BRITISH COLUMBIA | Ministry of Health

# Drug Coverage Decision for B.C. PharmaCare

**About PharmaCare** B.C. PharmaCare is a government-funded drug plan. It helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.

## Details of Drug Reviewed

| **Drug** | **budesonide** |
|---|---|
| Brand Name | Jorveza™ |
| Dosage Forms | 0.5 mg and 1 mg orodispersible tablets |
| Manufacturer | Avir Pharma Inc. |
| **Submission Type** | **New Submission** |
| Use Reviewed | For the induction and maintenance of clinico-pathological remission in adults with eosinophilic esophagitis (EoE) |
| Common Drug Review (CDR) | Yes, CDR recommended: **to Reimburse with clinical criteria and/or conditions**. Visit the CDR website for more details:<br>For the induction of clinico-pathological remission in adults with EoE:<br>www.cadth.ca/sites/default/files/cdr/complete/SR0634%20Jorveza%20-%20CDEC%20Final%20Recommendation%20October%2030%2C%202020_for%20posting.pdf<br>For maintenance of clinico-pathological remission in adults with EoE:<br>www.cadth.ca/sites/default/files/DRR/2021/SR0666%20Jorveza%20-%20CADTH%20Final%20Rec.pdf |
| Drug Benefit Council (DBC) | The DBC met on December 7, 2020, and September 13, 2021. The DBC considered various inputs including: the final reviews completed by the CDR on October 28, 2020, and August 23, 2021, which included clinical and pharmacoeconomic evidence review materials and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC also considered Patient Input Questionnaire responses from one patient and two patient groups, as well as patient input provided to the CDR, a Clinical Practice Reviews from two specialists, and Budget Impact Assessments (BIAs). |

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|---|---|
| **Drug Coverage Decision** | **Non-Benefit** |
| Date | August 18, 2022 |
| Reasons | **Drug coverage decision is consistent with the CDEC and DBC recommendations.**<br>• The CDEC recommended that Jorveza be reimbursed for the induction and maintenance of remission in EoE, with the condition of a price reduction. The DBC recommended not to list Jorveza at the submitted price for either the induction or maintenance of remission in EoE.<br>• The CDEC considered one randomized controlled trial (RCT) [BUL-1/EEA] comparing Jorveza with placebo for the induction of remission in EoE and one RCT (BUL-2/EER) for the maintenance of remission in EoE.<br>• The BUL-1/EEA trial demonstrated a statistically significant and clinically meaningful improvement of Jorveza 1 mg twice daily in inducing remission in EoE when compared to placebo, following six weeks of treatment. The BUL-2/EER trial demonstrated that when compared to placebo, the majority of patients having been brought into remission with a 6- or 12-week course of Jorveza 1 mg twice daily can be maintained in remission for 48 weeks with Jorveza 0.5 mg twice daily.<br>• The cost-effectiveness for Jorveza as induction or maintenance therapies compared with relevant treatments currently used for EoE in Canada is either unknown or uncertain respectively, and Jorveza is more costly than other pharmacological therapies currently in use in Canada for the treatment of EoE.<br>• The Ministry participated in the pan-Canadian Pharmaceutical Alliance negotiations with the manufacturer which were not able to address the concerns identified by the CDEC with respect to the uncertain cost-effectiveness and value for money. |
| Other Information | None |

**The Drug Review Process in B.C.**

A manufacturer submits a request to the Ministry of Health (Ministry).

An independent group called the Drug Benefit Council (DBC) gives advice to the Ministry. The DBC looks at:

- whether the drug is safe and effective
- advice from a national group called the Common Drug Review (CDR)
- what the drug costs and whether it is a good value for the people of B.C.
- ethical considerations involved with covering or not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes PharmaCare coverage decisions by taking into account:

- the existing PharmaCare policies, programs and resources
- the evidence-informed advice of the DBC
- the drugs already covered by PharmaCare that are used to treat similar medical conditions
- the overall cost of covering the drug

Visit The Drug Review Process in B.C. - Overview and Ministry of Health - PharmaCare for more information.

**This document is intended for information only.**
It does not take the place of advice from a physician or other qualified health care provider.

**Appendix A**

# Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

## FINAL

**Budesonide orodispersible tablets (Jorveza™)**
**Avir Pharma Inc.**

**Description:**

Drug review of **budesonide orodispersible tablets (Jorveza™)** for the following Health Canada approved indications:

**For the induction of clinico-pathological remission in adults with eosinophilic esophagitis (EoE).**

In their review, the DBC considered the following: the final reviews completed by the Common Drug Review (CDR) on October 28, 2020, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC also considered Patient Input Questionnaire responses from one patient and one patient group, patient input provided to the CDR, a Clinical Practice Reviews from a specialist, and a Budget Impact Assessment.

**Dosage Forms:**

Jorveza™ is available as budesonide orodispersible 1 mg tablet.

