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CADTH Reimbursement Recommendation

Budesonide (Jorveza)

Indication: Induction and maintenance of clinico-pathological remission in adults with eosinophilic esophagitis

Sponsor: Avir Pharma Inc.

Final recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Jorveza?

CADTH recommends that Jorveza should be reimbursed by public drug plans for the maintenance of remission in adults with eosinophilic esophagitis (EoE) if certain conditions are met.

What are the conditions for reimbursement?

Jorveza should only be reimbursed if prescribed by a specialist with experience in the diagnosis and management of EoE, and the cost of Jorveza is reduced.

Which patients are eligible for coverage?

Jorveza should only be covered for adult patients who have a confirmed diagnosis of EoE, in whom treatment with a proton pump inhibitor (PPI) did not work, and whose symptoms (dysphagia and pain during swallowing) have resolved after receiving induction treatment with Jorveza.

Why did CADTH make this recommendation?

- Evidence from 1 a clinical study demonstrated that Jorveza was more effective than placebo in maintaining remission both clinically and histologically in patients with EoE.
- Jorveza may address some of the needs that are important to patients, including sustaining disease control and symptom relief.
- CADTH was unable to estimate the cost-effectiveness of Jorveza due to limitations with the sponsor's pharmacoeconomic model and the available clinical information.
- Based on public list prices, the 3-year budget impact is expected to be approximately $8.6M.

Additional Information

What is EoE?

EoE is a chronic disease characterized by an inflamed esophagus. Symptoms of EoE include difficulty and pain when swallowing, heartburn, and chest pain. Left untreated, EoE can progress and cause narrowing of the esophagus, which may lead to choking and ultimately emergency endoscopic procedure. In Canada, in 2008, the incidence of EoE was 10.7 per 100,000 persons.

Unmet needs in EoE

The drugs most often used to treat EoE are PPIs and topical corticosteroids, but neither are approved for EoE in Canada, and many patients do not take these as prescribed. There is a need for an effective treatment to maintain remission in patients with EoE that is well tolerated and easy to administer.

How much does Jorveza cost?

Treatment with Jorveza to maintain remission is expected to cost approximately $3,413 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that budesonide should be reimbursed for the maintenance of clinico-pathological remission in adults with eosinophilic esophagitis (EoE) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

In 1 randomized, double-blind, phase III trial (Study BUL-2/EER, N = 204) in adult patients with a confirmed clinico-pathological diagnosis of EoE and clinico-pathological remission, statistically significantly more patients in the budesonide orodispersible tablets (budesonide) 0.5 mg twice daily group were free of treatment failure after 48 weeks of treatment than in the placebo group (between-group difference of 69.1% in favour of budesonide; 97.5% confidence interval [CI], 55.89 to 82.34; P < 0.0001). The median time to relapse was shorter for the placebo treated group (86 days) compared to the budesonide 0.5 mg treatment group (336 days). In addition,13.2% of patients in the budesonide 0.5 mg treatment group experienced a histological relapse versus 89.7% in the placebo group (between groups difference of −76.5%; 97.5% CI, −88.8 to −64.1; P < 0.0001), and 10.3% of patients in the budesonide 0.5 mg treatment group had a clinical relapse versus 60.3% in the placebo group (between groups difference of −50.0%; 97.5% CI, −65.7 to −34.3; P < 0.0001).

Patients identified the need for a treatment that provides sustained disease control and symptom relief; results of Study BUL-2/EER demonstrate that budesonide has the potential to address these needs.

