CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

TEZEPELUMAB (Tezspire)

(AstraZeneca Canada Inc.)

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

November 3, 2022

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0731
Name of the drug and Indication(s)	Tezepelumab (Tezspire) as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma.
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	X

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance

Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0731
Brand name (generic)	Tezspire (Tezepelumab)
Indication(s)	Tezepelumab is indicated as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma.
Organization	Asthma Canada
Contact information[a]	Name: Jenna Reynolds

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

As Asthma Canada is the only national charity, solely devoted to enhancing the quality of life for people living with asthma and respiratory allergies, we recognize that tezepelumab (Tezspire) is an important treatment option for Canadians living with severe asthma and urge you to reconsider the prescribing requirements as outlined in Section 5 (Prescribing) in the draft CADTH Reimbursement Review CADTH Reimbursement Recommendation (October 2022).

Tezepelumab is an important contribution as an add-on maintenance treatment for adult and pediatric patients aged 12 years and older with severe asthma. Tezepelumab provides a new approach to managing severe asthma – irrespective of phenotypes and across a range of biomarkers. Every

patient's underlying pathophysiology is different and patients deserve the choice and access to available medicines. More treatment choice and options lead to more benefit for patients and less burden on the Canadian healthcare system.

By limiting prescribing to only “an allergist or respirologist with experience managing severe asthma”, limits the choice and access for Canadians. As tezepelumab does not require phenotyping before administration, a general practitioner (GP) should be able to prescribe tezepelumab with a referral to a specialist for follow up appointments. This will remove the barrier of access and provide more options, improving health outcomes.

For our community, innovative drugs, including tezepelumab, have the potential to save lives.

Health outcomes for Canadians cannot improve unless treatment options are available and accessible. People living with severe asthma just want to live normal lives. They want to be able to go to work and be involved in the economic life of Canada. All Canadians should have equitable access to a comprehensive range of evidence-based medications to help meet their health needs, regardless of who they are, the setting they are in or where they live. Allowing a physician with expertise in the treatment of asthma to prescribe access to tezepelumab helps us reach this goal.

We urge you to amend the Prescribing reimbursement condition (5) to: physician with expertise in the treatment of asthma.

We appreciate your consideration in this matter.

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Asthma Canada*
Position	*Interim CEO*
Date	*Please add the date form was completed (01-11-2022)*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☐
	Yes	☒
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☐
	Yes	☒
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☒	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0731-000
Brand name (generic)	Tezspire™ (tezepelumab)
Indication(s)	Add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma.
Organization	AstraZeneca Canada (sponsor)
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

- AstraZeneca (AZ) agrees with CADTH's CDEC draft recommendation that tezepelumab should be reimbursed as add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma based on statistically significant and clinically meaningful reduction in annualized asthma exacerbation rate in the NAVIGATOR trial. AstraZeneca also agrees with CDEC's assessment that tezepelumab satisfies unmet patient needs, such as improving lung function, controlling symptoms, reducing exacerbations, and improving quality of life.

- Furthermore, AZ agrees with CADTH's budget impact model re-analysis; that the addition of tezepelumab to provincial drug formularies could represent a cost-savings of up to $348,107 for jurisdictions.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

- In the 'Pricing' section of the Reimbursement Conditions and Reasons table (pg. 5), CADTH indicates that: "*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.*" AZ disagrees with CADTH's re-analysis of the cost-effectiveness model, CADTH's noted limitations in the draft recommendation are not supported by the evidence, nor do they reflected with the comments and feedback provided by AZ. We do not agree with CADTH's suggestion that a price reduction of 95% would be required for tezepelumab to be considered cost-effective at a willingness to pay threshold of $50,000 per QALY. Such an assessment would lead to tezepelumab being priced similarly to ICS/LABA and well below genericized pricing. This does not recognize or value the innovation, the benefit tezepelumab provides to patients with severe asthma, or the added benefit tezepelumab provides versus comparator biologics. AZ requests that CADTH align its analysis to the base-case model submitted by the manufacturer to inform their pricing condition.

