CADTH

CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Review Report

BUDESONIDE (JORVEZA)

(AVIR Pharma Inc.)

Indication: For the induction of clinicopathologic remission in adults with eosinophilic esophagitis

Service Line:	CADTH Common Drug Review
Version:	Final
Publication Date :	December 2020
Report Length:	28 Pages

CADTH

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.

CADTH

Table of Contents

Tables

Figures

CADTH

Abbreviations

AE	adverse event
EoE	eosinophilic esophagitis
GERD	gastroesophageal reflux disease
ICER	incremental cost-effectiveness ratio
PPI	proton pump inhibitor
QALY	quality-adjusted life-year

Executive Summary

The executive summary comprises two tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Budesonide orodispersible tablets (Jorveza), 1 mg oral
Submitted price	Budesonide 1 mg orodispersible tablet: $5.50
Indication	Induction of clinicopathologic remission in adults with eosinophilic esophagitis
Health Canada approval status	NOC
Health Canada review pathway	Priority review
NOC date	November 5, 2019
Reimbursement request	As per indication
Sponsor	AVIR Pharma Inc.
Submission history	Previously reviewed: No

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, in accordance with the BUL-1/EEA trial
Treatment	Budesonide 1 mg orodispersible tablets (budesonide 1 mg) twice daily
Comparator	No treatment
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	1 year
Key data source	2019 BUL-1/EEA, the pivotal 6-week randomized controlled trial
Submitted results for base case (key scenario analyses are also reported)	Base case: ICER = $2,786 per QALY (0.10 incremental QALYs, $275 in incremental costs) Key scenarios: • clinical remission as efficacy outcome — ICER = $4,381 per QALY (0.08 incremental QALYs, $329 in incremental costs) • additional 6 weeks[a] duration of treatment — ICER = $3,042 per QALY (0.13 incremental QALYs, incremental costs)
Key limitations	• The 1-year time horizon does not adequately reflect the chronic recurrent nature of EoE or the need for repeated treatment. The model also does not appropriately reflect clinical practice within the 1-year time horizon. Thus, the analysis does not address the decision problem relevant to the reimbursement of a treatment for EoE in Canada. • Relevant comparators currently used in Canada, such as dietary modifications, off-label PPIs, and off-label inhaled steroids (topically administered), which budesonide 1 mg may displace or be added to, were not included in the model. • Due to a gap in evidence, the modelled population, based on patients in the BUL-1/EEA trial who were all refractory to PPIs, represents only a subset of the population captured in the Health Canada indication. • Utilities are not specific to EoE and the proxy values appear to be overestimated in some health states, increasing uncertainty with the results. • Gastroenterology visits were underestimated for patients who experienced a recurrence of EoE, leading to an underestimation of costs for patients in the recurrence health state.

Component	Description
	• Programming errors within the model lead to inappropriate increases in costs for both the budesonide 1 mg group and the no treatment group.
CADTH reanalysis results	• CADTH reviewers were unable to address the key limitations identified with the sponsor's Pharmacoeconomic Submission due to limitations with the available data and submitted model. • As such, CADTH was unable to report a base-case analysis estimating the cost-effectiveness of budesonide 1 mg in the full indicated population, over a relevant time horizon, against relevant comparators. Exploratory scenarios were conducted over shorter time horizons consistent with a single EoE flare, treatment, and assessment period. • Over a 12-week time horizon, six weeks of therapy with budesonide 1 mg used to induce clinicopathologic remission during a single EoE flare was associated with an ICER of $24,422 per QALY compared to no treatment. Considering a shorter time horizon (6 weeks) or increased duration of budesonide 1 mg treatment (12 weeks) increased the ICER to $74,129 per QALY and $31,133 per QALY, respectively.

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

[a] Patients receiving budesonide 1 mg who did not respond by week 6 could receive an additional six weeks of therapy, for a total of 12 weeks.

Conclusions

The CADTH clinical review findings indicate that budesonide 1 mg is effective for inducing clinicopathologic remission in patients with active eosinophilic esophagitis (EoE) after six weeks of treatment, though the results are more pronounced for clinicohistologic remission than for the symptomatic remission component. The CADTH clinical review also noted uncertainty in the meaningfulness of the observed improvement in health-related quality of life. No information was available on the comparative effectiveness of budesonide 1 mg with treatments that are currently used for EoE in Canada.

Due to structural limitations with the sponsor's model, CADTH was unable to estimate the cost-effectiveness of budesonide 1 mg over a relevant time horizon or compared with relevant comparators currently used for the treatment of EoE in Canada. CADTH was also unable to estimate the cost-effectiveness of budesonide 1 mg in the full population represented by the Health Canada indication, as there is a gap in evidence for patients with EoE who have not been shown to be refractory to proton pump inhibitors (PPIs). Furthermore, the identified limitations also highlighted that the sponsor's model is inadequate to estimate the cost-effectiveness of budesonide 1 mg over the submitted one-year time horizon.

In order to provide some economic information, CADTH estimated the cost-effectiveness of budesonide 1 mg compared with no treatment over a single treatment and assessment period for an EoE flare (considered to range from six to 12 weeks). Based on a time horizon of 12 weeks, with a maximum duration of therapy of six weeks, budesonide 1 mg was associated with an incremental cost-effectiveness ratio (ICER) of $24,422 per quality-adjusted life-year (QALY) compared with no treatment. If a shorter time horizon (six weeks) or an increased maximum duration of budesonide 1 mg treatment (12 weeks) is considered, the ICER increases to $74,129 per QALY and $31,133 per QALY, respectively. The cost-effectiveness of budesonide 1 mg compared with other therapies used in the treatment of EoE in Canada over any time horizon is unknown.

At the submitted price, the drug acquisition cost of budesonide 1 mg orodispersible tablets is $462 for a six-week course of therapy, which is more expensive than other pharmacological therapies currently in use in Canada for the treatment of EoE.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process.

Six Canadian and international patient group submissions were received for this review from these organizations: the Gastrointestinal Society (Canada), the Families Affected by Eosinophilic Disorders (UK), the American Partnership for Eosinophilic Disorders (US), the Campaign Urging Research for Eosinophilic Disease (US), ausEE Inc. (Australia), and the Spanish Association for Eosinophilic Esophagitis (Spain). As these patient groups are of mostly international origin, some input may not apply to current clinical practice or patient experiences in Canada.

The patient groups reported that key pharmacologic treatments for EoE included acid suppressors such as PPIs and corticosteroids (fluticasone and budesonide). Patients reported that corticosteroids generally resulted in remission; however, they are primarily off-label asthma medications that are swallowed from an inhaler or mixed with sweeteners to create a slurry, and the non-specific nature of drug delivery makes the effectiveness varied and uncertain. Systemic drugs such as prednisone were also reportedly used for short periods in acute situations but were not used chronically. The clinical experts consulted by CADTH indicated that systemic steroids are not typically used for EoE in Canada and thus it was appropriate that these were not considered as comparators in this review.

Patient groups expressed an unmet need for a treatment specifically designed for EoE that is reimbursed by public and private payers. Additionally, patients expressed a desire for a convenient medication with clear instructions to assist in adherence. Patients expressed a need for a treatment that improves their day-to-day quality of life (i.e., eating, working, and socializing) and indicated that an effective therapy that resolves clinicopathologic symptoms and has minimum long-term complications is of high importance. Patients with experience with budesonide 1 mg reported that while the medication wasn't curative, it was effective and easy to take for six to 12 weeks. One patient group indicated that further studies and patient follow-up should be conducted for assessment, treatment, and management after 12 weeks.

In their submission, the sponsor accounted for the improved quality of life experienced when EoE symptoms resolve, but did not account for the chronic nature of EoE or compare budesonide 1 mg to therapies currently in use for EoE. Ease of use relative to other available therapies was also not captured in the clinical studies or pharmacoeconomic submission.