The cost-effectiveness of budesonide as maintenance therapy is highly uncertain due to insufficient evidence on the long-term clinical efficacy and cost-effectiveness of the use of budesonide for reinductions in patients who relapsed while on budesonide therapy or not receiving budesonide therapy. As such, a base-case cost-effectiveness estimate could not be determined in patients with EoE who had achieved remission after induction with budesonide. If the price reduction recommended previously by CDEC for budesonide in the induction phase is achieved, the probability that budesonide is cost-effective in the maintenance phase will be improved.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Adult patients (≥ 18 years of age) with a confirmed clinico-pathological diagnosis of EoE according to established diagnostic criteria: 1.1. History of symptoms of esophageal dysfunction (at least 1 of the following: transient or self-cleared food impaction, dysphagia, chest pain, epigastric discomfort, vomiting/regurgitation) 1.2. History of peak eos ≥ 15 in at least 1 HPF; (magnification: 400x) found pathologically on endoscopy.	Patients enrolled in Study BUL-2/EER were adults (18 to 75 years of age) and had to have a confirmed clinico-pathological diagnosis of EoE.
2. Patients must have experienced resolution of symptoms (dysphagia and pain during swallowing) after receiving induction treatment with budesonide	Patients enrolled in Study BUL-2/EER had clinico-pathological remission after receiving induction treatment with budesonide.
3. Failed an adequate trial of PPI treatment before initiation of induction treatment with budesonide 3.1. PPI failure is defined as refractory symptoms after at least 4 weeks of PPI treatment at a standard dose (omeprazole 20 mg/day, pantoprazole 40 mg/day, esomeprazole 40 mg/day, lansoprazole 30 mg/day, or rabeprazole 20 mg/day).	All patients enrolled in Study BUL-2/EER were required to have a documented trial with PPIs before initiation of induction treatment with budesonide to exclude PPI-REE.
Renewal	
4. Response to treatment should be assessed 3 months after initiating maintenance treatment with budesonide, then every 12 months thereafter.	The clinical experts noted to CDEC that in clinical practice, the response to treatment is assessed 3 months after initiating maintenance therapy, then every 6 months to 1 year thereafter.
Discontinuation	
5. Patients who experience clinical relapse, histological relapse, food impaction that needed endoscopic intervention, or need for an endoscopic dilation while receiving budesonide as maintenance therapy, should discontinue budesonide.	There is insufficient evidence to demonstrate whether patients who relapse while receiving budesonide for the maintenance of remission would respond to a subsequent reinduction course of treatment with budesonide or in the same manner as they responded to the initial treatment course.
Prescribing	
6. The patient must be under the care of a specialist with experience in the diagnosis and management of EoE.	Accurate diagnosis and follow-up of patients with EoE are important to ensure that budesonide is prescribed to the most appropriate patients.
7. Budesonide should not be reimbursed when used in combination with other corticosteroids used to maintain remission in patient with EoE	There is no evidence to demonstrate that patients with EoE would derive additional benefit from treatment with budesonide when used in combination with other corticosteroids for the treatment of patient with EoE.

Reimbursement condition	Reason
Pricing	
8. A reduction in price	The cost-effectiveness of budesonide for maintenance therapy is highly uncertain. If the price reduction recommended previously by CDEC for budesonide in the induction phase is achieved, the probability that budesonide is cost-effective in the maintenance phase will be improved.

budesonide = budesonide orodispersible tablets; EoE = eosinophilic esophagitis; eos = eosinophils; hpf = high-power field; PPI = proton pump inhibitor; PPI-REE = PPI-responsive esophageal eosinophilia.

Implementation Guidance

1. The clinical experts indicated that PPI-naive patients would probably respond to budesonide in a similar manner to patients who failed to respond to PPI treatment. However, the clinical experts also indicated that PPI is usually prescribed as the first-line pharmacological treatment for inducing remission of EoE. CDEC agreed that patients must have failed an adequate trial of PPI treatment as outlined in the CDEC recommendation for induction of clinico-pathological remission in adults with EoE and consistent with the inclusion criteria of Study BUL-2/EER.
2. Patients eligible for reimbursement of budesonide for maintenance of remission must be transitioning directly from induction to maintenance therapy; the duration of induction therapy may vary between 6 and 12 weeks.
3. Budesonide are available in 2 strengths: 0.5 mg and 1 mg. The 1 mg twice daily dosage is recommended by Health Canada for the induction of remission, but only budesonide 0.5 mg twice daily is approved for the maintenance of remission.
4. There is insufficient evidence to demonstrate whether patients who relapse while receiving budesonide for the maintenance of remission would respond to a subsequent reinduction course of treatment with budesonide or in the same manner as they responded to the initial treatment course.

