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CADTH Reimbursement Recommendation

Tezepelumab (Tezspire)

Indication: As an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma.

Sponsor: AstraZeneca Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Tezspire?

CADTH recommends that Tezspire should be reimbursed by public drug plans for the treatment of severe asthma if certain conditions are met.

Which Patients Are Eligible for Coverage?

Tezspire should only be covered to treat patients with severe asthma who are 12 years of age and older if their asthma is not controlled despite using a high dose of inhaled corticosteroids (ICSs) and at least 1 additional medication, and if they have experienced 2 or more asthma exacerbations (also called asthma attacks) that resulted in hospitalization or required treatment with systematic corticosteroids for at least 3 days in the past year.

What Are the Conditions for Reimbursement?

Tezspire should only be reimbursed if prescribed by an allergist or respirologist with experience managing severe asthma and the cost of Tezspire is reduced. Tezspire should not be used in combination with other biologics.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Tezspire added on to standard of care reduced the frequency of asthma attacks compared to placebo in patients with moderate to severe asthma who were on medium- or high-dose ICSs and had 2 or more asthma attacks in the past year.
- In addition to reducing frequency of asthma attacks, Tezspire meets some other needs that are important to patients with asthma, such as improving lung function, controlling symptoms, and improving their quality of life.
- Based on CADTH's assessment of the health economic evidence, Tezspire does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Due to limitations in the submitted budget impact analysis, CADTH was unable to calculate a reliable estimate of additional costs to the drug plans.

Additional Information

What Is Asthma?

Asthma is a chronic lung disease which makes it difficult for people to breathe properly. Patients with asthma will likely need to see their physician more often, seek treatment in the emergency room, or become hospitalized. In rare instances, asthma can be fatal. Asthma is relatively common in Canada, and it is believed that more than 2.4 million people aged 12 and older have this disease in this country.

Unmet Needs in Asthma

There are patients whose asthma is not well controlled, despite receiving maximized doses of other drugs used for treating the disease. Uncontrolled asthma is characterized by frequent (2 or more per year) asthma exacerbations that result in patients having to seek medical attention on an urgent basis or be hospitalized.

How Much Does Tezspire Cost?

Treatment with Tezspire is expected to cost approximately $25,200 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that tezepelumab be reimbursed as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from a phase III, double-blind, randomized controlled trial (RCT), the NAVIGATOR trial (N = 1,061), demonstrated that tezepelumab was associated with a reduction in asthma exacerbations compared with placebo in patients who were on medium- or high-dose inhaled corticosteroids (ICSs) and had 2 or more exacerbations in the past year. In the NAVIGATOR trial, the annualized asthma exacerbation rate (AAER) over 52 weeks was 0.93 (95% confidence interval [CI], 0.80 to 1.07) with tezepelumab and 2.10 (95% CI, 1.84 to 2.39) with placebo, for a rate ratio of 0.44 (95% CI, 0.37 to 0.53; P < 0.001). Furthermore, tezepelumab improved pulmonary function, health-related quality of life (HRQoL), and symptoms of asthma. The results from the NAVIGATOR trial were supported by similar results from a phase II, double-blind, placebo-controlled RCT (PATHWAY; N = 550). Furthermore, a long-term extension study (DESTINATION; N = 951) suggested that the benefits of tezepelumab on exacerbations and symptoms may continue through 2 years of treatment with acceptable safety and tolerability.

Patients expect new treatments for severe asthma to improve lung function, control their symptoms, reduce exacerbations, improve quality of life, have fewer side effects, reduce reliance on oral corticosteroids (OCSs), and decrease the number of medications required to maintain asthma control. CDEC concluded that tezepelumab meets some of these needs, such as improving lung function, controlling symptoms, reducing exacerbations, and improving HRQoL.

Using the sponsor-submitted price for tezepelumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for tezepelumab was $1,334,178 per quality-adjusted life-year (QALY) compared with standard of care (consisting of high-dose ICSs and a long-acting beta-2 agonist [LABA] alone, and OCSs for OCS-dependent patients). At this ICER, tezepelumab is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold in the Health Canada indicated population. A reduction in price is therefore required.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Tezepelumab treatment should only be initiated in patients 12 years and older with severe asthma that meet all of the following criteria: 1.1. Asthma inadequately controlled with high-dose	The NAVIGATOR trial enrolled patients on medium- to high-dose ICS. However, clinical guidelines suggest maximizing ICSs before stepping up to biologic therapy. The NAVIGATOR and PATHWAY trials enrolled patients with 2 or more asthma exacerbations in the past year.	Clinically significant asthma exacerbations are defined as worsening of asthma resulting in administration of systemic corticosteroids for at least 3 days or hospitalization.

Reimbursement condition	Reason	Implementation guidance
ICSs, defined as ≥ 500 mcg of fluticasone propionate or equivalent daily, and one or more additional asthma controller(s) (e.g., LABAs) 1.2. Experienced 2 or more clinically significant asthma exacerbations in the past 12 months.		
2. A baseline assessment of asthma symptom control using a validated asthma control questionnaire must be completed before initiation of tezepelumab treatment.	A baseline assessment of asthma symptom control is needed to objectively assess response to therapy (see Renewal conditions).	–
Renewal		
3. The effects of treatment should be assessed every 12 months using the same asthma control questionnaire used at baseline.	To allow sufficient time for patients and clinicians to assess response.	A validated asthma control questionnaire includes the ACQ or the ACT. The same questionnaire must be used at the time of assessment for reimbursement renewal as was used at the start of treatment.
4. Reimbursement of treatment with tezepelumab should be discontinued if any of the following occur: 4.1. The 12-month asthma control questionnaire score has not improved from baseline, when baseline represents the initiation of treatment 4.2. The asthma control questionnaire score achieved after the first 12 months of therapy has not been maintained subsequently 4.3. The number of clinically significant asthma exacerbations has increased within the previous 12 months 4.4. In patients on maintenance treatment with OCSs, there has been no decrease in the OCS dose in the first 12 months of treatment 4.5. In patients on maintenance treatment with OCSs, the reduction in the dose of OCS achieved after the first	Asthma symptom control and reducing the frequency of exacerbations were identified as important outcomes by patients and the clinical expert. Tezepelumab reduced the AAER compared with placebo in the NAVIGATOR trial. Reducing the need for OCSs to control asthma was determined to be a clinically important outcome for patients and clinicians.	Maintenance OCS treatment is defined as receiving greater than the equivalent of prednisone 5 mg per day.