Economic Review

The current review is for budesonide 1 mg orodispersible tablets (Jorveza) for the induction of clinicopathologic remission of EoE in adults.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted an economic analysis exploring the cost-effectiveness of budesonide 1 mg orodispersible tablets (budesonide 1 mg) in a population of adult patients (age 18 to 75 years) diagnosed with EoE who were refractory to treatment with a PPI, as defined by the BUL-1/EEA trial in Lucendo et al. (2019),[2] i.e., refractory after at least standard dosages of a PPI for a four-week period. This population is different than the indicated population and the reimbursement request, which do not restrict the population to patients refractory to PPIs.

The recommended dosage of budesonide 1 mg is 2 mg daily (1 mg in the morning and 1 mg in the evening) for a usual duration of six weeks.[3] At the submitted price of $5.50 per 1 mg tablet, the cost per six-week course of budesonide 1 mg therapy is $462 per patient (see Appendix 1).

The sponsor's analysis compares budesonide 1 mg to no treatment, represented by the placebo group of the BUL-1/EEA trial, from the perspective of a Canadian health care payer over a time horizon of 52 weeks. A one-week cycle length was used.

Model Structure

The sponsor submitted a Markov state transition model with three health states: nonresponse, response, and recurrence (see Figure 1 in Appendix 3), where response was defined as clinic-histologic remission. Patients who were refractory to PPI treatment entered the model in the nonresponse health state and could move from nonresponse to response after any of the first six cycles representing the length of therapy in the BUL-1/EEA trial.[2] After these six cycles (i.e., six weeks), patients who were responders had a risk of entering the recurrence state. Patients who entered the recurrence state at any point between week 7 and week 52 were not re-treated and remained in the recurrence state for the remaining duration of the 52-week model. Mortality was not considered, as the sponsor deemed EoE not to have an impact on mortality and due to the short one-year time horizon.

Model Inputs

Patient age at baseline in the model was derived from the BUL-1/EEA trial inclusion criteria; other baseline characteristics were not explicitly considered. Clinical efficacy was based on the proportion of patients achieving clinicohistologic remission in the BUL-1/EEA trial by week 6, and assumed to occur at a linear rate from week 1 through week 6. Clinicohistologic remission was defined as a patient achieving both histologic remission (a peak eosinophil count of less than 16 eosinophils per high-power field) and clinical remission (symptom severity of 2 points or less on each numerical rating scale of 0 to 10 for dysphagia and odynophagia on each day of the week before the end of treatment).[2] Data from the trial's placebo group were used to inform the no-treatment group in the model. In the model, budesonide 1 mg was dosed at 1 mg twice daily, consistent with that given in the trial and as recommended in the product monograph,[3] for six weeks in the base case.

After six weeks, once treatment was stopped, patients in the model who had responded could have a recurrence. Recurrence was calculated from the time to symptom recurrence reported in the full study population of Dellon (2019),[4] an observational study of recurrence in patients with EoE who had achieved a histologic response of less than 15 eosinophils per high-power field after treatment with either oral viscous budesonide or swallowed fluticasone from a multidose inhaler.

As health utilities were not available in the literature for patients with EoE, the sponsor used moderate gastroesophageal reflux disease (GERD) (utility weight = 0.67) as a proxy for the nonresponse health state and mild GERD (utility weight = 0.78) as a proxy for patients who had a recurrence, both reported in Kartman et al. (2004).[5] Patients in the response (remission) health state were assumed to have a quality of life equivalent to the general population (utility weight = 0.87), as reported for the 25 to 44 years age group by the Alberta PROMS and EQ-5D Research and Support Unit,[6] given the mean age in the BUL-1/EEA trial was 37 years.[2]

Patients in the model could experience adverse events (AEs), depending on their health state. Patients within the nonresponse and recurrence health states had a risk of esophageal food impaction, based on converting the probability of impaction reported in a 10-year retrospective cohort study[7] to a weekly rate. It was assumed that 1.73% of food impactions lead to perforation of the esophagus due to esophageal dilation, as reported in a retrospective analysis of patients reporting to a Boston, US, emergency department with food impaction.[8] Patients also had a risk of AEs during the treatment period; AEs that occurred with at least 5% frequency in either group of the BUL-1/EEA trial were included. Patients using budesonide 1 mg in the trial had numerically higher rates of fungal infections; GERD; nervous system disorders; headaches; and vascular disorders while those receiving placebo had higher rates of asthma; respiratory, thoracic, and mediastinal disorders; and pharyngitis (see Table 10).

The sponsor provided an updated economic evaluation that included disutilities associated with AEs, rather than just costs. These disutilities are presented alongside the AEs in Table 10. For AEs that varied by treatment group, utility decrements were applied for the entire treatment period (six weeks), except for local fungal infections, which were assigned a duration of two weeks. For AEs that varied by health state, utility decrements were applied for the mean duration of hospital stay reported by the Ontario Case Costing Initiative for the event.[9]

The drug acquisition cost for budesonide 1 mg was supplied by the sponsor. All patients were assumed to have a gastroenterology consultation at week 6 to assess response. Those who responded were assumed to have no further consultations unless they had a recurrence. Nonresponders were assumed to visit their gastroenterologist for a consultation at week 12, week 24, week 36, and week 48, while patients who had a recurrence were assumed to visit once at the time of recurrence, and at week 24 and week 48, assuming the recurrence occurred before those time points. The cost of a gastroenterology consultation was obtained from the Ontario Schedule of Benefits for Physician Services (see Table 11). Most treatment group-related AEs were not associated with additional costs, with the exception of fungal infections and asthma, which triggered treatment costs for a 14-day course of fluconazole or a salbutamol inhaler, respectively (see Table 11). Costs associated with food impaction were substantially higher, with dysphagia accumulating 2.6 days of inpatient costs, while perforation of the esophagus accrued 13.3 inpatient hospital days.

Summary of Sponsor's Economic Evaluation Results

The sponsor submitted a probabilistic analysis of 5,000 iterations. The results of the deterministic analysis were very similar to the results of the probabilistic analysis.

Base-Case Results

For the induction of clinicohistologic remission in adults with EoE who were refractory to PPIs, when compared to no treatment and over a one-year time horizon from the perspective of a Canadian public health care payer, the sponsor concluded that budesonide 1 mg orodispersible tablets were associated with $275 in increased costs, yielding an additional 0.100 QALYs, for an ICER of $2,786 per QALY.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. no treatment ($/QALY)
No treatment	720	Reference	0.661	Reference	Reference
Budesonide 1 mg	995	275	0.760	0.099	2,786

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Source: Sponsor's Pharmacoeconomic Submission, Table 19.[10]

Sensitivity and Scenario Analysis Results

The sponsor conducted probabilistic scenarios, as well as probabilistic "complementary" analyses and deterministic sensitivity analyses.

Scenario analyses included considering a societal perspective (ICER = $859 per QALY), considering an analysis where efficacy was fitted with an exponential curve such that patients were more likely to respond earlier in treatment rather than later (ICER = $2,532 per QALY), and considering Crohn's disease as a utility proxy for EoE rather than GERD, with nonresponders assumed equivalent to moderate Crohn's disease (utility weight = 0.754) and patients in the recurrence state assumed equivalent to mild Crohn's disease (utility weight = 0.859) (ICER = $4,204 per QALY).

Deterministic sensitivity analyses were conducted by varying model parameters either to the range of their 95% confidence interval, if available, or by 25% around their mean. Of the parameters tested, the model was most sensitive to the relative efficacy of budesonide 1 mg compared to no treatment, the utility value for nonresponders and responders, and the probability of food impaction.

