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CADTH Reimbursement Recommendation

Elexacaftor–Tezacaftor–Ivacaftor and Ivacaftor (Trikafta)

Indication: For the treatment of cystic fibrosis in patients aged 2 and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator gene.

Sponsor: Vertex Pharmaceuticals (Canada) Incorporated

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Trikafta?

CADTH recommends that Trikafta be reimbursed by public drug plans for the treatment of cystic fibrosis (CF) in patients aged 2 to 5 years and older who have at least one F508del mutation in the *CFTR* gene, if certain conditions are met. The previous recommendation for Trikafta, for patients who initiate treatment at age 6 years or older, continues to apply to those patients.

What Are the Conditions for Reimbursement?

Patients who start treatment with Trikafta should be evaluated for response after 1 year, and the treating physician must provide evidence after that the patient is benefiting from the treatment. The cost of Trikafta must also be reduced.

Why Did CADTH Make This Recommendation?

For patients aged 2 to 5 years with CF, Trikafta was well tolerated and shown to improve lung function and reduce sweat chloride in an uncontrolled clinical trial. When used in patients aged 6 years and older, Trikafta was associated with meaningful improvements in lung function, nutritional status, and quality of life, and a reduced rate of pulmonary exacerbations. The committee acknowledged that conducting a comparative clinical study for Trikafta in patients aged 2 to 5 years may be ethically challenging, given the expected balance of risks and benefits of Trikafta in CF based on evidence in patients aged 6 years and older. Given the mechanism of action and efficacy data in patients with CF aged 6 years and older, Trikafta would be expected to benefit patients aged 2 to 5 years who have at least one F508del mutation in the *CFTR* gene.

Based on CADTH's assessment of the health economic evidence, Trikafta does not represent good value to the health care system at the public list price. A price reduction is therefore required.

Based on public list prices, Trikafta is estimated to cost the public drug plans approximately $136 million over the next 3 years.

Additional Information

What Is CF?

CF is a progressive, fatal, genetic disease that primarily affects the lungs and digestive system. Those living with CF lose the ability to breathe due to accumulated lung damage caused by chronic lung infections and

Summary

inflammation. F508del is the most common mutation in the *CFTR* gene that results in CF.

Unmet Needs in CF

There are significant unmet therapeutic needs for those living with CF. There are no treatments currently available that effectively meet the most important goals of CF therapy: to prolong survival, prevent the need for lung transplant, slow the decline in lung function over time, or reverse the course of the disease.

How Much Does Trikafta Cost?

Treatment with Trikafta is expected to cost $306,810 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that elexacaftor-tezacaftor-ivacaftor and ivacaftor (ELX-TEZ-IVA) be reimbursed for the treatment of cystic fibrosis (CF) in patients aged 2 to 5 years who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, only if the conditions listed in Table 1 are met.

The CDEC recommendation dated July 2022, for ELX-TEZ-IVA for the treatment of CF in patients who initiate treatment at age 6 years or older who have at least one F508del mutation in the *CFTR* gene, continues to apply to patients who are not included in the population of this recommendation.

Rationale for the Recommendation

CF is the most common fatal genetic disease affecting children and young adults in Canada. It is caused by mutations in the *CFTR* gene. Clinical expert input emphasized the importance of initiating treatment early in the disease course and that there is a significant unmet need for a treatment that would prevent disease progression and irreversible CF-related structural lung damage.

