Drug Coverage Decision for BC PharmaCare

About PharmaCare

BC PharmaCare is a publicly funded drug plan that helps B.C. residents pay for most prescription drugs and pharmacy services, and some medical devices and supplies.

Details of Drug Reviewed

Drug	elexacaftor/tezacaftor/ivacaftor
Brand name	Trikafta®
Dosage form(s)	elexacaftor 100 mg / tezacaftor 50 mg / ivacaftor 75 mg tablet and ivacaftor 150 mg tablet elexacaftor 50 mg / tezacaftor 25 mg / ivacaftor 37.5 mg tablet and ivacaftor 75 mg tablet elexacaftor 100 mg / tezacaftor 50 mg / ivacaftor 75 mg granules and ivacaftor 75 mg granules elexacaftor 80 mg / tezacaftor 40 mg / ivacaftor 60 mg granules and ivacaftor 59.5 mg granules
Manufacturer	Vertex Pharmaceuticals (Canada) Inc.
Submission type	**New Indication**
Use reviewed	Treatment of cystic fibrosis in patients aged two years and older who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to Trikafta based on clinical and/or in vitro data.
Canada's Drug Agency (CDA-AMC) Reimbursement Reviews (CRR)	CRR recommended **to Reimburse with clinical criteria and/or conditions**. Visit the CRR website for more details.
Drug Benefit Council (DBC)	The DBC reviewed Trikafta for patients aged two years and older who have at least one mutation in the CFTR gene that is responsive to Trikafta based on

	clinical and/or in vitro data on October 7, 2024 and advised that it not be listed at the submitted price.
Drug coverage decision	Coverage considered through the Expensive Drugs for Rare Diseases (EDRD) process.
Date	November 6, 2024
Reasons	The Ministry has reimbursed Trikafta for CF patients with at least one F508Del mutation that are aged two years and older since December 2023. In August 2024, CDA recommended that Trikafta be reimbursed for patients aged two and older who have at least one mutation in the CFTR gene that is responsive to Trikafta based on clinical and/or in vitro data because Trikafta demonstrated some advantages over the standard of care with respect to efficacy and safety. The Ministry participated in the pan-Canadian Pharmaceutical Alliance negotiations with the manufacturer which were able to address the concerns identified by CDA with respect to the cost-effectiveness and value for money.

The drug review process in B.C.

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

An independent group called the Drug Benefit Council (DBC) gives advice to the Ministry by considering:

- whether the drug is safe and effective
- advice from a national group called Canada's Drug Agency – L'Agence des médicaments du Canada (CDA-AMC)
- what the drug costs and whether funding it provides good value to the province
- ethical considerations of covering and not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes a BC PharmaCare coverage decision by taking into account:

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

Visit Ministry of Health - PharmaCare and BC PharmaCare – Drug reviews 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-Drug Benefit Council Decision

CONFIDENTIAL

Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta®)
Vertex Pharmaceuticals (Canada) Incoporated

Description:

Drug review of **elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta®)** for the following Health Canada-approved indication:

> For the treatment of cystic fibrosis (CF) in patients aged two years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or a mutation in the CFTR gene that is responsive based on clinical and/or in vitro data.

In its review, the DBC considered the Canada's Drug Agency (CDA) Draft Recommendation, posted on September 19, 2024, which included clinical and pharmacoeconomic evidence reviews and recommendations from the Canadian Drug Expert Committee (CDEC). The DBC also considered patient input provided to the CDEC, including two submissions received from Cystic Fibrosis Canada, as well as input from three clinician groups, and a Budget Impact Assessment.

Dosage Form:

1. Elexacaftor 100 mg / Tezacaftor 50 mg / Ivacaftor 75 mg and Ivacaftor 150 mg Tablets
2. Elexacaftor 50 mg / Tezacaftor 25 mg / Ivacaftor 37.5 mg and Ivacaftor 75 mg Tablets
3. Elexacaftor 100 mg / Tezacaftor 50 mg / Ivacaftor 75 mg and Ivacaftor 75 mg Granules
4. Elexacaftor 80 mg / Tezacaftor 40 mg / Ivacaftor 60 mg and Ivacaftor 59.5 mg Granules

Recommendation:

The Drug Benefit Council (DBC) recommends not to list elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta®) at the submitted price.

Reasons for the Recommendation:

1. **Summary**

- Results from one double-blind, phase 3, randomized controlled trial (RCT) (Study 124, N = 307; 18 CFTR mutations) demonstrated that, compared with placebo,

24 weeks of treatment with elexacaftor/tezacaftor/ivacaftor and ivacaftor (ELX-TEZ-IVA) was associated with clinically meaningful improvements in lung function (increase in percent predicted forced expiratory volume in one second [ppFEV1]), nutritional status (increase in body mass index [BMI]), health-related quality of life (HRQoL; increase in the Cystic Fibrosis Questionnaire-Revised [CFQ-R] respiratory domain score), a CF biomarker (reduction in sweat chloride [SwCl]), and a reduced rate of pulmonary exacerbations.