In terms of complementary analyses, the sponsor considered a scenario where efficacy was based on clinical remission rates from the BUL-1/EEA trial,[2] rather than the composite primary efficacy end point of clinicohistologic remission. This analysis reported budesonide 1 mg as associated with 0.08 additional QALYs compared to no treatment, at an incremental cost of $329, resulting in an ICER of $4,381 per QALY. The sponsor also considered a scenario where patients taking budesonide 1 mg who had not achieved a response by week 6 were given an additional six weeks of therapy for a total of 12 weeks of budesonide 1 mg, informed by the open-label period of the BUL-1/EEA trial. This analysis reported budesonide 1 mg as associated with 0.13 additional QALYs compared to no treatment at an incremental cost of $410, resulting in an ICER of $3,042 per QALY.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **Time horizon does not reflect the chronic nature of the condition:** EoE is a chronic condition where patients experience recurrences of inflammation requiring re-treatment or changes in therapy over time. CADTH requested that the sponsor submit a model capable of estimating the cost-effectiveness of budesonide 1 mg over a longer time horizon; however, the sponsor chose to maintain a one-year time horizon, citing the lack of available clinical data over a longer time horizon and the unpredictable nature of EoE flare-ups, which makes it difficult to model. As an example, the sponsor cited the nature, number, and duration of treatment courses with budesonide 1 mg and off-label therapies, adherence rates, frequency of medical visits, treatment responses, and recurrence rates as inputs that would require assumptions due to lack of clinical information.[11] While CADTH acknowledges that the lack of long-term data is a limitation, and extending the time horizon would rely on extrapolation and assumptions, limiting the model to one treatment period and one recurrence without re-treatment does not adequately capture the chronic and recurring nature of EoE. In clinical practice, patients who were not adequately controlled or experience recurrences would receive further treatment and either improve or fail to respond. These patients would accrue additional benefits and costs. The sponsor also cited the short-term use of both budesonide 1 mg and off-label medications currently used to treat EoE — presumably inhaled corticosteroids that are topically (orally) administered or PPIs — as another reason a longer time horizon was unnecessary. However, as budesonide 1 mg was not compared with these therapies, its relative short-term cost-effectiveness compared to them is also unknown. Furthermore, the 52-week model time horizon was considered inappropriate given the infeasibility of the subsequent treatment pathway assumptions within the sponsor's model.
    - Due to the structure of the model, CADTH was unable to conduct reanalyses to consider a longer time horizon.
    - CADTH conducted exploratory analyses over six-week and 12-week time horizons, consistent with the time period for the treatment and assessment of a single EoE flare before further treatment options would normally be offered.
- **Relevant comparators were not considered:** The sponsor compared budesonide 1 mg to no treatment, using the placebo group of the BUL-1/EEA trial as a proxy. However, therapies are currently used in Canada for the treatment of EoE that the availability of budesonide 1 mg may displace or supplement. These include dietary modifications, PPIs, and swallowed corticosteroids designed for inhalation, such as fluticasone or budesonide. As stated in the CADTH Guidelines for the Economic Evaluation of Health Technologies: Canada,[12] comparators should include those currently in use and potentially displaced by the new technology, and should be those that are widely used and that the decision-maker is currently funding. While not indicated for EoE, corticosteroids intended for inhalation and PPIs are accessible to patients with EoE,[13-15] and unlike in the BUL-1/EEA trial, which did not allow the introduction of new dietary restrictions during the trial,[2] patients in clinical practice can be introduced to or switched to different diet regimens if improvement is not observed. A current European guideline recommends that any of PPIs, diet modification, or topical corticosteroid therapy may be offered as first-line therapy,[16] though feedback from clinical experts consulted by CADTH suggested that no specific set of guidelines was followed across Canada.
    - Given the lack of comparative clinical effectiveness information — direct or indirect — CADTH was unable to conduct reanalyses to assess the cost-effectiveness of budesonide 1 mg with currently used treatments.
- Modelled population differs from the Health Canada indication: In order to enrol in the BUL-1/EEA trial, patients had to have been refractory to treatment with a PPI for four to

eight weeks. Patients with PPI-responsive esophageal eosinophilia (i.e., a typical EoE symptom presentation, where GERD is diagnostically excluded, and who demonstrated a clinicopathologic response to PPIs) were excluded from the trial. Health Canada approved budesonide 1 mg for the induction of clinicopathologic remission in adults with EoE without restrictions on prior PPI use.[3] There is an evidence gap between the population in which data exists and the broader, indicated population. No PPIs currently available in Canada have been approved by Health Canada for the treatment of EoE, and the positioning of PPIs in the treatment algorithm for EoE is not clear. Furthermore, the diagnosis of EoE has evolved since the study was undertaken. Recent international clinical guidelines have classified PPIs as a treatment for EoE rather than as a diagnostic criterion,[16, 17] and did not recommend that patients try PPI first and then switch to topical corticosteroids, but rather that either PPIs or topical corticosteroids be first-line pharmacological treatment.[16]

  - Given the lack of clinical data for the Health Canada indicated population, CADTH was unable to conduct reanalyses to adjust for this limitation. Cost-effectiveness information is only available for patients who received budesonide 1 mg after they were refractory to four to eight weeks of PPI therapy.

- **Utilities are not available for EoE and proxy values likely overestimated quality of life:** As health utilities are not available in the literature reflecting patients with EoE and were not derived by the sponsor from the clinical trial, the sponsor used moderate GERD as a proxy for patients who had not responded to treatment, and mild GERD as a proxy for those experiencing a recurrence of EoE-related inflammation. The use of proxy utility values increases the uncertainty of the potential magnitude of gains in QALYs for the indicated population. Additionally, the clinical experts consulted by CADTH did not consider that patients who experienced a recurrence would have a better quality of life than those who had not responded to treatment, and thus the utility value would be better modelled as the same for both health states. The utility value estimate used for patients in the response state was based on utility value for the general population, which is uncertain; it potentially overestimated quality of life for these patients. Although the mean age of patients in the BUL-1/EEA trial was 37,[2] using a general population average utility for 25 to 44 year olds[6] is not appropriate to represent the full population of 18- to 75-year-old patients that the sponsor was seeking to represent within its economic model. Additionally, as stated in the CADTH Clinical Review Report, there is uncertainty in the meaningfulness of the observed improvement in health-related quality of life within the BUL-1/EEA trial; this is relevant to consider given the sponsor's short-term model and interpretation of the QALY gains estimated within the economic model.
  - CADTH tested various alternate assumptions around utility values in exploratory analyses by incorporating a health utility derived from the general population aged 18 to 74 for responders[6] and by assuming both the nonresponse and recurrence states had a health utility equivalent to that of moderate GERD. Alternate assumptions, where the health utility for those in nonresponse and recurrence health states was consistent with mild or severe GERD, were also tested.
- **Gastroenterology visits underestimated during recurrence**: While the clinical experts consulted by CADTH agreed with the sponsor that patients who were responding to therapy would rarely visit their gastroenterologist, they felt the assumption that patients having a recurrence would visit less frequently than those who had not responded was not reflective of clinical practice.
  - CADTH undertook exploratory reanalyses that assumed an equivalent number of visits (every 12 weeks) for patients in the recurrence and nonresponse health states.
- **Programming errors within the model**: The sponsor's model contains a number of programming errors, including a one-week cost of additional budesonide 1 mg applied when a patient enters the recurrence state, and having patients in the nonresponse or recurrence health states visit gastroenterologists at set time points rather than at the frequencies described in the sponsor's Economic Evaluation Report.

- These errors were addressed as corrections to the sponsor's base-case analysis (see Table 5 for additional information).