Reimbursement condition	Reason	Implementation guidance
12 months of treatment is not maintained or improved subsequently.		
Prescribing		
5. Tezepelumab should be initiated by an allergist or respirologist with experience managing severe asthma.	To ensure tezepelumab is prescribed for appropriate patients.	—
6. Tezepelumab should not be used in combination with other biologics.	There is no evidence to support using a combination of biologics in patients with asthma.	—
Pricing		
7. A reduction in price.	The ICER for tezepelumab is $1,334,178 per QALY when compared with standard of care. A price reduction of 95% would be required for tezepelumab to be able to achieve an ICER of $50,000 per QALY compared to standard of care. Cost-effectiveness relative to other biologics is uncertain given the lack of direct head-to-head evidence and limitations with indirect comparisons. To ensure cost-effectiveness, tezepelumab should also be priced no more than the lowest-cost biologic that is publicly funded.	—

AAER = annualized asthma exacerbation rate; ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; ICER = incremental cost-effectiveness ratio; ICS = inhaled corticosteroid; LABA = long-acting beta-2 agonist; OCS = oral corticosteroid; QALY = quality-adjusted life-year.

Discussion Points

- No head-to-head trials have been conducted comparing tezepelumab with other biologics. CDEC noted that other biologics are used in patients with type 2/eosinophilic asthma only, whereas the indication for tezepelumab is not restricted to a specific phenotype of asthma. The sponsor submitted 2 indirect treatment comparisons (ITCs) and 3 additional ITCs were identified from the literature. The indirect evidence suggested that tezepelumab has similar efficacy and harms compared to other biologics used in asthma. However, due to methodological limitations and the degree of heterogeneity between the studies, the indirect evidence comparing tezepelumab to other biologics is uncertain. No firm conclusion could be drawn by CDEC regarding the comparative efficacy and safety of tezepelumab versus other biologics.
- Patients and clinicians indicated that there is a need for treatment options that would reduce the need for OCSs to control asthma. While results of the SOURCE trial (N = 150) — a phase III, double-blind RCT that compared tezepelumab to placebo in patients with OCS-dependent asthma — did not demonstrate superiority for tezepelumab over

placebo for the primary outcome of percent reduction in OCS dose while not losing asthma control, the clinical expert noted to CDEC that the placebo response was high. In addition, CDEC noted that only 23% and 26% of patients in the tezepelumab and placebo arms, respectively, were on a greater than 10 mg daily OCS dosage at baseline, which might have impacted the results of the study. The clinical expert also indicated that patients who are OCS-dependent are the most challenging to treat, and the chronic use of OCSs can have a significant negative impact on patient health, given the serious harms associated with this class of drugs. In their input to CADTH, patients with asthma also identified OCS side effects as a major concern for them.

- CDEC discussed the importance of assessing adherence to ensure tezepelumab is prescribed for appropriate patients with severe asthma. Global Initiative for Asthma (GINA) guidelines indicate that biologics are typically considered when asthma control is not achieved with daily high-dose ICSs with a LABA. CDEC noted that first assessing the patient's adherence to high-dose ICSs and asthma controllers (e.g., LABAs) is important for determining whether a biologic is needed.

Background

Asthma is a chronic respiratory disorder characterized by reversible airway obstruction. Hallmarks of asthma include inflammation, bronchoconstriction, and airway remodelling, as well as hyper-responsive airways and mucous production. Symptoms of asthma include wheezing, dyspnea, chest tightness, sputum production, and coughing, and these symptoms can be exacerbated by exogenous influences such as allergens, upper respiratory tract infections, or environmental factors such as smoke or cold air. Eosinophils are believed to be a major contributor to the inflammatory processes that are characteristic of the disease, according to the clinical expert consulted by CADTH on this review. It is estimated that 2.4 million Canadians aged 12 years or older suffer from asthma, or 12% of all children and 8% of adults.

The management of mild asthma is carried out using "relievers" such as short-acting beta-2 agonists (SABAs) or rapid-acting beta-2 agonists like formoterol, combined with controllers such as ICSs on an as-needed basis. Alternatively, regular, daily treatment with a low-dose ICS is used. If using regular, low-dose ICSs does not achieve good asthma control, then typically treatment is escalated to using long-acting bronchodilators, most commonly LABAs, always in combination with ICSs. OCSs are used for acute exacerbations on short-term basis "bursts," although some patients' asthma is severe enough to require OCSs on an ongoing basis, according to the clinical expert consulted by CADTH on this review. According to the clinical expert, the approach to managing asthma has evolved, such that patients are now routinely grouped into those who have type 2 inflammation and those who do not. Type 2 inflammation is mediated in part by cytokines such as IL-4, IL-5, and IL-13, and this explains why this phenotype may be more responsive to the biologics that target these cytokines. Monoclonal antibodies are the newest entrants into the asthma treatment paradigm, beginning with an IgE inhibitor (omalizumab) and, more recently, IL-5 inhibitors (mepolizumab, reslizumab, benralizumab), an IL-4 and IL-13 inhibitor (dupilumab), and now a thymic stromal lymphopoietin (TSLP) inhibitor, tezepelumab. According to the clinical expert, none of the monoclonal antibodies are intended to be used in the first line, but rather are reserved for those patients whose asthma is not well controlled with high doses of ICSs plus LABAs.