- Results from other trials included one long-term extension study (Study 125, same population as Study 124), one retrospective observational study (Study 14; N=422, 64 mutations) and four non-randomized studies involving patients with at least one N1303K mutation. There is no clinical data for 79 Fischer rat thyroid (FRT)-responsive mutations approved by Health Canada, thus of the 152 rare mutations approved by Health Canada, only 73 are supported by clinical evidence.
- A significant reduction in price would be required for ELX-TEZ-IVA to be considered cost-effective at a $50,000 per quality adjusted life-year (QALY) threshold.
- There is a high level of unmet need for this target population as they currently do not have access to CFTR modulator therapy in Canada.

2. Clinical Efficacy

- Study 124 was a 24-week, double-blind, placebo-controlled RCT in patients with FRT-responsive mutations (18 Health Canada-approved CFTR mutations). The 24-week duration and use of placebo control in Study 124 were considered acceptable for this condition.
- The primary end point of Study 124 was absolute change from baseline in ppFEV1 through Week 24.
- Key secondary end points of Study 124 were the absolute change from baseline in SwCl and the CFQ-R respiratory domain score through 24 weeks, BMI and body weight at 24 weeks, and the number of pulmonary exacerbations through Week 24.
- Treatment with ELX-TEZ-IVA resulted in a statistically significant improvement in ppFEV1 compared with placebo through 24 weeks (least squares (LS) mean difference of 9.2%), where the improvement from baseline was observed at all postbaseline assessments.
- Those in the ELX-TEZ-IVA group also demonstrated a statistically significant improvement in the CFQ-R respiratory domain score compared with those in the placebo group (LS mean difference of 19.5 points). Patients in the ELX-TEZ-IVA group had estimated pulmonary exacerbation event rate per year of 0.17 compared with 0.63 in the placebo group. Compared with placebo, treatment

with ELX-TEZ-IVA also demonstrated statistically significant reductions in SwCl through 24 weeks (LS mean difference of -28.3 mmol/L) and an increase in BMI at 24 weeks (LS mean difference of 0.47 kg/m^2).

- In the subset of patients less than 20 years of age, there was no statistically significant difference with ELX-TEZ-IVA compared with placebo for absolute change from baseline in body weight z-score (LS mean difference of 0.06), or BMI z-score (LS mean difference of 0.08).
- For the four clinical studies in patients with at least one N1303K mutation, the short-term results showed acute increases in ppFEV1 and weight that were suggestive of a clinically meaningful benefit with ELX-TEZ-IVA.
- For the 79 mutations that were assessed exclusively with the in vitro model, CDEC noted that the data was considered acceptable evidence by Health Canada to expand the indication for ELX-TEZ-IVA and that the sponsor has provided clinical evidence for those mutations that are more commonly harbored by CF patients living in Canada. The inclusion of CFTR mutations without clinical evidence in the approved indication was based primarily on biological plausibility and was supported by the CF specialists who provided input for this review.
- Additional information can be found in the CDA Draft Recommendation.

3. Safety

- The proportion of patients who experienced at least one adverse event (AE) was 94.1% in the ELX-TEZ-IVA group and 95.1% in the placebo group. Most AEs were mild or moderate in severity.
- Serious AEs (SAEs) occurred in 18 (8.8%) of patients in the ELX-TEZ-IVA group and 15 (14.7%) of patients in the placebo group, those which occurred in at least two patients in the treatment group included infective pulmonary exacerbations of CF (5 patients) and allergic bronchopulmonary aspergillosis (2 patients). Thirteen patients in the placebo group experienced infective pulmonary exacerbations of CF.
- Rashes occurred in 55 (26.8%) of patients in the ELX-TEZ-IVA group and 3 (2.9%) of patients in the placebo group, most of which were mild or moderate in severity.

4. Economic Considerations

- At the submitted price, treatment with ELX-TEZ-IVA is expected to cost approximately $306,600 annually per patient, regardless of strength or form.
- Using the sponsor submitted price for ELX-TEZ-IVA and publicly listed prices for all other drug costs, ELX-TEZ-IVA was associated with an incremental cost-

effectiveness ratio (ICER) of $1,122,823 per QALY gained compared to standard of care (SoC), in the overall patient population with non-F508del mutations.
- The CDA base case suggests that a price reduction of at least 79% is required for ELX-TEZ-IVA to be considered cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained versus SoC. The annual drug acquisition costs of ELX-TEZ-IVA would be $65,351 per patient at a 79% price reduction.
- No conclusions can be drawn about the comparative effectiveness of ELX-TEZ-IVA relative to the comparator that is reimbursed for patients in this setting. Therefore, CDEC concluded that there was not enough evidence to justify a greater cost for ELX-TEZ-IVA compared to other currently reimbursed treatments for CF.

5. Of Note

- CF is the most common fatal genetic disease affecting children and young adults in Canada. Patient input received by the DBC indicated the severe impacts that CF has on both patients and caregivers and emphasized that existing treatments are unable to affect the underlying disease.
- Although direct evidence is lacking, listing ELX-TEZ-IVA for those with rarer mutations would likely improve equity by improving access. Such patients tend to have compounded inequities as they tend to be from racial minority groups, lower socioeconomic status, and face other barriers such as food insecurities.
- Patients with rare mutations and their caregivers shared their hopes to access ELX-TEZ-IVA as they say the medication benefits those who can access it.
- Experts emphasize that there is a high level of unmet need for this target population as they currently do not have access to CFTR modulator therapy in Canada.