Discussion Points

- CDEC discussed that the duration of maintenance treatment with budesonide is unclear, and it is unclear if patients will relapse after budesonide is discontinued. The clinical experts indicated that the evidence from Study BUL-2/EER is not sufficient to identify patients who would successfully discontinue budesonide treatment after 48 weeks without relapse. However, the clinical experts noted that patients with a history of severe disease as manifested by food impactions or significant fibrosis would likely require chronic treatment with budesonide, and that duration of treatment should be determined by the treating physician.
- The BUL-2/EER trial excluded patients with severe strictures, which may limit the interpretation of the efficacy findings to patients who have strictures with a predominant inflammatory component.

- CDEC was unable to conclude whether budesonide would be efficacious in maintaining remission in patients who achieved remission using treatments other than budesonide. There is an absence of evidence to demonstrate the efficacy of budesonide for maintaining remission in this patient population.
- The CDEC recommendation for budesonide for the induction of clinicopathologic remission in adults with EoE limits treatment duration for the induction of remission to a maximum period of 6 weeks. In Study BUL-2/EER, no subgroup analysis by prior induction duration with budesonide (6 weeks versus 12 weeks) was conducted. The majority of patients (approximately 80%) had received induction treatment with 6 weeks of budesonide, with the remaining had their induction therapy with budesonide for 12 weeks. It is uncertain whether the course of therapy during the induction of remission may impact the response rate for the maintenance of remission.
- While patients in the BUL-2/EER study who experienced relapse while receiving budesonide for maintenance of remission were offered an open-label reinduction of remission treatment with budesonide 1 mg group twice daily for up to 6 weeks, the data available from the reinduction phase are unaudited. In addition, the open-label study design and lack of randomization could have overestimated subjective patient-reported outcomes such as clinical response.
- CDEC discussed that it might not be possible to identify patients who relapse due to nonadherence versus other reasons. Patients who relapse for any reason, including nonadherence to budesonide, should discontinue treatment with budesonide.

Background

Budesonide has a Health Canada indication for the induction and maintenance of clinico-pathological remission in adults with EoE. Budesonide is a non-halogenated glucocorticosteroid, which acts primarily as an anti-inflammatory by binding to the glucocorticoid receptor. Budesonide is formulated as a 0.5 mg or 1 mg orodispersible tablet, and the Health Canada–approved daily dose for the maintenance of remission is 1 mg budesonide as 1 of the 0.5 mg tablet in the morning and 1 of the 0.5 mg tablet in the evening. The duration of maintenance therapy is determined by the treating physician.

Sources of Information Used by the Committee

To make their recommendation, CDEC considered the following information:

- a systematic review that included 1 phase III, double-blind, randomized, placebo-controlled study in in adult patients with EoE
- patient perspectives gathered by patient groups, including the Gastrointestinal (GI) Society, Food Allergy Canada, and the EOS Network (formerly Families Affected by Eosinophilic Diseases [FABED])
- input from public drug plans and cancer agencies that participate in the CADTH review process
- three clinical specialists with expertise diagnosing and treating patients with EoE

- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

- A total of 3 patient group submissions were received for this review: Two Canadian patient organizations; the Gastrointestinal (GI) Society and Food Allergy Canada; and 1 international patient group, the EOS Network (formerly Families Affected by Eosinophilic Diseases [FABED]) from the UK.
- The patient groups gathered input through a variety of sources including results from published studies, a patient experience survey, telephone interviews with patients, experiences as a patient advocacy organization, social media commentary, and direct input from patients and caregivers.
- According to the patient input received, the symptoms of EoE vary among individuals and can include difficulty swallowing, choking, regurgitation, nausea, vomiting, fatigue, reflux, and abdominal and/or chest pain, as well as malnutrition and failure to thrive in the case of young children.
- It was noted that living with EoE has a significant impact on the daily lives of patients and their families — socially, mentally, and financially. Dietary restriction presents a significant burden to the lives of patients and/or caregivers, thereby having a negative impact on activities such as holidays and family gatherings, social engagements, travel, and dining away from home.
- The patient groups reported that corticosteroids generally reduce the number of eosinophils and improve symptoms; however, they are primarily asthma medications, used beyond the Health Canada indication, that are swallowed from an inhaler or as a "slurry" mixture, and the non-specific nature of drug delivery makes the effectiveness varied and uncertain.
- Patients expressed a desire for convenience in medication administration and a reliable mode of administration suited to EoE. Patients expressed a need for a treatment that improves their day-to-day quality of life (that is, eating, working, and socializing) and indicated that an effective therapy is one that reduces or eliminates symptoms, is easy to consume, and has minimum long-term complications.