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (see Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumptions	CADTH comments
Response to treatment occurs in a linear manner for the duration of treatment (6 weeks)	Acceptable for a single initial treatment. The sponsor conducted a scenario analysis exploring an exponential curve to represent time-to-response, which led to a minor reduction in the ICER. However, the sponsor's model does not account for treatment of subsequent flares/recurrences, which impacts the validity of the model.
Mortality was not considered in the model given the lack of mortality associated with EoE and the short time horizon.	Acceptable, given the model structure.
Patients who have not responded have a gastroenterologist visit at 6 weeks to assess results, then another at week 12, week 24, week 36, and week 48. Those who did respond but have a recurrence have a visit at 6 weeks to assess results, another at the time of the recurrence, and then visits at week 24 and week 48 if the recurrence happened prior to each time point.	Inappropriate. The sponsor's method of visit calculation leads to an extra visit beyond the assumption described in its report for almost all patients in either the nonresponse or recurrence health states. Nonresponders would likely be seen every 12 weeks rather than at both 6 weeks and 12 weeks and every 12 weeks thereafter, while the modelling of patients in the recurrence health state leads to some patients having a visit when they have their recurrence, and then immediately afterwards as well (e.g., a recurrence at week 23 followed by a visit at week 24). This was re-estimated in CADTH reanalyses; patients accrued the cost of a gastroenterology consult divided by the frequency at which those in their health state are assumed to visit, each week. This was considered a modelling error rather than a key limitation.
Rate of recurrence was derived from an observational study[4] of recurrence in patients with EoE who had achieved a histologic response of < 15 EOS/HPF after treatment with either oral viscous budesonide or swallowed fluticasone from a multidose inhaler.	Uncertain, but acceptable in the absence of data specific to budesonide 1 mg. Feedback from the clinical experts consulted by CADTH indicated that recurrence rates on withdrawal of the medication are high.

EoE = eosinophilic esophagitis; EOS = eosinophil; HPF = high-power field; ICER = incremental cost-effectiveness ratio.

CADTH Reanalyses of the Economic Evaluation

CADTH's appraisal of the sponsor's economic evaluation identified major limitations with the structure of the submitted economic model. The sponsor's model did not account for the chronic recurring nature of EoE and the expected use of budesonide 1 mg in clinical practice. Furthermore, the sponsor did not compare budesonide 1 mg to comparators considered to be relevant based on current treatment practices in Canada. An additional challenge is that the population studied does not align with the indicated population. Though this data gap is acknowledged and, based on correspondence with Health Canada, justified, it remains an area of uncertainty. As such, CADTH was unable to undertake reanalyses that would result in a reasonable estimate of the cost-effectiveness of budesonide 1 mg in the indicated population over a relevant time horizon against relevant comparators.

CADTH undertook exploratory analyses that incorporated revisions to the model to address errors identified in the sponsor's analysis, as well as to adjust utility values in the recurrence and response health states, and resource use in the recurrence state to address identified limitations (see Table 5). Scenario A, described in Table 5, assumes the same one-year

time horizon submitted by the sponsor. As the structure of the model was not flexible enough to allow patients who did not respond, or who responded and then had a recurrence, to receive and possibly respond to further or alternate treatment as would occur in clinical practice, this limits the validity of the 52-week analysis.

CADTH reviewers attempted to estimate the cost-effectiveness of budesonide 1 mg only during the first episode of EoE after a patient's initial failure to respond to PPI therapy. Patients in clinical practice would be assessed by their physicians either at the end of therapy (i.e., at six weeks), or at their next specialist appointment, which, according to the clinical experts consulted by CADTH, are often scheduled at 12 weeks after beginning therapy. Scenarios B, C, and D, also described in Table 5, explore time horizons of six weeks and 12 weeks, as well as maximum durations of budesonide 1 mg therapy of six weeks, as allowed in the double-blind period of the BUL-1/EEA trial, and 12 weeks for patients who did not respond by week 6, as allowed in the trial's open-label extension.[1, 2]

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Additional cycle of budesonide 1 mg cost at recurrence removed	Contrary to the assumptions described in the sponsor's submission,[a] and the dosing described in the clinical trial[b] and product monograph,[c] patients newly entering the recurrence state accrued a single additional cycle (i.e., 1 week) cost of budesonide 1 mg.	There is no additional cost of budesonide 1 mg when entering the recurrence state. Modelling the possibility of receiving further treatment upon recurrence would require a longer duration of that treatment and the potential to return to the remission health state.
2. Gastroenterology visits made consistent with sponsor's method description	Patients who respond and do not recur visit gastroenterologist at week 6. Patients who do not respond visit at week 6, week 12, week 24, week 36, and week 48. Patients who respond and recur visit at week 6 and then at their recurrence, and then at week 24 and week 48 if their recurrence was before these time points.	Patients visit the gastroenterologist at week 6 for assessment, and then accrue the cost of a gastroenterology visit every cycle divided by the assumed visiting frequency of the health state they are in (never for responders, every 12 weeks for nonresponders, and every 24 weeks when a recurrence happens). The cost is average.
Changes to derive the CADTH exploratory analyses		
1. Utility in recurrence state	Patients in recurrence state had health utility consistent with mild GERD (0.78) rather than moderate as nonresponders did (0.67).	Patients in recurrence state had the same health utility as those in the nonresponse state (0.67).
2. Resource use in recurrence state	Patients with recurrence also saw their gastroenterologist less frequently (every 24 weeks) than nonresponders (every 12 weeks).	Patients with recurrence saw their gastroenterologist at the same frequency as nonresponders (every 12 weeks).
3. Responder utility consistent with general population	Patients in the response state had a health utility consistent with the general population aged 25 to 44 years (0.87).[d]	Patients in the response state had a health utility consistent with the general population aged 18 to 75 years (0.84).[d]
CADTH combined exploratory analysis		1+ 2 + 3

CADTH scenario analyses		
CADTH scenarios	**Sponsor's value or assumption**	**CADTH value or assumption**
Scenario A: 1-year time horizon, maximum treatment duration of 6 weeks	As described in this table in sponsor's base case with corrections	As described in this table in corrections and CADTH combined exploratory analyses, with the time horizon and treatment duration specified in the CADTH scenarios
Scenario B: 6-week time horizon, maximum treatment duration of 6 weeks		
Scenario C: 12-week time horizon, maximum treatment duration of 6 weeks		
Scenario D: 12-week time horizon, maximum treatment duration of 12 weeks for patients who did not respond by week 6		

[a] Sponsor's Submission.[18]

[b] BUL-1/EEA trial[2]

[c] Jorveza product monograph[3]

[d] Alberta Population Norms for EQ-5D-5L.[6]

Results for the scenarios previously described can be found in Table 6. Reducing the time horizon has a substantial impact on the cost-effectiveness of budesonide, increasing the ICER to between $24,000 and $74,000 per QALY gained. Additional scenarios and a stepped analysis can be found in Appendix 4 (Table 13 and Table 14).

Table 6: Summary of CADTH Economic Reanalysis Scenarios

Scenario	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
A. 1-year time horizon, 6-week maximum duration of therapy				
Sponsor's inputs[a]	No treatment	704	0.662	Reference
	Budesonide 1 mg	952	0.760	2,538
CADTH inputs[b]	No treatment	702	0.662	Reference
	Budesonide 1 mg	987	0.733	3,994
B. 6-week time horizon, 6-week maximum duration of therapy				
Sponsor's inputs[a]	No treatment	133	0.076	Reference
	Budesonide 1 mg	600	0.084	64,960
CADTH inputs[b]	No treatment	133	0.076	Reference
	Budesonide 1 mg	600	0.083	74,129
C. 12-week time horizon, 6-week maximum duration of therapy				
Sponsor's inputs[a]	No treatment	259	0.153	Reference
	Budesonide 1 mg	667	0.173	19,610
CADTH inputs[b]	No treatment	207	0.153	Reference
	Budesonide 1 mg	641	0.170	24,422
D. 12-week time horizon, nonresponders using budesonide receive an additional 6 weeks of therapy (up to 12 weeks total)				
Sponsor's inputs[a]	No treatment	260	0.153	Reference
	Budesonide 1 mg	866	0.177	25,136
CADTH inputs[b]	No treatment	207	0.153	Reference
	Budesonide 1 mg	853	0.173	31,133

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[a] Inputs not related to the time horizon or the maximum duration of therapy are as described in the sponsor's base-case analysis, with corrections as described in Table 5.