- In the 'Key Limitations' Section of the Cost and Cost-Effectiveness table (pg. 15), CADTH indicated that: "*the assumption of increased mortality with 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 the evidence from the trial, literature, and opinion of the CADTH clinical expert*."

  To estimate the cost-effectiveness of tezepelumab in severe asthma patients, AZ submitted a model that was designed to capture the natural history of disease; AZ disagrees that the model overestimates asthma exacerbation-related mortality. Severe exacerbations are potentially life-threatening; the mortality risk associated with severe exacerbations is well documented in the literature, and is thus an important dimension to capture when modelling the natural history of disease.[1-3] The importance of this dimension is further recognized in the 2022 Global Strategy for Asthma Management and Prevention by the Global Initiative for Asthma (GINA) guidlines which state, "Severe exacerbations are potentially life threatening and their treatment requires careful assessment and close monitoring."[4] Exacerbation-related mortality risk is also recognized in several published cost-effectiveness analyses.[5-9]

  Although death from asthma is rare in Canada (with appropriate treatment), Canadian clinicians that were consulted throughout development of the model have also noted that patients experiencing exacerbations have a greater risk of mortality than patients who do not experience exacerbations. Additionally, as it is not feasible to obtain clinical trial data demonstrating the relative exacerbation-related mortality of different treatments and exacerbation types due to the impracticality (need for lengthy trial duration [e.g., lifetime] and a large number patients) and unethicality of capturing mortality benefit as part of a clinical trial, it is fair to assume that a reduction in exacerbations would correspond to reduced exacerbation-related mortality. Importantly, Canadian clinicians validated this assumption, noting that exacerbations would be the primary cause of asthma-related mortality and a reduction would be expected to lead to reduced mortality.

  AZ Proposed change:

  Based on the evidence from the literature and Canadian clinical expert opinion, AZ requests that **CADTH capture the mortality risk associated with severe exacerbations in the base case of their cost-effectiveness model.**

- In the 'Critical Appraisal' Section of the Indirect Comparisons (pg. 12) and in the 'Key Limitations' Section of the Cost and Cost-Effectiveness table (pg. 15), CADTH indicated that: "*there is uncertainty in the ITC results*" and "*there is substantial uncertainty in the results of the sponsor's indirect treatment comparisons.*" The sponsor-submitted ITC used to estimate the relative efficacy of tezepelumab compared to relevant biologics in the submitted model adhered to the National Institute for Health, Care Excellence Decision Support Unit Technical Support Document 2 and the CADTH Guidance Document on Reporting Indirect Comparisons, and demonstrated tezepelumab to be the most favorable treatment. Tezepelumab demonstrated non-statistically significant improvement (i.e., numerically favored) in AAER (annualized asthma exacerbation rate) rate ratios and reduction in exacerbations leading to hospitalization compared to benralizumab, dupilumab, mepolizumab, and omalizumab. Furthermore, a separate independent NMA by Ando et al. (2022) was published demonstrating the efficacy of tezepelumab compared to other biologics, and align with the results used in the model.[10]

  While the ITCs submitted to CADTH demonstrate tezepelumab's benefits compared to other currently available biologics, AZ acknowledges there is uncertainty. However, the magnitude of this uncertainty was built into and accounted for in the cost-effectiveness model, which still

demonstrated that, on average, tezepelumab was expected to dominate other currently available biologics.

AZ Proposed changes:
AZ proposes the following revision to the 'Key Limitations' section of the Cost and Cost-Effectiveness table (pg15) to improve clarity and transparency on the role that uncertainty in the ITC results has on cost-effectiveness: "There is no direct head-to-head evidence comparing tezepelumab and other biologics, and there is substantial uncertainty in the **relative effects from** the sponsor's indirect treatment comparisons, **however, despite the variation in incremental costs and QALYs, tezepelumab was expected to dominate other biologic treatments in probabilistic analyses.**"