For patients aged 2 to 5 years with CF, a 24-week, open-label, uncontrolled trial (Study 111 part B; N = 75) suggested that treatment with ELX-TEZ-IVA resulted in improvements from baseline in lung function (decrease in lung clearance index 2.5% [$LCI_{2.5}$] from baseline) and CF biomarkers (reduction in sweat chloride) and that the treatment was well tolerated. Study 111 was primarily designed to evaluate safety, tolerability, and pharmacokinetics of ELX-TEZ-IVA, as the regulatory submission was based on the extrapolation of efficacy data from the studies conducted in older patients with CF (i.e., those showing measurable levels of disease manifestations at baseline). Specifically, ELX-TEZ-IVA has demonstrated clinically meaningful improvements in lung function (increase in percent predicted forced expiratory volume in 1 second [$ppFEV_1$]), nutritional status (increase in body mass index [BMI] z score), and health-related quality of life (increase in Cystic Fibrosis Questionnaire – Revised [CFQ-R] respiratory domain scores), and a reduced rate of pulmonary exacerbations, including events that required IV antibiotics and/or hospitalization in clinical trials conducted in patients aged 6 to 11 years (Study 116 [N = 121] and Study 106B [N = 66]) and in patients aged 12 years and older (Study 102 [N = 405], Study 103 [N = 107], Study 109 [N = 107], and Study 104 [N = 259]). CDEC has previously acknowledged that ELX-TEZ-IVA meets some of the important needs identified by patients with CF and their caregivers, such as reducing CF exacerbations, improving health-related quality of life, improving lung function, and improving digestive health allowing people to maintain a healthy body weight; the committee acknowledged that, given the mechanism of action and efficacy data in patients with CF aged 6 years and older, ELX-TEZ-IVA would be expected to benefit patients aged 2 to 5 years who have at least one F508del mutation in the *CFTR* gene.

Using the sponsor-submitted price for ELX-TEZ-IVA and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for ELX-TEZ-IVA was $1,284,953 per quality-adjusted life-year (QALY) gained in the F/F genotype, $1,451,526 per QALY gained in the F/MF genotype, $1,284,853 per QALY

gained in the F/Gating genotype, and $1,644,869 per QALY gained in the F/RF genotype, compared to best supportive care. Additionally, ELX-TEZ-IVA was associated with an ICER of $838,687 per QALY gained when compared to LUM-IVA in the F/F genotype population. At these ICERs, ELX-TEZ-IVA is not cost-effective at a $50,000 per QALY gained willingness-to-pay threshold for the treatment of CF in patients aged 2 to 5 years who have at least one F508del mutation in the *CFTR* gene. A price reduction is required for ELX-TEZ-IVA to be considered cost-effective at a $50,000 per QALY gained threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Confirmed diagnosis of CF with at least one F508del mutation in the *CFTR* gene.	Study 111 enrolled patients with a confirmed diagnosis of CF. All patients enrolled had an F508del *CFTR* mutation that was either F/MF (69.3%) or F/F (30.7%). In addition, the indication approved by Health Canada for ELX-TEZ-IVA is limited to patients with at least one F508del mutation in the *CFTR* gene.	—
2. Aged 2 to 5 years.	Study 111 enrolled patients aged 2 to 5 years (inclusive). In addition, the indication approved by Health Canada for ELX-TEZ-IVA is limited to patients who are aged at least 2 years, and the scope of the current recommendation is focused on patients aged 2 to 5 years.	—
3. The following measurements must be completed before initiating treatment with ELX-TEZ-IVA: 3.1. number of days treated with oral and IV antibiotics for pulmonary exacerbations in the previous 6 months or number of pulmonary exacerbations requiring oral and/or IV antibiotics in the previous 6 months 3.2. weight, height, and BMI.	Establish baseline values to be used for renewal of reimbursement for treatment with ELX-TEZ-IVA.	Weight, height, and BMI for pediatric patients are collected and reported as z scores or percentiles in clinical practice in Canada.
Renewal		
4. For renewal after initial authorization, the physician must provide evidence of continuing benefit from treatment with ELZ-TEZ-IVA for subsequent renewal of reimbursement. Patients on therapy should be monitored for response (e.g., no decrease in BMI z score) using clinical judgment and/or standard procedures.	Clinical experts have noted that it is difficult to obtain objective measurements to assess response to treatment in patients aged 2 to 5 years.	—