Tezepelumab is indicated as an add-on maintenance treatment in adults and adolescents aged 12 years and older with severe asthma. Tezepelumab is a TSLP inhibitor. It is available as subcutaneous injections, and the dosage recommended in the product monograph is 210 mg every 4 weeks.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- a review of 3 clinical trials and 1 long-term extension study in patients aged 12 years and older with severe asthma
- patients' perspectives gathered by 2 patient groups, Asthma Canada and the Lung Health Foundation
- input from public drug plans and cancer agencies that participate in the CADTH review process
- one clinical specialist with expertise diagnosing and treating patients with asthma
- input from 1 clinician group, the AllerGen Clinical Investigator Collaborative
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Patient input for this review was received from Asthma Canada and the Lung Health Foundation (formerly known as the Ontario Lung Association). Patients reported that living with asthma negatively impacts their psychological and social well-being, and results in poor quality of life. The patients indicated that their asthma impacts their ability to complete daily activities, attend school or work, participate in outdoor and/or physical activity, and interferes with social interactions. Patients also reported loss of productivity at school or work due to their asthma, leading to a decrease in performance or quality of work or schoolwork. Parents and caregivers expressed concern about accessing adequate and necessary medical care as severe exacerbations can cause loss of consciousness or hypoxia, in addition to urgent emergency department (ED) care to restore airway functions. Patients and parents/caregivers noted that there was an unmet need for treatment options for severe asthma. Even with currently available treatment, 1 in 4 respondents indicated that they have poor symptom control. Patients and parents/caregivers noted several barriers to accessing health care providers (e.g., respirologists, specialized asthma clinics) including travel time and cost, missed school or work, and the financial burden of prescription refills. Patients reported that the long-term use of OCSs provided some degree of inflammation control after failing other options, but indicated that it is associated with notable side effects. The side effects associated with these treatments were reported to be a great source of distress. Patients and caregivers identified the following treatment priorities: the ability to control their day-to-day symptoms, the ability to control exacerbation, reduction of cost or coverage for current and upcoming treatments, and reduction in medication-associated side effects. Other key

treatment outcomes highlighted by patients included improvement in quality of life, reduction in the number of medications required to maintain asthma control, and treatments with minimal side effects.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

According to the clinical expert consulted by CADTH on this review, half of all patients with type 2 asthma remain poorly controlled with existing non-biologic interventions. Although various measures, including improved adherence to therapy, can improve control in these patients, there is a subset of approximately 5% who remain poorly controlled regardless of the intervention. There is also a minority of patients who have non–type 2 asthma, who are unlikely to benefit from current biologics.

According to the clinical expert, tezepelumab can treat patients with type 2 and non–type 2 asthma, and there are no other biologics that can reduce exacerbation frequency in patients with non–type 2 disease. They believe that tezepelumab could be used in the first line in patients with type 2 asthma or in patients who fail to improve on other biologics, as airway inflammation in type 2 asthma may be driven by factors other than those targeted by current biologics.

The definition of severe asthma can vary; therefore, an indication for use in severe asthma is imprecise, according to the clinical expert, although there is no evidence of efficacy in patients who are OCS-dependent. The subset of patients who are OCS-dependent likely only represents a relatively small segment of patients with asthma in Canada.

According to the clinical expert consulted by CADTH, relevant outcomes to assess treatment response include improved HRQoL, decreased frequency of exacerbations, and improved asthma control, which would include improvement or stabilization of forced expiratory volume in 1 second (FEV_1), elimination of airflow reversibility to bronchodilator, and reduction in symptoms. Once the patient meets the criteria for initiation, clear stopping rules are difficult to develop, as asthma control can be impacted by environmental factors, for example. Initiation of a drug should be limited to respirologists or allergists with experience using biologics, and once started, tezepelumab could be maintained by a generalist.

Clinician Group Input

Input was received from 6 clinicians on behalf of the AllerGen Clinical Investigator Collaborative (CIC). The clinician group indicated that while there are treatments that are effective for patients with severe eosinophilic asthma (T2 high), there are no effective treatment options for those patients who have severe asthma that is not persistently T2 high asthma. Members of CIC agreed that the use of tezepelumab in asthma should be restricted to patients with severe asthma, regardless of their eosinophilic asthma (T2) status. According to CIC, severe exacerbation risk remains the single most important outcome to improve in severe asthma. CIC suggested that tezepelumab should be discontinued if patients continue to experience severe exacerbation while on treatment. The only other reason cited for discontinuation by CIC was side effects.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH 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
Relevant comparators	
The comparator in the submitted trials was placebo, whereas other biologics indicated for severe asthma are potentially relevant comparators.	Comment from the drug plans to inform CDEC deliberations.
Other biologics indicated for severe asthma include omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. Health Canada indications for these agents generally relate to specific phenotypes — allergic (omalizumab) and eosinophilic (mepolizumab, reslizumab, benralizumab). The indication for dupilumab is broader and includes "severe asthma with a type 2/eosinophilic phenotype or oral corticosteroid-dependent asthma." Omalizumab is reimbursed in Alberta and Ontario for patients with allergic asthma refractory to optimized standard therapy and a history of exacerbations. Mepolizumab and benralizumab are reimbursed by most public drug plans for patients with eosinophilic asthma refractory to optimized standard therapy and a history of exacerbations or dependence on OCSs. At the time the drug plans provided input for this review, dupilumab was undergoing pCPA negotiations for severe asthma with type 2 or eosinophilic phenotype or OCS-dependent asthma. The pCPA negotiations for duplimab concluded without agreement on June 28, 2022. Reslizumab is not currently funded by any of the jurisdictions, as pCPA negotiations concluded without agreement in 2019.	Comment from the drug plans to inform CDEC deliberations.
Considerations for initiation of therapy	
The sponsor is positioning tezepelumab as the preferred first-line biologic across all patients with severe asthma, noting it has clinical benefit across all asthma phenotypes, irrespective of biomarker status. Should initiation criteria for tezepelumab include any restrictions related to diagnostic phenotype or biomarker status?	The clinical expert indicated that phenotyping will likely not matter with this drug, as it appears to have efficacy across all phenotypes. CDEC further noted that there is limited evidence supporting restrictions related to diagnostic phenotype or biomarker status.
Is alignment with the following aspects of initiation criteria for other biologics for severe asthma reviewed by CADTH appropriate? • Patient must have a documented diagnosis of asthma. • Patient is inadequately controlled with high-dose ICSs, defined as greater than or equal to 500 mcg of fluticasone propionate or equivalent daily, and one or more additional asthma controller(s) (e.g., LABAs). • Patient has experienced 2 or more clinically significant asthma exacerbations in the past 12 months. • A baseline assessment of asthma symptom control using a validated	The clinical expert believed that alignment with each of the following criteria would be appropriate: • Patients should have confirmed asthma. • Patients should be on high-dose ICSs with a LABA or other agent. • The included studies enrolled patients with 2 or more asthma exacerbations in the past year, so that should be reflected in the initiation criteria. • ACQ > 1.5 is uncontrolled. The clinical expert believed it was difficult to determine whether