[b] Inputs not related to the time horizon or the maximum duration of therapy are as described in Table 5, CADTH"s combined exploratory analysis.

For scenario B, where both the maximum treatment duration and the time horizon were six weeks, a 35% reduction in the drug acquisition cost of budesonide 1 mg would be required to achieve an ICER of less than $50,000 per QALY.

Issues for Consideration

Budesonide nebules: In addition to swallowed fluticasone powder for inhalation, swallowed budesonide suspension for inhalation, available in nebules, has been used to treat EoE in Canada. According to the clinical experts consulted by CADTH, the suspension is typically mixed with a sweetener or other vehicle to make it more palatable and increase viscosity to prolong contact with the esophagus. Health Canada stipulates that the compounding of pharmaceuticals should only occur if there is a lack of product availability and not solely for economic reasons;[19] however, some off-label use of budesonide nebules may continue to occur despite the availability of budesonide 1 mg. At the Ontario Drug Benefit Formulary list price, budesonide nebules used in this manner are less expensive than the submitted price for budesonide 1 mg (see Table 8 in Appendix 1).

Duration of therapy: The clinical experts consulted by CADTH indicated that, given the tendency for specialists to see patients every three months, as well as the increase in clinicohistologic responders from 57.6% of patients to 84.7% when nonresponders were offered an additional six weeks of budesonide 1 mg therapy reported in the BUL-1/EEA trial,[2] it is likely that some clinicians may choose to prescribe 12 weeks of budesonide 1 mg tablets, despite the product monograph statement that the usual duration of therapy is six weeks.[3] While the sponsor included a scenario where nonresponders were given an additional six weeks of budesonide 1 mg therapy, which was further explored in CADTH reanalyses, the clinical effectiveness and cost-effectiveness of patients receiving an initial prescription for 12 weeks is unknown. At the submitted price, the cost of 12 weeks of budesonide therapy would be $924.

Treatment efficacy in Canadian practice: The CADTH clinical review indicated that the study patients represented a population that was more likely to respond to budesonide 1 mg. How the drug may be used and its effectiveness in a real-world setting (i.e., as an add-on for those patients on concurrent treatment with dietary restriction, PPI, or other therapies) is unknown.

Maintenance therapy: A guideline by Lucendo et al.[16] indicated that for patients who respond to topical corticosteroids, continued long-term treatment is effective in maintaining remission in a proportion of patients. This recommendation is in line with guidance provided by the clinical experts consulted by CADTH regarding long-term treatment with topical corticosteroids, who indicated that some patients might require long-term maintenance therapy with budesonide for one year in order to maintain remission. Patients from the BUL-1/EEA trial who had no clinical symptoms at the end of treatment or withdrawal visit could participate in a double-blind, randomized, placebo-controlled maintenance of remission trial, if eligible.[20] This trial is not yet complete, and budesonide 1 mg is not currently indicated for maintenance use in Canada.[3] On March 26, 2020, the Committee for Medicinal Products for Human Use of the European Medical Agency adopted a change to the duration of treatment allowing the use of budesonide 0.5 mg or 1 mg twice daily as maintenance therapy for EoE, recommended for adult patients with long-standing disease or a high extent of esophageal inflammation in their acute disease state. The duration of this maintenance therapy is to be determined by the treating physician.[21]

Overall Conclusions

The BUL-1/EEA trial demonstrated that budesonide 1 mg was effective in inducing clinicohistologic remission in 57.6% of patients by week 6, compared to 0% of patients in the placebo group.[2] This aligns with the findings of the CADTH clinical review, although the reviewers noted that the results were more pronounced for clinicohistologic remission than the symptomatic remission component. The CADTH clinical review also noted uncertainty in the meaningfulness of an observed improvement in health-related quality of life, while highlighting the lack of available information on the comparative effectiveness of budesonide 1 mg with treatments that are currently used for EoE in Canada. Feedback provided from patient group input indicated that budesonide 1 mg tablets appear to meet the need for a medication with clear instructions to assist adherence.

Due to structural limitations with the sponsor's model, CADTH was unable to estimate the cost-effectiveness of budesonide tablets over a relevant time horizon or against relevant comparators already in use for the treatment of EoE in Canada. CADTH was also unable to estimate the cost-effectiveness of budesonide in the full population represented by the Health Canada indication, as there is a gap in evidence regarding patients with EoE who have not been shown to be refractory to PPIs. The sponsor's model is inadequate to estimate the cost-effectiveness of budesonide 1 mg over the submitted one-year time horizon.

CADTH estimated the cost-effectiveness of budesonide 1 mg compared to no treatment over a single EoE flare (considered to range from six to 12 weeks), including the treatment and assessment period. Based on a time horizon of 12 weeks, with a maximum duration of therapy of six weeks — the "usual duration of therapy" specified in the product monograph — budesonide 1 mg was associated with an ICER of $24,422 per QALY compared to no treatment. Considering a shorter time horizon (six weeks) or an increased maximum duration of budesonide 1 mg treatment (12 weeks) increase the ICER to $74,129 per QALY and $31,133 per QALY, respectively. The cost-effectiveness of budesonide 1 mg compared to other therapies used in the treatment of EoE in Canada over a 12-week time horizon is unknown, as is the cost-effectiveness over longer time horizons.

At the submitted price, the drug acquisition cost of budesonide orodispersible tablets is $462 for a six-week course of therapy, which is more expensive than other pharmacological therapies currently in use in Canada for the treatment of EoE.

Appendix 1: Cost Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts. Comparators may be recommended (appropriate) practice or actual practice. Existing product listing agreements are not reflected in the table and, as such, the table may not represent the actual costs to public drug plans.

Table 7: CADTH Cost Comparison Table for Eosinophilic Esophagitis

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily cost ($)	Course cost ($)
Budesonide (Jorveza)	**1 mg**	**Orodispersible tablet**	**5.5000[a]**	**2 mg daily: 1 mg in the morning and 1 mg in the evening**	**11.00**	**6 weeks: 462**
Topical steroids						
Fluticasone propionate (Flovent)	50 mcg 125 mcg 250 mcg	HFA metered dose inhaler, 120 doses	24.9300 43.0000 86.0000	500 mcg to 1,000 mcg daily in divided doses, swallowed	1.43 to 2.87	3 months: 129 to 258
Proton pump inhibitors						
Dexlansoprazole (Dexilant)	30 mg 60 mg	Delayed release cap	2.2461[b]	30 mg to 60 mg daily	2.25	3 months: 202
Esomeprazole (generic)	20 mg 40 mg	Delayed release tab or cap	0.5500[c]	20 mg to 40 mg daily[d]	0.55	3 months: 50
Lansoprazole (generic)	15 mg 30 mg	Delayed release cap	0.5000	30 mg once or twice daily[d]	0.5 to 1.00	3 months: 45 to 90
Omeprazole (generic)	20 mg	Regular or delayed release tab or cap	0.2287	20 mg to 40 mg daily[d]	0.23	3 months: 21 to 41
Pantoprazole (generic)	20 mg 40 mg	Enteric coated tab	0.1803[c] 0.1875	40 mg once or twice daily[d]	0.19 to 0.38	3 months: 17 to 34
Rabeprazole (generic)	10 mg 20 mg	Enteric coated tab	0.0669 0.1338	20 mg once or twice daily[d]	0.13 to 0.27	3 months: 12 to 24

Cap = capsule; GERD = gastroesophageal reflux disease; HFA = hydrofluoralkane; tab = tablet.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed December 2019), unless otherwise indicated, and do not include dispensing fees.

