, the durability of the treatment effect could not be assessed due to the short duration of, and the low number of patients entering, the follow-up period.

Harms Results

Key harm results are summarized in Table 2.

Adverse Events

During the 52-week study period, the proportion of patients who reported at least 1 adverse event (AE) was 84% and 82% in the placebo and mepolizumab groups, respectively. The 3 most common AEs reported in the placebo and mepolizumab groups, respectively, were nasopharyngitis (23% and 25%), headache (22% and 18%), and sinusitis (11% and 5%). The following AEs were reported in less than 10% but greater than 5% of patients in either treatment groups: epistaxis, asthma, nasal polyps, back pain, upper respiratory tract infection, acute sinusitis, cough, bronchitis, oropharyngeal pain, otitis media, and arthralgia.

Serious Adverse Events

Serious AEs were reported in 7% and 6% of patients in the placebo and mepolizumab groups, respectively. No single serious AE was reported in more than 1% of patients in either treatment groups.

Withdrawals Due to Adverse Events

In total, 2% of patients in each group discontinued treatment due to any AE. The AEs contributing to withdrawal to treatment were not specified.

Mortality

Death occurred in 1 patient in the placebo group. The 1 death was related to a fatal myocardial infarction during the follow-up period after week 52.

Notable Harms

Potential opportunistic infections were reported by 2.48% and 1.46% of patients in the placebo and mepolizumab groups, respectively. Opportunistic infections reported by patients

in the placebo group included herpes zoster, oral herpes, candida infection, and oropharyngeal candidiasis. In the mepolizumab group, herpes zoster, oral herpes, and candida infections were reported. Serious infections were reported by 2% and 0.49% of patients in the placebo and mepolizumab groups, respectively. Serious infections reported included acute sinusitis, cellulitis, and influenza in the placebo group, and pneumonia in the mepolizumab group. Local injection site reactions were reported by 1.0% patients in the placebo group and 2.43% of patients in the mepolizumab group. Systemic site reactions were reported in 0.50% and 0.97% of patients in the placebo and mepolizumab groups, respectively. No anaphylaxis events were reported in either arm. In the placebo group, serious cardiac vascular and thromboembolic events were reported in 1.0% of patients and serious ischemic events were reported in 0.50% of patients. In the mepolizumab group, serious cardiac disorders, serious cardiac vascular and thromboembolic events, and serious ischemic events were reported in 1 patient each.

Critical Appraisal

The SYNAPSE trial was limited by between-group imbalances at baseline. First, a greater proportion of patients in the placebo group than in the mepolizumab group initiated therapy with a leukotriene receptor antagonist before treatment with the study drug (17% versus 12%); therefore, a potential confounding effect of leukotriene receptor antagonists cannot be ruled out. Second, a greater proportion of patients in the placebo group than in the mepolizumab group had 2 surgeries or more (60% versus 48%) at baseline. Although it is unclear whether the need for more surgery was a function of disease severity or disease duration, it is a potential marker of treatment resistance. More patients in the mepolizumab group than in the placebo group experienced at least 1 asthma exacerbation in the 12 months before screening (26% versus 15%) and at least 1 asthma exacerbation requiring systemic corticosteroids but not requiring hospitalization or emergency department visit in the 12 months before screening (20% versus 12%). Overall, these baseline imbalances may have an impact on the assessment of differences in treatment effects between groups, yet the magnitude and direction of the bias remain uncertain.

Other between-group imbalances, namely, greater use of concomitant medications and greater protocol deviations in the placebo group, may have influenced the treatment effect. During the treatment period, a greater proportion of patients in the placebo group initiated concomitant treatment with any systemic corticosteroids compared with the mepolizumab group (46% versus 34%). Likewise, a greater proportion of patients in the placebo group versus the mepolizumab group, albeit a low percentage overall, made use of a rescue short-acting beta-2 agonist inhaler (9% versus 1%). According to the clinical expert consulted by CADTH, the use of systemic corticosteroids for any reason or use of a rescue corticosteroid (but not a short-acting beta-2 agonist) medication for asthma may improve nasal polyp symptoms, thereby potentially introducing bias in the results against mepolizumab. Although the effect of these additional interventions could not be assessed due to the small percentage of patients requiring their use during the study period, it is possible that that placebo group benefited from the additional therapies.

Another imbalance worth noting is that a greater proportion of patients in the placebo group discontinued treatment compared with the mepolizumab group (17% versus 11%) and a substantial proportion of patients were documented with an incomplete (42% versus 31%, respectively) or missing (6% versus 4%, respectively) end point assessment. While the majority of missed or incomplete assessments were due to missing clinical chemistry, hematology, and/or urinalysis due to a spoiled sample, missed visits or phone call related to patient diary, improved HRQoL and work productivity occurred in 10% and 5% of patients in

the placebo and mepolizumab groups, respectively. To mitigate discontinuation and missed assessments, patients were assigned their worse observed score before withdrawal or missed assessment. However, the high percentage of any major protocol violations (65% in the placebo group versus 55% in the mepolizumab group) may have compromised the quality of the data from this trial, which may have affected the assessment of efficacy outcomes.