Drug program implementation questions	Clinical expert response
asthma control questionnaire must be completed before initiation of treatment.	someone who had 2 exacerbations in the past year should be excluded even if their ACQ is < 1.5. The clinical expert indicated that it is difficult to exclude someone if their ACQ is 1 because they might have just come off a steroid burst for a recent exacerbation.
Considerations for continuation or renewal of therapy	
Is alignment with renewal criteria for other biologics for severe asthma reviewed by CADTH (e.g., mepolizumab, benralizumab, dupilumab) appropriate?	CDEC and the clinical expert indicated that the renewal criteria for tezepelumab should be aligned with the renewal criteria for other biologics.
Considerations for prescribing of therapy	
There appears to be no evidence to support use of tezepelumab in combination with other biologics indicated for severe asthma and combination use would significantly increase costs.	CDEC and the clinical expert reported that there is no evidence to support combinations of biologics.
Is alignment with the following prescribing criteria for other biologics for severe asthma reviewed by CADTH (e.g., mepolizumab, benralizumab, dupilumab) appropriate? • Patients should be managed by a physician with expertise in treating asthma. • Should not be used in combination with other biologics used to treat asthma.	CDEC and the clinical expert indicated that tezepelumab should be restricted to respirologists and allergists for initiation. Family physicians would be able to maintain a patient once initiated by a specialist. CDEC and the clinical experts noted that there is no evidence supporting the use of combinations of biologics to treat asthma.
System and economic issues	
Mepolizumab and benralizumab have successfully completed pCPA price negotiations. There could be confidential prices for omalizumab in some jurisdictions. At the time the drug plans provided input on this review, dupilumab for asthma was under active negotiations through pCPA. Negotiations with pCPA concluded without agreement on June 28, 2022.	Comment from the drug plans to inform CDEC deliberations.

ACQ = Asthma Control Questionnaire; CDEC = Canadian Drug Expert Committee; ICS = inhaled corticosteroid; LABA = long-acting beta-2 agonist; OCS = oral corticosteroid; pCPA = pan-Canadian Pharmaceutical Alliance.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

Three multinational, sponsor-funded, double-blind (DB) RCTs were included in this systematic review. The NAVIGATOR trial randomized 1,061 patients who were on medium- or high-dose ICSs and who had 2 or more exacerbations in the past year, 1:1, to either tezepelumab or placebo over a treatment course of 52 weeks. The primary outcome was AAER and key secondary outcomes included the AAER in patients with baseline eosinophils less than 300 cells/μL, change from baseline in pre-bronchodilator FEV_1, Asthma Quality of Life Questionnaire Standardized for Ages 12 and Older (AQLQ[S]12+), and the Asthma Control Questionnaire-6 (ACQ-6). The SOURCE trial randomized 150 patients with OCS-dependent

asthma, 1:1, to either tezepelumab or placebo over a treatment course of 48 weeks. The primary outcome was the percent reduction in OCS dose while not losing asthma control, and key secondary outcomes included AAER; time to first asthma exacerbation; rate of asthma exacerbation associated with ED visit, urgent care visit, or hospitalization; and patients who did not experience an asthma exacerbation over 48 weeks. The PATHWAY trial was a phase II, DB RCT that randomized 550 patients on medium- to high-dose ICSs and at least 2 exacerbations (or 1 severe asthma exacerbation) in the past year, 1:1:1:1, to 3 different doses of tezepelumab (including the proposed dose in the draft product monograph) or placebo, over a treatment course of 52 weeks. Results are reported for the tezepelumab treatment group in the PATHWAY trial that received the dose recommended in the draft product monograph (i.e., 210 mg subcutaneous every 4 weeks) only; results from the other tezepelumab arms are not reported in this review. The primary outcome was AAER, and secondary outcomes included subgroups based on the primary outcome, change from baseline in FEV_1, and ACQ-6.

Across studies, the mean age of patients was between 49 and 53.5 years, and the majority were female, ranging from 59% to 68% of patients across studies. In the NAVIGATOR trial, 62% of patients were White and 28% were Asian, while 84% of patients in the SOURCE trial and 91% of patients in the PATHWAY trial were White. In the NAVIGATOR trial, 60% of patients had 2 exacerbations in the past 12 months and the remainder had more than 2, while in the PATHWAY trial, 78% of patients had 1 or 2 exacerbations and the remainder had 3 or more. In the SOURCE trial, which did not require more than 1 exacerbation in the past 12 months per protocol, 43% of patients had 1 exacerbation, 35% had 2, and 23% had more than 2 exacerbations. In the NAVIGATOR trial, 75% of patients were on high-dose ICSs and the remainder were on medium-dose ICSs, while in the SOURCE trial, all but 1 patient were on high-dose ICSs. Per protocol, all patients in the SOURCE trial were on OCSs at baseline, while in the NAVIGATOR trial 9% were on OCSs, and 8% were on OCSs in the PATHWAY trial.