Reimbursement condition	Reason	Implementation guidance
5. Assessment for clinical response should occur every 12 months.	Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment.	—
Discontinuation		
6. Patient has undergone lung transplant.	Patients who had had a solid organ transplant were excluded from the main studies of ELX-TEZ-IVA, and clinical experts in Canada indicated that the treatment should be discontinued in patients who have received lung transplant.	—
Prescribing		
7. Prescribing of ELX-TEZ-IVA and monitoring of treatment response should be limited to CF specialists.	Care for patients with CF is complex and is managed through specialized CF clinics in Canada.	—
8. ELX-TEZ-IVA should not be reimbursed in combination with other *CFTR* modulators.	There is no evidence for the use of ELX-TEZ-IVA in combination with other available *CFTR* modulators. 1. ELX-TEZ-IVA is a combination product containing the same active components of Symdeko (TEZ-IVA) and Kalydeco (IVA). 2. IVA is also a component of Orkambi (LUMIVA).	—
Pricing		
9. A reduction in price.	The ICER for ELX-TEZ-IVA ranged from $1,284,853 to $1,644,869 per QALY gained in comparison with BSC, depending on the genotype. A price reduction of at least 94% (for both granules and tablets) is required for ELX-TEZ-IVA to achieve an ICER of $50,000 per QALY gained in all 4 genotypes compared to BSC.	—
Feasibility of adoption		
10. The feasibility of adoption of ELX-TEZ-IVA must be addressed.	At the submitted price, the budget impact of ELX-TEZ-IVA is expected to be greater than $40 million in all 3 years.	—

BMI = body mass index; BSC = best supportive care; CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire Revised; ELX = elexacaftor; ICER = incremental cost-effectiveness ratio; IVA = ivacaftor; LUM = lumacaftor; ppFEV$_1$ = percent predicted forced expiratory volume in 1 second; RCT = randomized controlled trial; QALY = quality-adjusted life-year; TEZ = tezacaftor; WTP = willingness to pay.

Discussion Points

- There was uncertainty in the clinical evidence; therefore, the committee deliberated on ELX-TEZ-IVA considering the criteria for significant unmet need that are described in section 9.3.1 of *Procedures for CADTH Reimbursement Reviews*. Considering the rarity and severity of the condition, and the absence of clinically effective alternatives, the committee concluded that the available evidence reasonably suggests that ELX-TEZ-IVA could substantially reduce morbidity and/or mortality associated with CF.

- The committee noted that nearly all patients in Canada aged 12 years and older who are eligible for treatment have initiated therapy with ELX-TEZ-IVA and that it is anticipated that nearly all patients aged 6 to 11 years will have initiated treatment with ELX-TEZ-IVA by the end of 2023. For those who have initiated treatment with ELX-TEZ-IVA, the clinical experts consulted by CADTH and the sponsor have indicated that initial renewal criteria were met for all patients in Canada who started the therapy and wanted to continue (i.e., 100% of patients met the renewal criteria recommended by CADTH and/or applied by the public drug programs).
- The committee noted that input from patient groups, clinician groups, and the clinical experts consulted by CADTH emphasized the importance of initiating treatment with ELX-TEZ-IVA early in the disease course to try to prevent disease progression and irreversible damage. The clinical experts consulted by CADTH noted that many parents and caregivers would seek to initiate treatment for their child as early as possible (i.e., beginning at 2 years of age) and are anxiously awaiting access to ELX-TEZ-IVA for those who are currently younger than 6 years.
- The committee discussed the applicability of the existing reimbursement conditions for those aged 6 years and older to those aged 2 to 5 years. The clinical experts noted that the following baseline measurements that are currently recommended by CADTH would be challenging to implement, uninformative, and/or not relevant for patients aged 2 to 5 years: baseline FEV_1 (spirometry is not performed in patients younger than 6 years); baseline frequency of pulmonary exacerbations (exacerbations can be infrequent and it would be challenging establish a reliable baseline); and CFQ-R respiratory domain score (this is not routinely obtained in pediatric clinics and the instrument has not been validated for the age group of interest). The clinical experts noted that those aged 2 to 5 years would have growth parameters monitored in routine clinical practice. However, it was noted that a majority of patients with CF aged 2 to 5 years do not show reductions in age-standardized BMI and that BMI percentile can fluctuate in younger patients, especially following periods of acute illness.
- The regulatory submission for ELX-TEZ-IVA for patients aged 2 to 5 years is based on the extrapolation of efficacy data from older age groups to a younger population based on comparable pharmacokinetic exposures and safety. The committee agreed with the clinical experts consulted by CADTH that, given the mechanism of action and efficacy data in patients with CF aged 6 years and older, ELX-TEZ-IVA would be expected to benefit patients aged 2 to 5 years who have at least one F508del mutation in the *CFTR* gene.
- CDEC discussed ethical and equity considerations related to ELX-TEZ-IVA, including those related to the significant burden of living with CF. The committee also discussed how patients aged 2 to 5 years may be considered particularly vulnerable given that they are dependent on their parents to provide the necessities of life, and in the context of CF, to advocate and facilitate access to their diagnosis and support for their condition. CDEC discussed how the extrapolation of efficacy of ELX-TEZ-IVA in patients aged 2 to 5 years may be ethically justified in pediatric populations where it can avoid exposing vulnerable patients to unnecessary research, and discussed extending access to therapy in these patient populations. The clinical experts consulted by CADTH noted that when considering possible benefits and harms, they would prescribe ELX-TEZ-IVA for children aged 2 to 5 years, given