Clinician Input

Input from clinical experts consulted by CADTH

- The clinical experts indicated that budesonide would take the role of the compounded topical corticosteroids, which will not, by itself, present a treatment paradigm shift.
- The clinical experts indicated that patients who would be best suited for maintenance treatment with budesonide are those who responded to the initial treatment with budesonide after failure to respond to PPI therapy and who symptomatically recur more than once per year or who have a history of severe disease as manifested by food impactions or significant fibrosis, patients with severe endoscopic disease, and who are intolerant or non-compliant with fluticasone or other formulation of budesonide. The clinical experts identified patients least likely to benefit from budesonide are those who

respond to PPI treatment or other topical steroids (such as fluticasone propionate or budesonide slurry).

- The clinical experts also indicated while maintenance therapy, in general, would imply continuous treatment, in clinical practice, treatment might be titrated, intermittent, persistent, or stopped, the decision is affected by symptoms, complications, strictures, and persistent inflammation on endoscopy.
- The clinical experts agreed that budesonide for the treatment of EoE should be prescribed by specialists in gastroenterology or managing allergies who have expertise in EoE.

Drug Program Input

Input was obtained from the jurisdictions participating in CADTH reimbursement reviews. The following were identified as key factors that could impact the implementation:

- The duration of maintenance therapy
  - The clinical experts also indicated that the evidence from the BUL-2/EER trial is not sufficient to provide criteria on which patients would be able to stop treatment after 48 weeks and don't relapse; however, from clinical experience, the clinical experts think that patients with a history of severe disease as manifested by food impactions or significant fibrosis need to stay on 0.5 mg budesonide twice daily for a long period (as on a case-by-case basis).
- The use of 1 mg budesonide twice daily off-label for the maintenance of remission
  - The clinical experts indicated that disease severity before remission would guide dosing decisions and that patients with more severe illness tend to need more aggressive therapy. However, the clinical experts indicated that they would try first to maintain the remission using the budesonide 0.5 mg twice daily dosage; if the patient relapse, then reinduction of remission using the budesonide 1 mg twice daily dosage will be tried. After achieving remission again using the 1 mg budesonide twice daily dose, patients would be switched back to the 0.5 mg budesonide twice daily for maintenance of remission. Patients who relapse again while on the 0.5 mg budesonide twice daily would have their dosage increased to 1 mg budesonide twice daily for reinduction of remission. After achieving remission on the 1 mg budesonide twice daily dose, patients would remain on the 1 mg budesonide twice daily for the maintenance of remission. It should be noted that a maintenance dose of 1 mg twice daily is above the Health Canada–approved dose of 0.5 mg twice daily.
- Use of budesonide in PPI-naive patients
  - The clinical experts indicated that PPI-naive patients would probably respond in a similar manner as patients who failed to respond to PPI treatment. However, they also indicated that PPI is currently the first line of treatment unless a patient who is PPI-naive presents with food impaction and severe disease, then the treating physician would initiate treatment with budesonide.
- The use of budesonide in pediatric patients
  - The clinical experts indicated that budesonide might be used off-label in the pediatric population; however, there are some concerns about the safety aspect and what dose to prescribe. They also mentioned that pediatric patients are already prescribed off-label fluticasone propionate and budesonide slurry, and it would be much easier to teach children to use budesonide than teaching them how to swallow fluticasone

propionate and budesonide slurries. In addition, the taste of fluticasone propionate and budesonide slurry is problematic toward adherence in this patient population.