Efficacy Results

Mortality

Across all studies, there was 1 death in the tezepelumab group and 2 deaths in the placebo group. The 2 deaths in the placebo group were due to unknown cause and heart failure, both in the NAVIGATOR trial. The patient in the tezepelumab group died in the SOURCE trial, due to cardiac arrest.

Acute Asthma Exacerbation

AAER was the primary outcome of both the NAVIGATOR and PATHWAY trials. All results reported for the PATHWAY trial include only the proposed Health Canada dosing. In the NAVIGATOR trial, AAER over 52 weeks was 0.93 (95% CI, 0.80 to 1.07) with tezepelumab and 2.10 (95% CI, 1.84 to 2.39) with placebo, for a rate ratio of 0.44 (95% CI, 0.37 to 0.53; $P < 0.001$). In the PATHWAY trial, AAER over 52 weeks was 0.20 (95% CI, 0.13 to 0.30) with tezepelumab and 0.72 (95% CI, 0.59 to 0.88) with placebo, for a rate ratio of 0.29 (95% CI, 0.16 to 0.51; $P < 0.001$). In the SOURCE trial, the rate ratio for AAER over 48 weeks was 0.69 (95% CI, 0.44 to 1.09).

AAER associated with an ED visit or hospitalization was 0.06 (95% CI, 0.04 to 0.09) with tezepelumab and 0.28 (95% CI, 0.20 to 0.39) with placebo, for a rate ratio of 0.21 (95% CI, 0.12 to 0.37) in the NAVIGATOR trial; and was 0.16 (95% CI, 0.06 to 0.44) with tezepelumab and 0.28 (95% CI, 0.13 to 0.58) with placebo in the SOURCE trial, for a rate ratio of 0.59 (95% CI, 0.19 to 1.82). AAER associated with a hospitalization was 0.03 (95% CI, 0.01 to 0.06) with

tezepelumab and 0.19 (95% CI, 0.12 to 0.30) with placebo, for a rate ratio of 0.15 (95% CI, 0.07 to 0.33; P < 0.001) in the NAVIGATOR trial; and in the PATHWAY trial was 0.02 (95% CI, 0.00 to 0.07) with tezepelumab and 0.14 (95% CI, 0.08 to 0.22) with placebo, for a rate ratio of 0.14 (95% CI, 0.03 to 0.71).

Change in Pulmonary Function

The pre-bronchodilator FEV_1 increased in both the tezepelumab and placebo groups in the NAVIGATOR trial, a least square (LS) mean (standard error [SE]) change from baseline to 52 weeks of 0.23 litres (0.018) with tezepelumab and 0.10 litres (0.018) with placebo for a LS mean difference (MD) between groups of 0.13 litres (95% CI, 0.08 to 0.18; P < 0.001). In the SOURCE trial, the change from baseline to week 48 was 0.21 (0.046) litres with tezepelumab and −0.04 (0.046) litres with placebo, for a LS MD between groups of 0.26 litres (95% CI, 0.13 to 0.39). In the PATHWAY trial, the LS mean (SE) change from baseline to week 52 was 0.076 litres with tezepelumab and −0.056 litres with placebo, for a LS MD between groups of 0.132 (95% CI, 0.033 to 0.231).

Reduction in OCSs

Reduction in OCS use was the primary outcome of the SOURCE trial. The cumulative odds ratio (OR) for patients having a reduction in OCS dose was 1.28 (95% CI, 0.69 to 2.35; P = 0.434). Therefore, tezepelumab failed to demonstrate superiority over placebo for the primary outcome of this study.

Reduction in Use of Rescue Medication

Reduction in daily rescue medication was observed in both the tezepelumab and placebo groups in the NAVIGATOR trial, a LS mean (SE) change from baseline of −2.53 (0.137) puffs with tezepelumab and −2.36 (0.137) puffs with placebo, for a LS MD between groups of −0.17 (95% CI, −0.55 to 0.21). Rescue medication use also declined in both groups in the SOURCE trial, a LS mean (SE) change from baseline to 48 weeks of −0.85 (0.280) puffs with tezepelumab and −0.37 (0.268) puffs with placebo, for a LS MD between groups of −0.47 (95% CI, −1.24 to 0.29).

Health-Related Quality of Life

Mean (standard deviation [SD]) AQLQ(S)12+ scores increased (i.e., improved) from baseline to 52 weeks in the NAVIGATOR trial, both in the tezepelumab (1.48 [1.26]) and placebo (1.16 [1.17]) groups, with a difference between groups of 0.33 (95% CI, 0.20 to 0.47; P = 0.001). In the SOURCE trial, the LS mean (SE) change from baseline to week 48 was 0.94 (0.124) with tezepelumab and 0.58 (0.123) with placebo, for a difference between groups of 0.36 (95% CI, 0.01 to 0.70). In the PATHWAY trial, the LS mean (SE) change from baseline to week 52 was 1.17 (not reported [NR]) with tezepelumab and 0.97 (NR) with placebo, for a difference between groups of 0.20 (95% CI, −0.09 to 0.48). AQLQ(S)12+ responders were also reported, defined as those having a change from baseline of 0.5 or greater. In the NAVIGATOR trial, 78% of patients in the tezepelumab group and 72% of patients in the placebo group were responders, for an odds ratio (OR) of 1.36 (95% CI, 1.02 to 1.82). In the SOURCE trial, 62% of patients in the tezepelumab group and 52% of patients in the placebo group were responders, for an OR of 1.66 (95% CI, 0.81 to 3.43). In the PATHWAY trial, 73% of patients in the tezepelumab group and 62% of patients in the placebo group were responders.