**Recommendations:**

1. The Drug Benefit Council (DBC) recommends not to list budesonide orodispersible (Jorveza™) at the submitted price.

**Of Note:**

- If a significant reduction in price is achieved, the Ministry should base its listing criteria on those recommended by CDEC:

**Initiation criteria**

1. Patients who have all of the following characteristics:
   1.1. Confirmed clinico-pathological diagnosis of EoE according to established diagnostic criteria:
   1.1.1. History of symptoms of esophageal dysfunction (at least one of the following: transient or self-cleared food impaction, dysphagia, chest pain, epigastric discomfort, vomiting/regurgitation)
   1.1.2. Peak eosinophils ≥ 15 in at least one high-power field (HPF); (magnification: 400x) found pathologically on endoscopy.
   1.2. No evidence of any other clinically evident causes for the patient's symptoms other than EoE.

1.3. Failed an adequate trial of proton pump inhibitor (PPI) treatment. PPI failure is defined as refractory symptoms after four 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).

2. Budesonide should not be used in combination with other corticosteroids used to treat EoE.
3. The maximum duration of authorization of budesonide is six weeks.

**Prescribing conditions**

1. The patient must be under the care of a specialist with experience in the diagnosis and management of EoE.

**Reasons for the Recommendation:**

**1. Summary**

- In one pivotal, phase III -blind, randomized, multicenter, placebo-controlled study, Study BUL-1/EEA, budesonide 1 mg twice daily was associated with a statistically significant and clinically meaningful improvement in the percentage of patients who achieved clinico-pathological remission after six weeks of treatment.
- There is uncertainty in the benefits and safety of using budesonide in patients who have not previously been treated with a PPI.
- The study was not of sufficient duration to assess how long the remission would be maintained, and further evidence is needed to support the use of budesonide for an additional six weeks of treatment (i.e., twelve weeks total).
- The role of budesonide in the maintenance of EoE after induction is unclear, given that there is currently no evidence available for the use of budesonide as a maintenance treatment; this is under investigation in an ongoing study.
- There is no evidence to demonstrate whether patients who relapse would respond to a subsequent course of treatment with budesonide or in the same manner as they responded to the initial treatment course.
- At the submitted price, the drug acquisition cost of budesonide 1 mg orodispersible tablets is higher than other pharmacological therapies currently in use in Canada for the treatment of EoE.
- Budesonide (in the form a slurry compounded from budesonide nebulizers mixed with sucralose) is sometimes used off-label to treat patients with EoE

**2. Clinical Efficacy**

- The DBC considered the CDEC systematic review, which included one study (BUL-1/EEA), a pivotal, phase III, double-blind, randomized, multicenter, placebo-controlled study that compared the efficacy and tolerability of a six-week treatment period with budesonide orodispersible to placebo for the induction of clinico-pathological remission in adult patients with active EoE.
- Patients enrolled in the trial were adults (18 to 75 years of age) with a confirmed clinico-pathological diagnosis of EoE, active symptomatic and histological EoE, and must have undergone a documented trial with PPIs in order to exclude PPI-responsive esophageal eosinophilia.
- Treatment with budesonide 1 mg twice daily was associated with a statistically significant and clinically meaningful improvement in the percentage of patients who achieved clinico-pathological remission after six weeks of treatment.

- At week 6, 93.2% of patients in the budesonide treatment group, but none of the patients in the placebo group, achieved histological remission, and 59.3% of patients in the budesonide group achieved resolution of symptoms versus 13.8% in the placebo group.
- Study BUL-1/EEA was not of sufficient duration to assess how long the remission would be maintained. The efficacy of continuing treatment for an additional six weeks with budesonide (twelve weeks total) in the BUL-1/EEA study is uncertain due to the limitations associated with the open-label induction phase of the BUL-1/EEA study.
- All patients in Study BUL-1/EEA were required to have a documented trial with PPIs to exclude PPI-responsive esophageal eosinophilia. Given the lack of evidence for using budesonide 1 mg in patients with EoE who are PPI-naive, there is uncertainty in the benefits and safety of using budesonide in patients who have not previously been treated with a PPI.
- There is no evidence to demonstrate whether patients who relapse would respond to a subsequent course of treatment with budesonide 1 mg in the same manner as they responded to the initial treatment course.
- For detailed information on the systematic review of budesonide orodispersible (Jorveza™) please see the CDEC Final Recommendation at: https://www.cadth.ca/budesonide-0.

**3. Safety**

- A higher proportion of patients in BUL-1/EEA reported treatment-emergent adverse events (TEAEs) following treatment with budesonide 1 mg in comparison to patients treated with placebo. The most frequently reported TEAE in the budesonide 1 mg group were suspected adverse events (AEs) of candidiasis.
- No deaths and no serious adverse events (SAEs) occurred during the study in any of the treatment groups. No AEs in the budesonide 1 mg group led to discontinuation of the treatment.
- For detailed information on the safety and tolerability of budesonide orodispersible, please see the CDEC Final Recommendations at the links above.