Overall, the study population represented the patients who were more likely to adhere to the long-term use of the study drug. The 4-week run-in period further excluded those patients who met the study eligibility criteria (severe CRSwNP with at least 1 surgery for recurrent nasal polyps and who were refractory to SOC) but who were intolerant or poorly adherent to the study drug or procedures (i.e., 21% failed the continuation criteria). An enrichment design tends to overestimate the treatment effectiveness in the clinical practice setting. Finally, clinical improvements noted in the placebo group during the treatment period raise the question of how much of the maintained treatment effect observed during the follow-up period in the mepolizumab group was due to mepolizumab versus SOC with intranasal steroids because full onset of action of intranasal steroids may be delayed for some patients. As noted by the clinical expert, adherence to persistent daily intranasal corticosteroids may have led to the placebo group maintaining the modest improvement experienced during the treatment period. Consequently, uncertainty exists in how much of the treatment effect observed in the mepolizumab group was due to the efficacy of mepolizumab versus the effectiveness of MF therapy, although both groups were on intranasal corticosteroid therapy. All these factors contributed to the difficulty in interpreting and assessing the generalizability of efficacy results.

Indirect Comparisons

No indirect treatment comparisons were included in the sponsor's submission to CADTH or identified in the literature search.

Other Relevant Evidence

No long-term extension studies or other relevant studies were included in the sponsor's submission to CADTH or identified in the literature search.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Add-on maintenance treatment with INCS in adult patients with severe CRSwNP inadequately controlled by INCS alone.
Treatment	Mepolizumab plus standard of care (INCS and nasal saline irrigation with intermittent oral corticosteroids for severe symptoms)
Submitted price	$2,100.61 per 100 mg, lyophilized powder or solution in pre-filled autoinjector or solution in safety syringe

Component	Description
Treatment cost	$27,308 per year
Comparator	SOC alone
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	10 years
Key data source	SYNAPSE pivotal trial informed relevant efficacy and safety parameters
Key limitations	• There is uncertainty in the magnitude of treatment effect with mepolizumab with respect to endoscopic improvement and relief of nasal obstruction, and limited evidence on the duration of this treatment effect based on the available trial data. • Assessment of response at 24 weeks as assumed in the sponsor's base case may not align with the expected management of CRSwNP in clinical practice and is not aligned with the sponsor's proposed reimbursement criteria (1 year). The time point at which response is assessed affects the magnitude of benefit and incremental costs associated with mepolizumab. • The sponsor's submission incorporated treatment-specific utility values. This approach likely double counts treatment benefits with mepolizumab and is counter to best practice guidance which recommends the use of health state–specific utilities with differences in QALYs driven by treatment efficacy. • Assessment of response according to a quality-of-life scale (SNOT-22) was used in the sponsor's base case as opposed to response according to the nasal polyp or congestion score (NPS/NCS), which were the primary end points in the SYNPASE trial. The NPS and NCS are considered more objective measures of response, and some differences in response were observed based on the measure used, which affects the estimated cost-effectiveness of mepolizumab. • A lifetime time horizon, rather than the 10-year time horizon used by the sponsor, is more appropriate for a decision problem considering a population of patients with CRSwNP due to its chronic nature. Although this had minimal impact in the sponsor's base case, this limitation is of greater concern when the treatment effect of mepolizumab is expected to wane.
CADTH reanalysis results	• The CADTH reanalysis removed treatment-specific utilities and applied health state–specific utilities. CADTH was unable to address the limitations concerning the lack of long-term clinical efficacy data. • The CADTH reanalysis found that mepolizumab is associated with an ICER of $380,251 per QALY gained (incremental costs: $176,515; incremental QALYs: 0.46) and the probability of cost-effectiveness at a WTP threshold of $50,000 per QALY is 0%. • A price reduction of approximately 86% is required to achieve cost-effectiveness at this threshold. Scenarios exploring the uncertainty surrounding the duration of treatment effect, measurement of response, and the time point at which response is assessed led to substantial changes in the results and suggest even greater price reductions with mepolizumab may be required.

CRSwNP = chronic rhinosinusitis with nasal polyps; ICER = incremental cost-effectiveness ratio; INCS = intranasal corticosteroids; LY = life-year; OCS = oral corticosteroid; QALY= quality-adjusted life-year.

Budget Impact

CADTH identified several key limitations with the sponsor's analysis This included the target population size was associated with uncertainty; the inputs used to derive the target population, although plausible, may have limited generalizability to the Canadian context; the availability of mepolizumab may increase the anticipated diagnosis rate of CRSwNP, increasing the eligible population size; and the market uptake of mepolizumab is uncertain and based on internal sponsor forecasting which could not be validated by CADTH. Furthermore, uncertainty surrounding treatment eligibility was raised by the drug

plans, particularly the requirement of prior nasal polyp surgery, bilateral nasal polyps, or prior treatment with intranasal corticosteroid for 8 weeks before initiation with mepolizumab, which could not be addressed by CADTH. CADTH did not undertake a reanalysis of the sponsor's budget impact analysis due to key limitations primarily focused on uncertainty in parameters used to derive the target population and market shares. CADTH accepted the sponsor's base case, which estimated the budget impact of mepolizumab to be $30,401,285 in year 1, $34,843,638 in year 2, and $38,893,040 in year 3, for a 3-year total of $104,137,963. When these parameters were tested in scenario analyses, the results were significantly affected by an increase in the number of patients diagnosed with CRSwNP and the anticipated uptake of mepolizumab.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Meeting date: September 28, 2022

Regrets: 2 expert committee members did not attend

Conflicts of interest: None