- Time interval follow-up for assessment.
  - The clinical experts indicated that treatment response should be assessed 3 months after initiating maintenance therapy, then every 6 months to 1 year thereafter. The clinical experts also indicated that efficacy is assessed based on symptoms and that they would not provide endoscopy and histology during scheduled follow-ups for maintenance therapy to determine effectiveness, given that they try to rationalize the use of endoscopy, where endoscopy is conducted once every 1 to 2 years.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

The BUL-2/EER trial (N = 204) was a pivotal phase III, double-blind (DB), randomized, multi-centre, placebo-controlled study that compared the efficacy and tolerability of a 48-week treatment with 2 different doses of budesonide effervescent tablets (budesonide 0.5 mg twice daily and budesonide 1 mg twice daily) with placebo for the maintenance of clinico-pathological remission in adult patients with EoE. Patients enrolled in the trial were adults (18 to 75 years of age) with a confirmed clinicopathologic diagnosis of EoE, and clinico-pathological remission achieved either in the open-label induction phase of BUL-2/EER or the induction trial BUL-1/EEA (was reviewed by CDEC for the induction of remission indication) and must have undergone a documented trial with PPIs to exclude PPI-responsive esophageal eosinophilia (PPI-REE).

Clinico-pathological remission was defined as fulfilling both criteria at end of treatment visit of either the open-label induction phase of the BUL-2/EER study or the induction trial BUL-1/EEA:

- histological remission, i.e., peak of < 16 eosinophils (eos)/mm^2 high-power field (HPF)
- resolution of symptoms (i.e., no or only minimal problems) defined as a severity of ≤ 2 points on 0 to 10-point NRS for dysphagia and a severity of ≤ 2 points on 0 to 10-point numerical rating scale (NRS) for pain during swallowing on each day in the week before the end of treatment visit.

Patients were assigned to 1 of 3 treatment groups via a central randomization procedure using a 1:1:1 allocation ratio to receive either budesonide 0.5 mg orodispersible tablet (budesonide 0.5 mg) twice daily, budesonide 1 mg orodispersible tablet (budesonide 1 mg) twice daily or a placebo orodispersible tablet (placebo) twice daily. The budesonide and placebo treatments were identical in physical appearance, which assured treatment blinding. No stratification of randomized treatment assignment was performed. The percentage of patients free of treatment failure after 48 weeks of treatment was the primary end point. The percentage of patients with histological relapse, change in the peak eos/mm^2 hpf from baseline, the percentage of patients with a clinical relapse, the percentage of patients with a total weekly Eosinophilic Esophagitis Activity Index Patient Reported Outcome (EEsAI-PRO) score of ≤ 20, and the percentage of patients in deep disease remission were key secondary end points. Heath-related quality of life (HRQoL) was assessed using the modified Short Health Scale (modSHS) and the Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A)

questionnaire. modSHS and EoE-QoL-A were exploratory outcomes in the BUL-2/EER trial. Budesonide 1 mg twice daily is not an approved dosage for the maintenance of remission in Canada and therefore this review focused on the budesonide 0.5 mg twice daily dosage only.

In the BUL-2/EER trial, the average age of the participants was 36 years, and the majority were men (84%, and 81% for the budesonide 0.5 mg, and placebo study arms, respectively). All baseline parameters of disease activity, including histological results, endoscopic as well as patients' and investigators' assessments, showed low values for disease activity in all treatment groups, which is representative of the EoE patients who are in remission. The disease duration since diagnosis and disease duration since first symptoms were shorter in the placebo group than in the budesonide 0.5 mg group, where the mean time since an established EoE diagnosis was 4.3 years and 3.3 years for the budesonide 0.5 mg and placebo study groups, respectively, with a mean time since symptom onset of 12.6 years, and 9.6 years, respectively. In addition, fewer patients in the placebo group (5.9%) had a previous esophageal dilatation compared to the budesonide 0.5 mg group (19.1%). Forty patients (58.8%) in the budesonide 0.5 mg group and 30 patients (44.1%) in the placebo group received previous treatment with any topical steroids. Only 1 patient (1.5%) in the budesonide 0.5 mg group, and none of the patients in the placebo group received previous treatment with systemic corticosteroids. Approximately 80% of the patients enrolled in the BUL-2/EER trial had their induction therapy with budesonide for 6 weeks, with the remaining having their induction therapy with budesonide for 12 weeks.