**4. Economic Considerations**

- At the submitted price, the drug acquisition cost of budesonide 1 mg orodispersible tablets for six week of treatment is higher than other pharmacological therapies currently in use in Canada for the treatment of EoE.
- The CADTH re-analysis of the sponsor's economic model suggested that over a 12-week time horizon, six weeks of therapy with budesonide 1 mg used to induce clinical-pathological 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.
- 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.

**5. Of Note**

- One patient and one patient group responded to the Patient Input Questionnaires.
- The patient group noted the most common symptoms of EoE are dysphagia (difficulty swallowing), food impactions (food getting stuck in the esophagus), and non-swallowing associated chest pain. EoE impairs patients' social and psychological functioning and significantly impacts their health-related quality of life.
- A potentially life-threatening complication of EoE is esophageal perforation/rupture.

- There are no licensed medicinal products currently available for the treatment of EoE in Canada; PPIs and topical corticosteroids are used off-label to treat EoE.
- Topical corticosteroids, fluticasone propionate multi-dose inhaler and nebulized budesonide are generally prescribed.
- No patients reported they had tried budesonide orodispersible tablet but the patient group noted that budesonide was an effective treatment for EoE.
- Budesonide can be administered by mixing the budesonide nebulizer solution with sucralose or another thickener to form an aqueous gel (or slurry) for the patient to drink.

# Appendix B:

## Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

## FINAL

**budesonide orodispersible (Jorveza™)**
**Avir Pharma Inc.**

**Description:**

Drug review of **budesonide orodispersible (Jorveza™)** for the following Health Canada approved indications:

**For the maintenance of clinico-pathologic remission of eosinophilic esophagitis (EoE) in adults.**

In their review, the DBC considered the following: the final reviews completed by the Canadian Agency for Drugs and Technologies in Health (CADTH) on August 23, 2021, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC also considered Patient Input Questionnaire responses from one patient group, as well as patient input provided to the CDR, a Clinical Practice Reviews from a specialist, and a Budget Impact Assessment [and anything else].

**Dosage Forms:**

Jorveza™ is available as budesonide orodispersible 0.5 mg or 1 mg tablet.

**Recommendations:**

2. The Drug Benefit Council (DBC) recommends not to list budesonide orodispersible (Jorveza)™ at the submitted price.

**Of Note:**

- If the Ministry is able to negotiate a significant price reduction, the reimbursement conditions recommended by CDEC are an appropriate basis for coverage.

**Reasons for the Recommendation:**

**6. Summary**

- A pivotal phase III, double-blind, randomized, multi-centre, placebo-controlled study demonstrated that Jorveza was more effective than placebo in maintaining remission both clinically and histologically in patients with EOE.

- Patients identified the need for a treatment that provides sustained disease control and symptom relief, and there is no other drug approved in Canada for the maintenance of clinico-pathologic remission EoE in adults.
- CADTH was unable to estimate the cost-effectiveness of Jorveza™ due to limitations in the manufacturer's pharmacoeconomic model and in the available clinical information.

**7. Clinical Efficacy**

- The DBC considered the CADTH systematic review, which included a pivotal phase III, double-blind (DB), randomized, multi-centre, placebo-controlled study (BUL-2/EER) comparing the efficacy and tolerability of a 48-week treatment with two different doses of budesonide effervescent tablets (0.5 mg twice daily and 1 mg twice daily) with placebo for the maintenance of clinico-pathological remission in adult patients with EoE.
- In BUL-2/EER, statistically significantly more patients in the budesonide orodispersible tablets 0.5 mg twice daily group were free of treatment failure after 48 weeks of treatment than in the placebo.
- 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, and 10.3% of patients in the budesonide 0.5 mg treatment group had a clinical relapse versus 60.3% in the placebo group.
- For detailed information on the systematic review of budesonide orodispersible (Jorveza™), please see the CDEC Final Recommendation at: https://www.cadth.ca/budesonide-1.

**8. Safety**

- In BUL-2/EER, the majority of patients reported at least one 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 one treatment-emergent adverse event.
- The most frequently reported treatment emergent adverse event in the budesonide 0.5 mg twice daily treatment group was candidiasis, occurring in 12 patients (17.6%) versus none such events in the placebo group. Candidiasis is a known adverse event caused by the immunosuppressive action of budesonide.
- For detailed information on the safety and tolerability of budesonide orodispersible (Jorveza™), please see the CDEC Final Recommendations at the links above.

**9. Economic Considerations**

- The CADTH reanalysis of the manufacturer submission found that the cost-effectiveness of budesonide as maintenance therapy is highly uncertain due to limitations with the sponsor's pharmacoeconomic model and the available clinical information.
- CADTH recommended that a significant price reduction (similar to the price reduction recommended by CDEC in a previous submission for budesonide in the induction phase) would improve the probability that budesonide is cost-effective in the maintenance phase.

**10. Of Note**

- Patients identified the need for a treatment that provides sustained disease control and symptom relief.
- The drugs most often used to treat EoE are proton pump inhibitors and topical corticosteroids, none of which are approved in Canada for EoE.