Symptoms

Symptoms were assessed using the ACQ-6. In the NAVIGATOR trial, ACQ-6 scores decreased (i.e., improved) from baseline to week 52 in both the tezepelumab and placebo groups, for a

difference versus placebo of 0.33 (95% CI, 0.20 to 0.47; P < 0.001). ACQ-6 responders were also reported in the NAVIGATOR trial, defined as those having a change from baseline of 0.5 or greater. In the NAVIGATOR trial, 86% of patients in the tezepelumab group and 77% of patients in the placebo group were responders, for an OR of 1.99 (95% CI, 1.43 to 2.76). In the SOURCE trial, the LS mean (SE) change from baseline to 48 weeks for tezepelumab was −0.87 (0.125) and −0.51 (0.123) with placebo, for a difference between groups of −0.37 (95% CI, −0.71 to −0.02). In the PATHWAY trial, the LS mean (SE) change from baseline to week 52 was −1.20 (NR) with tezepelumab and −0.91 (NR) with placebo, for a difference between groups of −0.29 (95% CI, −0.56 to −0.01).

Harms Results

Adverse events (AEs) in the tezepelumab versus placebo groups occurred in 77% versus 80% of patients, respectively, in the NAVIGATOR trial; 72% versus 86%, respectively, in the SOURCE trial; and 66% of patients in both groups in the PATHWAY trial.

The most common AE was nasopharyngitis, occurring in 21% versus 21% of patients in the NAVIGATOR trial, 15% versus 25% of patients in the SOURCE trial, and 14% versus 12% of patients in the PATHWAY trial (in the tezepelumab versus placebo groups, respectively). Other common events (occurring in at least 10% of the patients in any group, in any study) were upper respiratory tract infection, headache, and asthma.

Serious AEs (SAEs) in the NAVIGATOR trial, for tezepelumab versus placebo, occurred in 9% versus 13% of patients. In the SOURCE trial, they occurred in 15% versus 21% of patients, and in the PATHWAY trial they occurred in 10% versus 13% of patients. The most common SAE was asthma.

AEs resulting in discontinuation of the study drug occurred in 2% versus 4% of patients in the NAVIGATOR trial, 3% in both groups in the SOURCE trial, and 2% versus 1% of patients in the PATHWAY trial, in the tezepelumab versus placebo groups, respectively.

Notable harms in the CADTH systematic review protocol included infections. Severe infections occurred in the tezepelumab versus placebo groups in 9% versus 8% of patients in the NAVIGATOR trial, respectively, and 5% versus 9% of patients in the SOURCE trial, respectively. In the PATHWAY trial, infections were reported as SAEs rather than severe infections, and these occurred for tezepelumab versus placebo in 1% versus 3% of patients. There were no opportunistic infections and no helminth infections reported across the studies. Injection site reactions occurred infrequently across the studies. In the NAVIGATOR trial, injection site reactions occurred in 1.5% versus 0.9% of patients in the tezepelumab versus placebo groups, respectively; in the SOURCE trial, there were none with tezepelumab and 1.3% of patients in the placebo group experienced these events. In the PATHWAY trial, these events were reported by injection volume, and at the 1mL volume they occurred for tezepelumab versus placebo in 1.5% versus 2.9% of patients, and at the 1.5 mL volume they occurred in 1.5% versus 1.4% of patients, respectively. Hypersensitivity reactions reported as SAEs were infrequent, occurring in 1 patient in both the tezepelumab and placebo groups in the NAVIGATOR trial, and in no patients in the other studies.

Critical Appraisal

Although the NAVIGATOR and SOURCE trials accounted for multiplicity, early failure of the hierarchy in the SOURCE trial meant that all of the P values for the key secondary outcomes should only be considered supportive and not meant for drawing conclusions. Although the

number of study withdrawals was generally low (less than 5%) across studies, there appeared to be additional missing data for many of the continuous outcomes, such as patient-reported outcomes like ACQ-6, AQLQ(S)12+, and EQ-5D-5L. The missing data also exceed the reported number of treatment withdrawals; thus, it is unclear why the data were missing. In the SOURCE trial, at baseline there were fewer patients with more than 2 asthma exacerbations in the past year in the tezepelumab group compared to the placebo group, and this may have biased results in favour of tezepelumab if patients in the placebo group were more prone to having an asthma exacerbation.

With respect to external validity, the clinical expert consulted by CADTH on this review noted that 25% of patients in the NAVIGATOR trial were on medium-dose ICSs, suggesting that these patients may have been undertreated rather than having severe asthma. The clinical expert noted that they would not start a patient on a biologic for asthma until they had tried high-dose ICSs. The lack of an active control, particularly another biologic, in any of the included trials is a limitation, as it is only indirect comparisons that are available to assess the relative efficacy and harms of tezepelumab compared to other biologics.

Indirect Comparisons

Description of Studies

Currently, there are no head-to-head trials that have compared the efficacy of tezepelumab with other biologics used to treat patients with severe uncontrolled asthma. The sponsor submitted 2 ITCs that were a network meta-analysis (NMA), and match-adjusted indirect comparisons (MAICs)/simulated treatment comparisons (STCs). Three additional ITCs were identified after a systematic search of the literature performed by CADTH. Of the sponsor-submitted ITCs, both the NMA and the MAICs/STCs compared tezepelumab with dupilumab, mepolizumab, benralizumab, omalizumab, and reslizumab for uncontrolled moderate to severe asthma in adults and adolescents.[10,11] The 3 ITCs that were identified by CADTH indirectly compared tezepelumab with dupilumab, benralizumab, mepolizumab, reslizumab, and omalizumab. Data on reslizumab are not reported in this document because reslizumab was not considered as a relevant comparator in the CADTH systematic review protocol.

Efficacy Results

In the sponsor-submitted NMA, no differences were identified in terms of reduction of AAER, reduction of hospitalization due to AAER, FEV_1 improvement, symptom reduction (change in ACQ), and OCS reduction of ≥ 50%, when comparing tezepelumab with dupilumab, mepolizumab, benralizumab, and omalizumab. The results of the sponsor-submitted MAICs/STCs were aligned with what was reported in the sponsor's NMA. Findings from the 3 published ITCs were also aligned with the results reported in the sponsor's NMA.