Efficacy results

The percentage of patients free of treatment failure after 48 weeks of DB treatment were 73.5% in the budesonide 0.5 mg twice daily group, and 4.4% in the placebo group. The difference between the budesonide 0.5 mg group and placebo group was 69.1% (97.5% confidence interval [CI], 55.89 to 82.34; $P < 0.0001$), which was clinically relevant and statistically significant in favour of budesonide 0.5 mg twice daily treatment group. The median time to relapse was shorter for the placebo-treated group (86 days), as compared to the budesonide 0.5 mg treatment group (336 days). The clinical experts consulted by CADTH considered the definition of treatment failure is comprehensive given that it considered both clinical and histological aspects of deterioration of the disease, and almost any indication of lapse of control was noted as treatment failure.

The percentage of patients with histological relapse was 13.2% in the budesonide 0.5 mg twice daily group, and 89.7% in the placebo group. The difference between the budesonide 0.5 mg group and placebo group was −76.5% (97.5% CI, −88.8 to −64.1; $P < 0.0001$), which was statistically significant in favour of the budesonide 0.5 mg twice daily treatment group.

Clinical relapse during the DB phase was observed in 10.3% of the patients in the budesonide 0.5 mg twice daily group, and in 60.3% of the patients in the placebo group. The difference between the budesonide 0.5 mg group and placebo group was −50.0% (97.5% CI, −65.7 to −34.3; $P < 0.0001$), which was statistically significant in favour of the budesonide 0.5 mg twice daily treatment group.

None of the patients in the budesonide 0.5 mg treatment group and 1 patient in the placebo group experienced a food impaction during the treatment phase which needed endoscopic intervention. No patient needed an endoscopic dilation at any time during the DB treatment phase.

In the BUL-2/EER trial, HRQoL was assessed using EoE-QoL-A and modSHS. The difference between the budesonide 0.5 mg twice daily group and the placebo treatment group in mean absolute changes (95% CI) from baseline to end of treatment (EOT) of the DB phase for EoE-QoL-A (30 items), EoE-QoL-A (24 items), EoE-QoL-A eating/diet impact (10 items), and EoE-QoL-A eating/diet impact (four items) were 0.46 (0.27 to 0.66), 0.49 (0.30 to 0.68), 0.65 (0.39 to 0.92), and 0.75 (0.49 to 1.02), respectively. These between-group differences were in favour of the budesonide 0.5 mg twice daily group. The difference between the budesonide 0.5 mg twice daily group and the placebo treatment group in mean absolute changes (95% CI) from baseline to EOT of the DB phase for symptom burden, social function, disease-related worry, and general well-being of the modSHS were −22 (−30.5 to −13.9), −15 (−23.6 to −7.3), −12 (−19.4 to −3.7), and −12 (−18.9 to −4.3), respectively. These between-group differences were in favour of the budesonide 0.5 mg twice daily group. A minimal important difference (MID) for the EoE-QoL-A and modSHS was not identified for patients with EoE. Also, the analysis of modSHS and EoE-QoL-A were not specifically tested for statistical significance with methods adjusted for multiplicity, despite reporting a 95% CI. It is likely, however, that the budesonide 0.5 mg twice daily group maintained the patients' HRQoL, while the HRQoL deteriorated in patients who received placebo.

The percentage of patients with a total weekly EEsAI-PRO score of 20 or less (which indicate disease severity rated as remission) at the end of the DB phase were 72.1% in the budesonide 0.5 mg twice daily group and 20.6% in the placebo group. The difference between the budesonide 0.5 mg group and placebo group was 51.5% (95% CI, 35.1 to 67.9; P < 0.0001), which was statistically significant in favour of budesonide 0.5 mg twice daily treatment group.

The percentage of patients in deep disease remission; that is, deep clinical and deep endoscopic and histological remission (based on the peak number of eos per hpf) at EOT were 39.7% in the budesonide 0.5 mg twice daily group and 0% in the placebo group. The difference between the budesonide 0.5 mg group and placebo group was 39.7% (97.5% CI, 26.4 to 53.0; P < 0.0001), which was statistically significant in favour of the budesonide 0.5 mg twice daily treatment group.