[a] Sponsor's submitted price.

[b] IQVIA Delta PA wholesale price (accessed December 2019).

[c] Saskatchewan Formulary list price (accessed December 2019).

[d] Standard and double-dose recommendations for the treatment of GERD or erosive esophagitis, as per individual product monographs and the 2014 National Institute for Health and Care Excellence *Clinical Guideline 184: Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management*, Appendix A.[22]

Table 8: CADTH Cost Comparison Table for Eosinophilic Esophagitis and Other Budesonide Products

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily cost ($)	Course cost ($)
Budesonide (Pulmicort Nebuamp)	0.125 mg/mL 0.250 mg/mL 0.500 mg/mL	Nebuamp suspension	0.1714 0.4630 0.6839	2 mg daily, swallowed, in divided doses	2.74	8 weeks: 153

Note: All prices are from the Ontario Drug Benefit Formulary (accessed December 2019), unless otherwise indicated, and do not include dispensing fees.

Appendix 2: Submission Quality

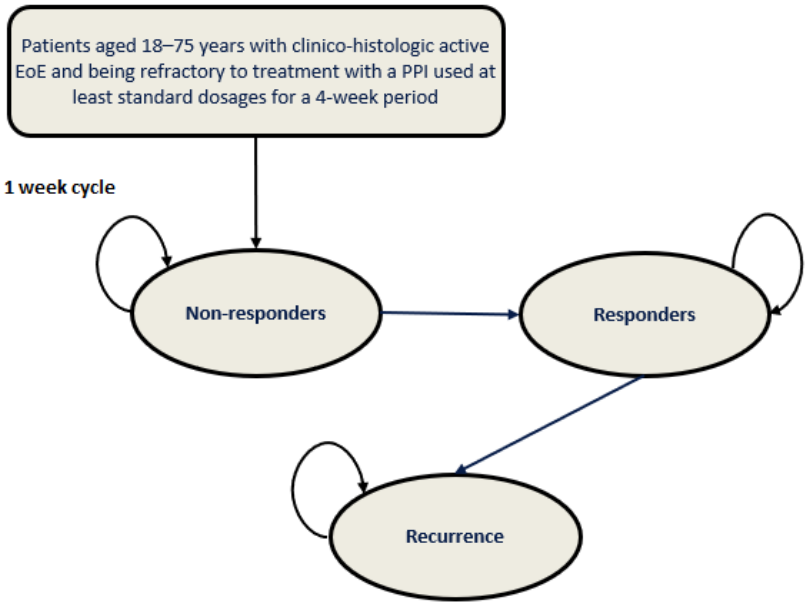
Table 9: Submission Quality

Description	Yes	No	Comments
Population is relevant, with no critical intervention missing and no relevant outcome missing	☐	☒	Population is patients with EoE who had not responded to PPIs, whereas the indicated population was adult patients with EoE. Patients with EoE are currently treated with diet restrictions, PPIs, and/or topical corticosteroids, while the model assumes they are not treated. See the Appraisal of the Sponsor's Economic Evaluation section.
Model has been adequately programmed and has sufficient face validity	☒	☐	The model was generally adequately programmed, although inefficiencies slow the model as later iterations are run.
Model structure is adequate for decision problem	☐	☒	EoE is a chronic condition where patients will have recurrences throughout their lifetime requiring re-treatment and impacting costs and quality of life. The sponsor was given the opportunity to provide a model with a more flexible and longer time horizon but declined, citing a lack of data to inform such an analysis.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☒	☐	No comments.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☐	☒	Analyses were adequate within the confines of the model structure; however, the model structure was not adequate to inform the decision problem.
The submission was well organized and complete, and the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	☐	☒	The information was well organized and easy to locate; however, the methods reporting was sometimes inaccurate in subtle ways (e.g., gastroenterology visits, extra budesonide 1 mg costs, confusion regarding number of iterations run).

EoE = eosinophilic esophagitis; PPI = proton pump inhibitor.

Appendix 3: Detailed Information on the Submitted Economic Evaluation

Figure 1: Model Structure

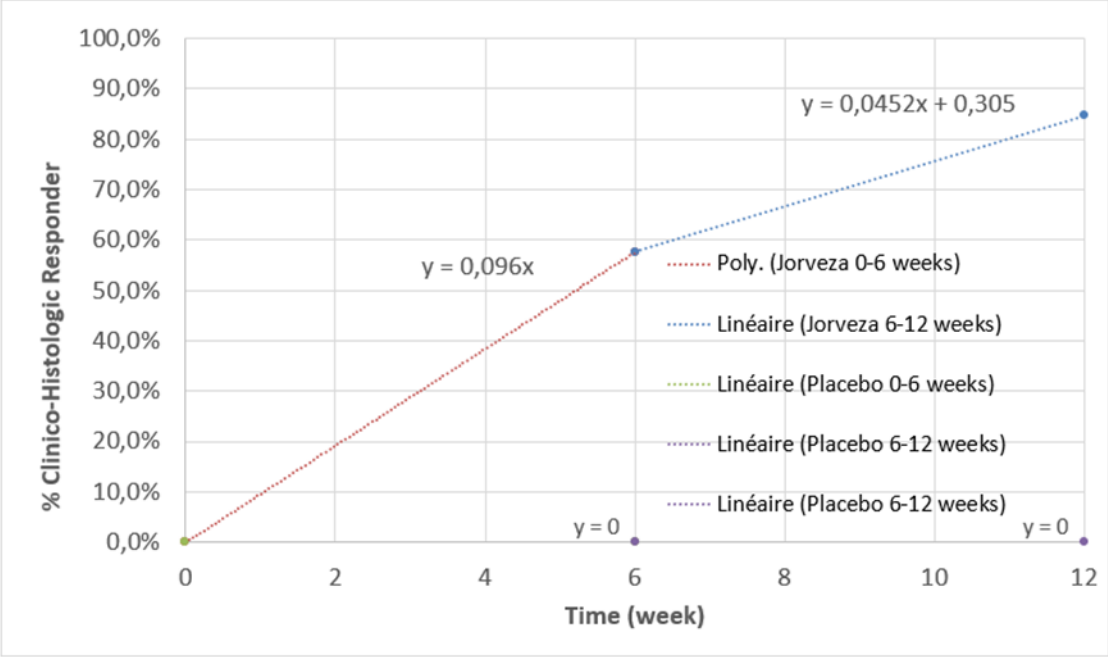


EoE = eosinophilic esophagitis; PPI = proton pump inhibitor.

Source: Sponsor's Pharmacoeconomic Submission, Figure 2.[10]

Transition from the nonresponse to the response state during the first six weeks of the model was derived from the 57.6% (95% CI, 38.2% to 72.0%) of budesonide 1 mg patients and 0% of placebo patients who had achieved clinicohistologic remission at week 6 of the BUL-1/EEA trial,[2] as shown in Figure 2.