Harms Results

Safety outcomes (i.e., any AEs) were assessed in 1 published ITC by Ando et al. (2022), which compared tezepelumab with mepolizumab, benralizumab, and dupilumab. No difference in risk of AEs was found in this ITC.

Critical Appraisal

Due to the considerable methodological limitations of the ITCs — such as heterogeneity across the included studies and the significantly reduced effective sample size after the match adjustment in the MAICs/STCs, as well as no subgroup analysis for the severe

uncontrolled asthma group — there is uncertainty in the ITC results. No definitive conclusion can be drawn regarding the comparative effectiveness and safety profile between tezepelumab and other relevant biologics in the treatment of adults and adolescents aged 12 years and older with severe asthma as an add-on maintenance treatment.

Other Relevant Evidence

Description of Studies

DESTINATION is a phase III, multi-centre, DB, randomized, placebo-control, parallel group, long-term extension (LTE) study for patients who completed the NAVIGATOR or SOURCE trials. The DESTINATION trial was designed to provide evidence of the long-term safety and tolerability of tezepelumab 210 mg administered every 4 weeks subcutaneously in adults and adolescents with severe, uncontrolled asthma for up to 2 continuous years, including 1 year of treatment in the predecessor NAVIGATOR and SOURCE parent studies. Adults (aged 18 to 80 years) and adolescents (aged 12 to 17 years) who had continued to receive the investigational product and attended the end of treatment visit in 1 of the parent studies were eligible for enrolment. A total of 951 patients were enrolled and randomized into the DESTINATION trial: 827 patients from the NAVIGATOR trial and 124 from the SOURCE trial. Patients previously randomized to 210 mg tezepelumab in either parent study were assigned to and remained on 210 mg tezepelumab administered every 4 weeks subcutaneously in the DESTINATION trial (tezepelumab plus tezepelumab group). Patients previously randomized to the placebo arm in the parent studies were re-randomized in a 1:1 ratio to either 210 mg tezepelumab (placebo plus tezepelumab group) or matching placebo (placebo plus placebo group) administered every 4 weeks subcutaneously. Patients recruited from the SOURCE trial were followed post-treatment for 12 weeks. Patients who enrolled from the NAVIGATOR trial who completed 100 weeks of tezepelumab treatment were eligible for either 12 weeks of follow-up or a 36-week extended follow-up. The primary outcome for the DESTINATION trial was to evaluate the long-term safety of tezepelumab in patients with severe asthma. The secondary outcome was to assess the effect of tezepelumab on AAER over 104 weeks. This review of the DESTINATION trial focused on the results from the tezepelumab plus tezepelumab and placebo plus placebo groups.

Efficacy Results

Asthma Exacerbations

Among patients enrolled into the LTE from the NAVIGATOR trial, tezepelumab plus tezepelumab resulted in a reduction in the rate of asthma exacerbation compared to placebo plus placebo (AAER, 0.50; 95% CI, 0.40 to 0.63). Similarly, treatment with tezepelumab plus tezepelumab reduced the rate of asthma exacerbations associated with hospitalization or ER visits compared with placebo plus placebo (AAER, 0.39; 95% CI, 0.22 to 0.69)

In patients who enrolled into the LTE from the SOURCE trial, AAER for asthma exacerbations between tezepelumab plus tezepelumab and placebo plus placebo was 0.66 (95% CI, 0.37 to 1.19). For asthma exacerbations associated with hospitalization or ER visits, AAER for tezepelumab plus tezepelumab versus placebo plus placebo was 0.27 (95% CI, 0.05 to 1.63).

Asthma Control

Improvement from baseline ACQ-6 score over the LTE study period was observed in the tezepelumab plus tezepelumab group compared to the placebo plus placebo group in patients who were originally enrolled in the NAVIGATOR trial (LS MD, 0.31; 95% CI, −0.47 to

−0.14). Similar trends in ACQ-6 were observed in patients originally enrolled in the SOURCE trial; the tezepelumab plus tezepelumab group saw an improvement in ACQ-6 over the LTE study period compared to placebo plus placebo (LS MD, −0.74; 95% CI; −1.12 to −0.25).

Harms Results

Among patients who entered the DESTINATION trial from the NAVIGATOR trial, 66.7% of patients in the tezepelumab plus tezepelumab group and 71.4% of patients in the placebo plus placebo group reported at least 1 AE during the LTE study period. Among patients who remained on tezepelumab during the LTE period, AEs leading to discontinuation of the investigational product were reported by 4 patients (1%), and AEs leading to death were reported by 7 patients (1.7%). Among those who continued to received placebo in the LTE period, AEs leading to discontinuation of the investigational product were reported by 2 patients (1%) and AEs leading to death were reported by 1 patient (0.5%). Finally, SAEs during the LTE study period were reported in 35 patients (8.4%) and 22 patients (10.7%) in the tezepelumab plus tezepelumab and placebo plus placebo groups, respectively. Notable harms of interest reported during the LTE study period included hypersensitivity (0.5% in both the tezepelumab plus tezepelumab arm and placebo plus placebo arm) and injection site reactions (0.5% and 1.5% in the tezepelumab plus tezepelumab arm and placebo plus placebo arm, respectively).

Among patients who entered the DESTINATION trial from the SOURCE trial, 71.1% of patients in the tezepelumab plus tezepelumab group and 68.8% of patients in the placebo plus placebo group reported at least 1 AEs during the LTE study period. Within the tezepelumab plus tezepelumab group during the LTE period, there were no AEs leading to discontinuation of the investigational product, and there was 1 reported AE (1.7%) leading to death. Within the placebo plus placebo group in the LTE period, there were no reported AEs leading to discontinuation of the investigational product or death. Finally, SAEs during the LTE study period were reported in 7 patients (11.7%) and 4 patients (12.5%) in the tezepelumab plus tezepelumab group and placebo plus placebo group, respectively. No notable harms of interest were reported among patients who enrolled into the DESTINATION trial during the LTE study period.