- In the 'Prescribing' section of the Reimbursement Conditions and Reasons table (pg. 5), CDEC recommends that: "*Tezepelumab should be initiated by an allergist or respirologist with experience managing severe asthma.*" While AZ recognizes that respirologists and allergists are key healthcare professionals (HCPs) in the management of severe asthma and will represent most HCPs prescribing Tezepelumab, there are other HCPs such as some family physicians or internists who have clinical expertise in severe asthma and have treated and managed patients with severe asthma which may have included the prescribing of biologics. As noted by Asthma Canada and Lung Health Foundation, "patients and parents/caregivers [have] noted several barriers to accessing healthcare providers (e.g., respirologists, specialized asthma clinics)" (Page 7). Given patients express difficulty accessing specialist care, restrictions on eligible prescribers will likely further exacerbate patient access to needed biologic treatment to decrease their risk of exacerbation and improve symptom control. With tezepelumab's demonstrated clinical benefit across all asthma phenotypes, irrespective of biomarker status, HCPs with expertise in asthma patients can have confidence that tezepelumab will provide benefit in all severe asthma patients. AZ proposes that this language be updated to account for the barriers that currently exist in accessing HCPs, and that this is a consideration during provincial implementation.

  AZ Proposed changes:
  AstraZeneca requests that CADTH update the prescribing criteria for tezepelumab to include: Tezepelumab should be initiated by an allergist or respirologist **or a physician with expertise in treating severe asthma patients**.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification.		

AZ requests that CADTH make minor changes to the Reimbursement Conditions and Reasons Initiation 'Implementation Guidance' to align with the provincial criteria of other currently available biologics:

- Page 4, Clinically significant asthma exacerbations are defined as worsening of asthma resulting in administration of systemic corticosteroids for at least 3 days **or an emergency department visit** or hospitalization.

[a] CADTH may contact this person if comments require clarification.

Sponsor's References

1. Watson L, Turk F, James P, Holgate ST (2007) Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. Respiratory medicine 101 (8): 1659-1664.
2. Krishnan V, Diette GB, Rand CS, Bilderback AL, Merriman B et al. (2006) Mortality in patients hospitalized for asthma exacerbations in the United States. American journal of respiratory and critical care medicine 174 (6): 633-638.
3. Roberts NJ, Lewsey JD, Gillies M, Briggs AH, Belozeroff V et al. (2013) Time trends in 30 day case-fatality following hospitalisation for asthma in adults in Scotland: a retrospective cohort study from 1981 to 2009. Respiratory medicine 107 (8): 1172-1177.
4. Global Initiative for Asthma (2022). Diagnosis of Exacerbations. In: Global Strategy for Asthma Management and Prevention. Available online at: www.ginasthma.org. Accessed November 2022.
5. Rind DM, McQueen RB, Herron-Smith S, Herce-Hagiwara B, Gutierrez E et al. (2022) The effectiveness and value of tezepelumab for severe asthma: A summary from the Institute for Clinical and Economic Review's California Technology Assessment Forum. Journal of Managed Care & Specialty Pharmacy 28 (5): 577-580.
6. González-Barcala FJ, Muñoz-Gall X, Mariscal E, García A, Yang S et al. (2021) Cost-effectiveness analysis of anti–IL-5 therapies of severe eosinophilic asthma in Spain. Journal of Medical Economics 24 (1): 874-882.
7. Tohda Y, Matsumoto H, Miyata M, Taguchi Y, Ueyama M et al. (2021) Cost-effectiveness analysis of dupilumab among patients with oral corticosteroid-dependent uncontrolled severe asthma in Japan. Journal of Asthma 1-12.
8. Sullivan PW, Li Q, Bilir SP, Dang J, Kavati A et al. (2020) Cost-effectiveness of omalizumab for the treatment of moderate-to-severe uncontrolled allergic asthma in the United States. Current medical research and opinion 36 (1): 23-32.
9. Tan LE, Tan WHG, Aziz MIA, Koh MS, Tay TR et al. (2022) Assessing the cost-effectiveness of mepolizumab as add-on therapy to standard of care for severe eosinophilic asthma in Singapore. Journal of Asthma 59 (1): 189-199.
10. Ando K, Fukuda Y, Tanaka A, Sagara H (2022) Comparative Efficacy and Safety of Tezepelumab and Other Biologics in Patients with Inadequately Controlled Asthma According to Thresholds of Type 2 Inflammatory Biomarkers: A Systematic Review and Network Meta-Analysis. Cells 11 (5): 819.