Harms results

In the BUL-2/EER trial, the majority of patients reported at least 1 treatment-emergent adverse event, where 87 patients (83.8%) in the budesonide 0.5 mg twice daily group and 61 patients (89.7%) in the placebo group experienced at least 1 treatment-emergent adverse event.

No death occurred and during the DB phase, only for 3 patients (4.4%) in the budesonide 0.5 mg twice daily group and none of the patients in the placebo group reported serious adverse events (SAEs), all SAEs were not related to study medication as assessed by the investigator. Moreover, only 10% of patients in the budesonide 0.5 mg twice daily group, in contrast to 62% of patients in the placebo group, experienced an adverse event (AE) leading to premature withdrawal of the investigational products, most often due to deterioration/relapse of EoE or an esophageal food impaction. Bolus impaction leading to discontinuation of DB the investigational products was observed in 2 patients of the placebo group. No patient needed a dilatation during the DB phase.

The most frequently reported treatment-emergent adverse drug reactions (ADRs) in the budesonide 0.5 mg twice daily treatment group were 17 suspected ADRs of candidiasis, occurring in 12 patients (17.6%) versus none such events in the placebo group. These are known ADRs caused by the immunosuppressive action of budesonide. It is noteworthy that

not all macroscopically suspected fungal infections were confirmed by the Grocott staining. In 5 patients, the suspected candidiasis was histologically confirmed, and finally, in 4 patients, the suspected candidiasis was both histologically confirmed and clinically manifested.

Critical appraisal

The patients' baseline characteristics and prior treatment experience appeared to be roughly balanced at baseline between groups, despite the disease duration since diagnosis and disease duration since first symptoms were shorter in the placebo group than in the budesonide 0.5 mg group, where the mean time since an established EoE diagnosis was 4.3 years, and 3.3 years in the budesonide 0.5 mg, and placebo study groups, respectively, with a mean time since symptom onset of 12.6 years, and 9.6 years, respectively. In addition, fewer patients in the placebo group (5.9%) had a previous esophageal dilatation compared to the budesonide 0.5 mg group (19.1%). The impact of this imbalance on the treatment effect assessment is unknown. A large number of patients discontinued from the trial could also have biased the results on patient-reported outcomes (PROs), HRQoL, and other exploratory outcomes. For example, only 23 out of 68 patients (33.8%) in the placebo group completed the 48 weeks DB phase. Also, MID in the EoE population is not available for any of the PROs assessed. Subjective recall biases in the assessment of clinical relapse would be highly likely, particularly when such recall was differential between treatment groups, due perhaps to patients' or the assessing physicians' awareness of the treatment assignment due to drug-related side effects. Such as, for example, 19.1% of patients in the budesonide 0.5 mg group had suspected AEs of candidiasis, whereas no such events were reported in the placebo group. Moreover, the majority of patients in the placebo group had experienced aggravated conditions of the disease (64.7% versus 16.2%, placebo versus 0.5 mg budesonide, respectively) during the 48 weeks treatment period, which may have led to a recall of more severe or worsening experience of symptoms or pains among patients on placebo than their counterparts on active treatments.

Patients enrolled in the BUL-2/EER trial were deemed to be similar to patients with EoE in Canada, even though no Canadian study site was included in this trial. Only patients with clinico-pathological remission defined as fulfilling both histological remission and resolution of symptoms criteria after receiving budesonide were enrolled, hence results may not be generalizable to patients who achieved clinico-pathological remission using other treatments. If careful medical monitoring was not ensured, patients with cardiovascular disease, diabetes mellitus, osteoporosis, active peptic ulcer disease, glaucoma, cataract, or infection were excluded from the trial, which limit the generalizability of the trial results for patients with other disease comorbidities. The BUL-2/EER trial was designed to demonstrate a superiority over placebo at week 48 and it was unclear how long the patients would remain in remission while on treatment, also it is not clear whether patients would relapse after they stop treatment. Hence the optimal duration of maintenance treatment was not explored. The BUL-2/EER trial excluded patients with severe strictures, which may limit the interpretations of the efficacy findings to patients who have strictures with a predominant inflammatory component.