Critical Appraisal

The DESTINATION trial provided additional data on the long-term efficacy of tezepelumab relative to placebo. Statistical hypothesis testing was not part of the design. Blinding may have been compromised via accidental publishing of individual test results on the investigator's portal (on November 23, 2021) by the lab vendor before the primary database lock, which may have potentially led to unblinding for investigators who may have viewed the data. There were several imbalances between treatment groups among those who enrolled from the SOURCE trial. First, fewer patients in the placebo plus placebo group completed the treatment protocol. Second, a greater proportion of patients in the placebo plus placebo group reported the use of additional controller medications at baseline. Although the direction of any bias is unclear, it is possible that the differential dropout rate between the 2 treatment groups may have introduced attrition bias in favour of the tezepelumab plus tezepelumab group. Likewise, while the direction of any bias is unclear, it is possible that the differential use of controller medication may have been a surrogate of disease severity and biased the results in favour of the tezepelumab plus tezepelumab group. Overall, the DESTINATION study population represented the population of patients with severe, uncontrolled asthma and severe, OCS-dependent asthma as derived from the parent NAVIGATOR and SOURCE studies, respectively. Patient enrolment from the parent studies into the DESTINATION trial was

greater than 90%. At LTE baseline, patient characteristics were similar to the parent studies' baseline. Completion of the LTE was greater than 96% across all treatment groups from the NAVIGATOR trial. While completion of the LTE was lower among patients who entered the LTE from the SOURCE trial, completion of the LTE remained greater than 80%. Given that the patients enrolled in the LTE study were originally from the NAVIGATOR and SOURCE parent studies, and the eligibility criteria remained the same, it is reasonable to expect that the same limitations to generalizability are relevant to the DESTINATION trial.

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 in adults and adolescents 12 years and older with severe asthma
Treatment	Tezepelumab plus standard of care (SoC)
Submitted price	Tezepelumab, 210 mg: $1,938.46 per pre-filled syringe or pen
Treatment cost	At the recommended dose of 210 mg every 4 weeks, the annual cost of treatment with tezepelumab is $25,200
Comparator	SoC alone (high-dose ICS/LABA, OCS for OCS-dependent patients)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (50 years)
Key data source	NAVIGATOR trial, SOURCE trial
Key limitations	• The sponsor's submitted model lacks clinical validity. Asthma control, defined using ACQ-6, was dichotomized (controlled vs. uncontrolled), with a threshold score of 1.5 used to classify patients as uncontrolled. This dichotomization implies that a patient whose ACQ score improved by as little as 0.01 (e.g., from 1.50 to 1.49) would be considered to have controlled asthma and would receive the utility benefit for the "controlled" health state ([redacted]) instead of the "uncontrolled" health state ([redacted]). Likewise, the model assumes that prior asthma control will influence the disutility associated with a severe exacerbation. The CADTH clinical expert felt this lacked clinical validity. • The assumption of increased mortality with a severe asthma exacerbation in the model implies a substantial survival benefit with tezepelumab that has not been shown in clinical trials. Although evidence shows tezepelumab reduces exacerbations there is no evidence to suggest it reduces fatal exacerbations. The model also overestimates the number of individuals who die from an asthma exacerbation based on evidence from the trial, literature, and opinion of the CADTH clinical expert. • The sponsor incorporated a treatment-specific utility value for those who receive tezepelumab. The sponsor's utilities indicate that treatment with tezepelumab results in improved quality of life independent of whether it improves asthma control and reduced exacerbations. The sponsor assumes that patients treated with tezepelumab, who experience a severe exacerbation that is treated in the community setting, will have a higher utility than those not on tezepelumab with controlled asthma for example. The CADTH clinical expert felt this lacked face validity.

Component	Description
	• The assessment of response modelled in the analysis does not adequately reflect the management of asthma in clinical practice. The sponsor assumed that treatment response would be assessed after 26 weeks, with response defined as any reduction in rate of exacerbation or chronic OCS use from baseline; non-responders were assumed to discontinue tezepelumab and receive background therapy alone. According to the CADTH clinical expert, initial treatment response would likely be assessed based on change in ACQ score and lung function (i.e., FEV_1). • The model does not accurately predict the rate of exacerbations or hospitalizations as observed from the trial and the sponsor declined to send a model populated with only NAVIGATOR data for validation purposes. This further limits CADTH's ability to validate the model. • There is limited evidence on the duration of the treatment effect with tezepelumab. The sponsor assumed that the clinical effects of tezepelumab on asthma exacerbations observed in 52-week trials would be maintained for approximately 50 years. • The comparative clinical efficacy of tezepelumab relative to other biologic treatments for severe asthma is highly uncertain. There is no direct head-to-head evidence comparing tezepelumab and other biologics, and there is substantial uncertainty in the results of the sponsor's ITCs.
CADTH reanalysis results	• The CADTH reanalysis assumed no mortality benefit associated with tezepelumab, used utility values associated with health-states only, and removed response assessment at 26 weeks. CADTH was unable to address the lack of head-to-head comparative clinical data to other biologics and concerns with transparency over how transition probabilities were derived. • The CADTH reanalysis found that tezepelumab is associated with an ICER of $1,334,178 per QALY gained, and the probability of cost-effectiveness at a WTP threshold of $50,000 per QALY is 0%. • A price reduction of approximately 95% is necessary to achieve cost-effectiveness at this threshold. Cost-effectiveness of tezepelumab relative to other biologics available in Canada could not be determined.

Budget Impact

Due to the high degree of uncertainty and inability to change the model structure, CADTH could not generate a reliable base-case estimate. CADTH was limited to conducting scenario analyses. Based on these analyses, CADTH found that the drug spend on tezepelumab is highly sensitive to the size of the eligible population and to displacement of SoC, due to uptake in those not eligible for other biologics. Estimates from these scenario analyses ranged from cost savings of $348,107 to a budget impact of $17,356,108, based on public list prices.

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: Four expert committee members did not attend.

Conflicts of interest: None