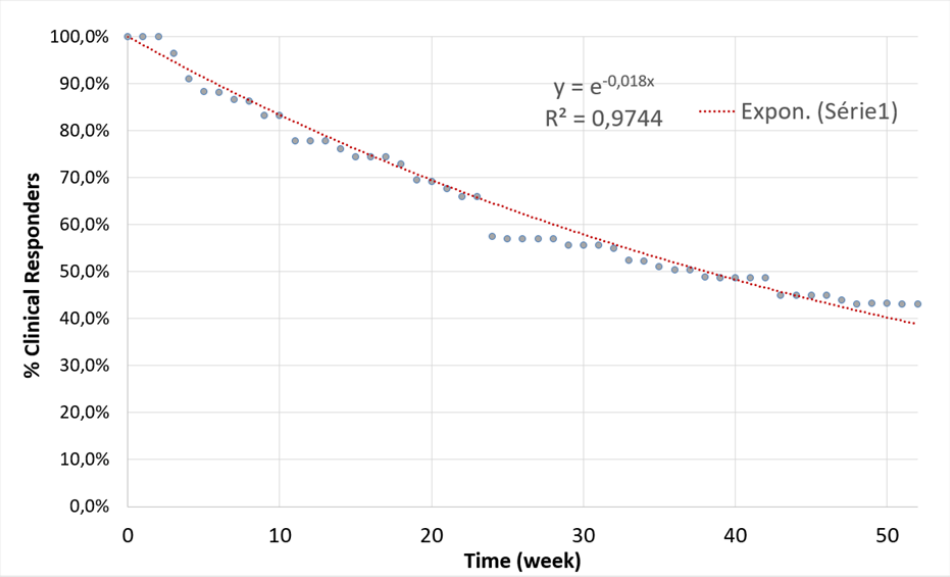
Figure 2: Sponsor-Estimated Trendline for Clinicohistologic Remission



Linéaire = linear; Poly = polynomial.
Note: The sponsor's base case assumed budesonide 1 mg treatment stopped at six weeks, consistent with the blinded portion of the BUL-1/EEA trial and represented by the red line (y = 0.096x). A complementary analysis assumed budesonide 1 mg nonresponders would receive an additional six weeks of budesonide 1 mg therapy, consistent with the open-label portion of the BUL-1/EEA trial and represented by the blue line (y = 0.0452x + 0.305).[1, 2]
Source: Figure 3, Sponsor's Pharmacoeconomic Submission.

Recurrence rates in responding patients once treatment was discontinued at week 6 were derived from a 2019 observational study[4] following a randomized controlled trial[23] (see Figure 3).

Figure 3: Sponsor-Estimated Trendline for Recurrence After Treatment Discontinuation



Expon = exponential.

Source: Sponsor's Pharmacoeconomic Submission, Figure 6.[10]

The probability of AEs as well as the disutility and duration assigned for each event can be found in Table 10. Most AEs were assumed to have a duration equivalent to treatment duration (six weeks), while fungal infections were assigned a duration of two weeks and food impaction-related events were assigned durations equivalent to mean length of hospital stay for the events in question.

Table 10: Probability and Disutility of Treatment-Related Adverse Events by Treatment Group

Probability of adverse event	Budesonide 1 mg	No treatment (placebo)	Disutility	Duration of utility decrement
Adverse events that vary by treatment group				
Histologically confirmed local fungal infection	16.9%	0.0%	−0.0300	14 days
Gastroesophageal reflux disease	5.1%	0.0%	−0.0216	42 days
Nervous system disorders	8.5%	3.4%	−0.0494	42 days
Asthma	0.0%	6.9%	−0.0213	42 days
Blood cortisol, decreased	5.1%	0.0%	0	42 days
Headache	6.8%	3.4%	−0.0297	42 days
Respiratory, thoracic, and mediastinal disorders	3.4%	6.9%	−0.0277	42 days
Vascular disorders	5.1%	0.0%	−0.0059	42 days
Pharyngitis	1.7%	6.9%	−0.0009	42 days
Adverse event that vary by health state				
Esophageal food impaction[a]	0.07%		−0.3530	2.6 days[b]

Probability of adverse event	Budesonide 1 mg	No treatment (placebo)	Disutility	Duration of utility decrement
Perforation of esophagus[a] due to dilation	1.73% of those with impaction		−0.3295 (weighted average)	13.3 days[c]
Treated conservatively	67.1% of perforations		−0.2420	13.3 days[c]
Treated surgically	32.9% of perforations		−0.5080	13.3 days[c]

[a] Applies only in nonresponse and recurrence health states.

[b] All patients with food impaction were assumed to have dysphagia, with the utility decrement for dysphagia applied for the mean length of a dysphagia-related hospital stay from the Ontario Case Costing Initiative Cost Analysis Tool.[9]

[c] Mean length of hospital stay for perforations from the Ontario Case Costing Initiative Cost Analysis Tool.[9]

Source: Sponsor's Pharmacoeconomic Submission, tables 3, 5, and 6;[10] probability of adverse events by treatment group is as reported in the BUL-1/EEA trial.

Initial costs related to diagnosis and treatment initiation were assumed to be equal between groups and were not included. Other costs are outlined in Table 11.

Table 11: Resource Use and Costs

Resource	Cost	Frequency/duration
Gastroenterology visit: On treatment	$105.25[a]	Once at week 6
Gastroenterology visit: Post-treatment	$105.25[a]	Response: None Nonresponse: At week 12, week 24, week 36, and week 48 Recurrence: When recurrence occurred, as well as at week 24 and week 48 if the recurrence occurred prior to that time point
Confirmed local fungal infection Fluconazole Physician visit Total	 $32.05 $77.20 $109.25	14 days
Asthma Salbutamol inhaler Physician visit Total	 $5.00[b] $77.20[a] $82.20	Once
Esophageal dysphagia	$4,613	2.6 days of inpatient care[9]
Perforation of the esophagus	$21,411	13.3 days of inpatient care[9]

Source : Sponsor's Pharmacoeconomic Submission, tables 8, 9, and 10.[10]

[a] Ontario Ministry of Health Schedule of benefits for physician services.[24]

[b] Ontario Drug Benefit Formulary list price.[14]

Detailed Results of the Sponsor's Base Case

A description and summary of the sponsor's base case can be found in the main report and in Table 3. More detailed cost and QALY breakdowns can be found in Table 12. The increased cost associated with budesonide 1 mg is due to its drug acquisition cost, partially offset by decreased resource and AE costs. The vast majority of QALY gains are due to the clinic-histologic response of patients treated with budesonide 1 mg compared to no treatment, represented by the placebo group of the BUL-1/EEA trial,[2] with a very small QALY benefit due to lower AE rates.

Table 12: Cost and QALY Breakdown of Sponsor's Probabilistic Base Case

	Budesonide 1 mg, mean (SD)	No treatment, mean (SD)	Incremental ($)
Costs ($)			
Drug costs	487 (7)	0 (0)	487
AE costs	141 (40)	193 (56)	−52
Resource use costs[a]	367 (42)	526 (0)	−159
Total costs	**995 (66)**	**720 (56)**	**275**
QALYs			
QALYs associated with response	0.329 (0.09)	0.000 (0.00)	0.329
QALYs associated with nonresponse	0.302 (0.09)	0.667 (0.03)	−0.365
QALYs associated with recurrence	0.131 (0.04)	0.000 (0.00)	0.131
Disutilities associated with AEs	−0.002 (0.00)	−0.006 (0.00)	0.004
Total QALYs	**0.760 (0.03)**	**0.661 (0.03)**	**0.090**

AE = adverse event; QALY = quality-adjusted life-year.

[a] Gastroenterology consultations.

Source: Sponsor's Pharmacoeconomic Submission, model base-case results.[10]

Appendix 4: CADTH Detailed Reanalyses and Sensitivity Analyses of the Economic Evaluation

Results of CADTH Exploratory Analyses

When considering only a six-week time horizon as representing the initial EoE episode (scenario B), CADTH's reanalyses found that six weeks of budesonide 1 mg therapy was associated with an additional 0.007 QALYs at an additional cost of $467, leading to an ICER of $74,129 per QALY when compared to no treatment. However, rather than at six weeks, patients are likely to be evaluated at 12 weeks (three months) in clinical practice, at which point further treatment decisions may be made that cannot be explored within the submitted model. Assuming this 12-week time horizon, six weeks of budesonide 1 mg therapy was associated with an ICER of $24,422 per QALY compared to no treatment (scenario C). When patients who had not responded after six weeks were given an additional six weeks of budesonide 1 mg, for a total of 12 weeks, budesonide 1 mg was associated with an ICER of $31,133 per QALY compared to no treatment (scenario D).