Indirect Comparisons

No indirect evidence was submitted by the sponsor. An independent search conducted by CADTH did not find any published indirect evidence that met the inclusion criteria of the CADTH review protocol.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults diagnosed with EoE who were refractory to treatment with a PPI, and who achieved clinico-histological remission after a 6- or 12-week induction with budesonide
Treatment	Budesonide orodispersible tablets 0.5 mg twice daily[a]
Submitted price	$4.68 per budesonide 0.5 mg orodispersible tablet
Treatment cost	The annual cost of maintenance therapy with budesonide is $3,413 per patient
Comparator	No maintenance treatment with budesonide[a]
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	Lifetime (46 years)
Key data source	BUL-2/EER maintenance trial
Submitted results for base case	Base Case: ICER = $28,806 per QALY ($50,502 incremental costs, 1.75 incremental QALYs)
Key limitations	• Modelled target population was for patients who were refractory to or who had relapsed on PPI therapy, which differs from the Health Canada indicated population and the reimbursement request, which does not restrict based on experience with PPIs. • The clinical data for maintenance treatment with budesonide is limited to 48 weeks. As such there is uncertainty regarding several key efficacy parameters: ◦ There is limited information on the efficacy of reinduction with budesonide post-recurrence; ◦ The rate of subsequent recurrences after reinduction with budesonide is unknown. • Relevant comparators currently in use for the treatment of EoE in Canada were not considered, such as PPIs and swallowed steroid products designed for inhalation. • The utility associated with active EoE was slightly overestimated given the source of the proxy data. • Clinical data are based on a population of patients who had 6 or 12 weeks of budesonide induction therapy, which does not align with the prior CDEC recommendation for induction in which patients should only receive 6 weeks of treatment.

Component	Description
CADTH reanalysis results	• Given the structure of the sponsor's model and the absence of clinical information for treatment of subsequent recurrence, CADTH was unable to estimate a revised base case. CADTH did examine the cost-effectiveness of budesonide for a single maintenance period up to the first recurrence (i.e., no reinduction) aligning with the available clinical evidence. In doing so, CADTH also corrected the sponsor's model to address limitations with the calculation of utility values. • CADTH estimated that budesonide maintenance therapy was associated with an ICER of $26,645 ($6,478 incremental costs, 0.24 incremental QALYs) compared to no maintenance therapy over a lifetime time horizon, in patients who were refractory to or who had recurred on PPI therapy, and who had responded to initial induction therapy with budesonide when only a single maintenance period up to the first recurrence (i.e., no reinduction) was considered. CADTH considered shorter time horizons to address concerns related to overestimating the predicted clinical benefits from a single maintenance course of budesonide therapy in the absence of additional subsequent treatment; the ICER increased with shorter time horizons. • While the ICER is lower than reported by the sponsor for CADTH's reanalyses, the results are uncertain due to the limitations associated with the available clinical data and do not reflect how budesonide will likely be used in practice over multiple inductions and maintenance treatments. As such the cost-effectiveness of budesonide beyond the initial maintenance treatment is uncertain.

EoE = eosinophilic esophagitis; ICER = incremental cost-effectiveness ratio; PPI = proton pump inhibitor; QALY = quality-adjusted life-year.

[a]Reinduction treatment with budesonide 1 mg twice daily was allowed in the sponsor's base case.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- the modelled population differed from the population represented by the full Health Canada indication
- relevant comparators were omitted
- Non-insured Health Benefits (NIHB) program beneficiaries were double counted and overestimated
- discontinuation due to nonadherence was not accounted for
- the proportion of patients who would undergo induction with budesonide tablets was overestimated
- the population who will receive maintenance therapy after achieving remission is uncertain.

Based on CADTH reanalyses, the budget impact of reimbursing budesonide tablet maintenance therapy after successful induction is expected to be $1,912,994 in year 1, $2,759,703 in year 2, and $4,003,349 in year 3, for a 3-year total budget impact of $8,676,046 ($8,616,914, when not including markups or dispensing fees). The model was most sensitive to assumptions around the population of patients who would be eligible for treatment with budesonide tablets, particularly in relation to whether patients would need to be refractory to or have recurred illness while using PPIs.

Members of the Canadian Drug Expert Committee

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Meeting date: June 16, 2021

Regrets: One CDEC member did not attend.

Conflicts of interest: None