As an example, a step-wise analysis of the changes made by CADTH to the sponsor's model, as described in Table 5, is presented for scenario A in Table 13.

Table 13: Example Summary of the Stepped Analysis of the CADTH Exploratory Reanalysis Results, Scenario A — One-Year Time Horizon

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Sponsor's base case	No treatment	720	0.661	Reference
	Budesonide 1 mg	995	0.760	2,786
Sponsor's corrected base case	No treatment	704	0.662	Reference
	Budesonide 1 mg	952	0.760	2,538
CADTH reanalysis 1: Utility in recurrence	No treatment	703	0.662	Reference
	Budesonide 1 mg	952	0.742	3,118
CADTH reanalysis 2: Resource use in recurrence	No treatment	703	0.662	Reference
	Budesonide 1 mg	988	0.760	2,911
CADTH reanalysis 3: Response utility	No treatment	702	0.661	Reference
	Budesonide 1 mg	952	0.750	2,812
CADTH combined exploratory analysis (1 through 3)	No treatment	702	0.662	Reference
	Budesonide 1 mg	987	0.733	3,994

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

In order to explore uncertainty within the CADTH reanalysis scenarios, sensitivity analyses were run on scenario C. These included using clinical remission as the clinical efficacy outcome rather than clinic-histologic remission, and assuming the health utility of active EoE (nonresponse and recurrence) was equivalent to mild or severe GERD, respectively, rather than moderate GERD. As shown in Table 14, the model is sensitive to changes in assumption around the definition of response to therapy and the severity of active EoE on quality of life.

Table 14: Sensitivity Analyses Around CADTH Scenario C

Scenario	Input change from Scenario C	Drug	ICER ($/QALY)
CADTH scenario C	No changes Clinical input: Clinicohistologic remission Active EoE utility equivalent to moderate GERD (0.67)	No treatment	Reference
		Budesonide 1 mg	24,422
Clinical remission	Clinical input: Clinical remission	No treatment	Reference
		Budesonide 1 mg	33,268
Active EoE QoL impact is less severe	Active EoE utility equivalent to mild GERD (0.78)	No treatment	Reference
		Budesonide 1 mg	65,425
Active EoE QoL impact is more severe	Active EoE utility equivalent to severe GERD (0.49)	No treatment	Reference
		Budesonide 1 mg	12,097

EoE = eosinophilic esophagitis; GERD = gastroesophageal reflux disease; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; QoL = quality of life.

References

1. Clinical Study Report: BUL-1/EEA. Double-blind, randomized, placebo-controlled, phase III trial on the efficacy and tolerability of a 6-week treatment with budesonice effervescent tablets vs. placebo for induction of clinico-pathological remission in adult patients with active eosinophilic esophagitis [CONFIDENTIAL internal sponsor's report]. Freiburg (DE): Dr. Falk Pharma GmbH; 2017.
2. Lucendo AJ, Miehlke S, Schlag C, et al. Efficacy of Budesonide Orodispersible Tablets as Induction Therapy for Eosinophilic Esophagitis in a Randomized Placebo-Controlled Trial. *Gastroenterology.* 2019;157(1):74-86 e15.
3. Jorveza (budesonide): 1 mg, orodispersible tablets [product monograph]. Blainville (QC): AVIR Pharma Inc.; 2019 Nov 5.
4. Dellon ES, Woosley JT, Arrington A, et al. Rapid Recurrence of Eosinophilic Esophagitis Activity After Successful Treatment in the Observation Phase of a Randomized, Double-Blind, Double-Dummy Trial. *Clin Gastroenterol Hepatol.* 2019.
5. Kartman B, Gatz G, Johannesson M. Health state utilities in gastroesophageal reflux disease patients with heartburn: a study in Germany and Sweden. *Med Decis Making.* 2004;24(1):40-52.
6. Alberta Population Norms for EQ-5D-5L. Edmonton (AB): Alberta PROMS and EQ5D Research and Support Unit: https://apersu.ca/about-eq-5d/norms/. Accessed 2020 Jan 29.
7. Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc.* 2014;79(4):577-585 e574.
8. Sengupta N, Tapper EB, Corban C, Sommers T, Leffler DA, Lembo AJ. The clinical predictors of aetiology and complications among 173 patients presenting to the Emergency Department with oesophageal food bolus impaction from 2004-2014. *Aliment Pharmacol Ther.* 2015;42(1):91-98.
9. Ontario Case Costing Analysis Tool. Toronto (ON): Ontario Ministry of Health and Long-Term Care; 2019: https://stage.hsim.health.gov.on.ca/hdbportal/. Accessed 2020 Jan 23.
10. Pharmacoeconomic evaluation - Updated Version. In: CDR submission: Jorveza (budesonide), 1 mg, orodispersible tablets [CONFIDENTIAL sponsor's submission]. Blainville (QC): AVIR Pharma Inc.; 2020 Jan.
11. Avir Pharma response to January 17th 2020 CDR request for additional information regarding Jorveza CDR review. [CONFIDENTIAL additional sponsor's information]. Avir Pharma 2020 March 1.
12. Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa (ON): CADTH; 2017: https://www.cadth.ca/dv/guidelines-economic-evaluation-health-technologies-canada-4th-edition. Accessed 2020 Feb 7.
13. B. C. Government. BC PharmaCare formulary search. 2019; https://pharmacareformularysearch.gov.bc.ca. Accessed 2020 Feb 7.
14. Ontario Ministry of Health Long-Term C. Ontario drug benefit formulary/comparative drug index. 2019; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2020 Feb 14.
15. Saskatchewan Drug Plan. Saskatchewan Online Formulary Database. 2020; http://formulary.drugplan.ehealthsask.ca/SearchFormulary. Accessed 2020 Mar 14.
16. Lucendo AJ, Molina-Infante J, Arias A, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterol J.* 2017;5(3):335-358.
17. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. *Gastroenterology.* 2018;155(4):1022-1033.e1010.
18. Pharmacoeconomic evaluation. In: CDR submission: Jorveza (budesonide), 1 mg, orodispersible tablets [CONFIDENTIAL sponsor's submission]. Blainville (QC): AVIR Pharma Inc.; 2019 Nov
19. Policy on manufacturing and compounding drug products in Canada (POL-0051). Ottawa (ON): Health Canada; 2009: https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/policy-manufacturing-compounding-drug-products.html#a51. Accessed 2020 Apr 20.
20. Dr. Falk Pharma GmbH. Maintenance of remission with budesonide orodispersible tablets vs. placebo in eosinophilic esophagitis (EOS-2). Clinical Trials.gov. Bethesda (MD): U.S. National Library of Medicine; 2020: https://clinicaltrials.gov/ct2/show/NCT02493335. Accessed 2020 Mar 23.
21. Committee for Medicinal Products for Human Use. Assessment report: Jorveza (budesonide) [License extension] London (GB): European Medicines Agency; 2020 March 26: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/jorveza. Accessed 2020 Apr 3.
22. Gastro-oesophageal reflux disease and dyspepsia in adults: Investigation and management, Appendix A: Dosage information on proton pump inhibitors. [CG184]. 2014; https://www.nice.org.uk/guidance/cg184/chapter/Appendix-A-Dosage-information-on-proton-pump-inhibitors. Accessed 2019 Dec 18.
23. Dellon ES, Woosley JT, Arrington A, et al. Efficacy of Budesonide vs Fluticasone for Initial Treatment of Eosinophilic Esophagitis in a Randomized Controlled Trial. *Gastroenterology.* 2019;157(1):65-73 e65.
24. Ontario Ministry of Health Long-Term C. Schedule of benefits for physician services under the Health Insurance Act: effective March 1, 2016. Toronto (ON): The Ministry of Health and Long-Term Care; 2015: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20181115.pdf. Accessed 2020 Feb 7.