the expected benefits of treatment to prevent the onset of CF-related structural lung damage. The committee also noted the potential advantages of using ELX-TEZ-IVA as an orally administered medication, including potential benefits for patients impacted by low socioeconomic status. The committee discussed potential disparities in access related to inconsistencies in insurance coverage or reimbursement of ELX-TEZ-IVA within Canada, and the significant costs associated with the use and implementation of ELX-TEZ-IVA.

- CDEC discussed the absence of direct or indirect comparisons for ELX-TEZ-IVA versus other *CFTR* modulators approved for use in patients aged 2 to 5 years. The committee discussed the ethical challenges of conducting a comparative clinical study in this age group and potential concerns regarding the absence of clinical equipoise, given the evidence from patients aged 6 years and older where ELX-TEZ-IVA was shown to be superior to all other *CFTR* modulators currently marketed in Canada.
- The sponsor's submitted pharmacoeconomic evaluation assessed the cost-effectiveness of ELX-TEZ-IVA to best supportive care (BSC) or lumacaftor-ivacaftor (LUM-IVA) (for the F/F genotype only) over a 2- to 5-year-old patient's entire lifetime. CDEC discussed how this decision problem does not accurately reflect the current landscape of CF treatment, as the majority of patients aged 6 years and older are currently being treated with ELX-TEZ-IVA, and thus a more appropriate decision problem would be to assess the cost-effectiveness of starting ELX-TEZ-IVA in patients aged 2 to 5 years versus waiting to initiate treatment at age 6 years or older. The cost-effectiveness of ELX-TEZ-IVA in the latter scenario is unknown.

Background

Trikafta is a fixed-dose combination product containing elexacaftor, tezacaftor, and ivacaftor co-packaged with ivacaftor (ELX-TEZ-IVA). ELX-TEZ-IVA is available as both oral tablets and oral granules in the following dosage strengths.

Tablets for patients aged 6 years and older:

- elexacaftor 50 mg, tezacaftor 25 mg, and ivacaftor 37.5 mg, co-packaged with a tablet containing ivacaftor 75 mg
- elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg, co-packaged with a tablet containing ivacaftor 150 mg.

Granules for patients aged 2 years to younger than 6 years:

- elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg (granules), with ivacaftor 75 mg (granules)
- elexacaftor 80 mg, tezacaftor 40 mg, and ivacaftor 60 mg (granules), with ivacaftor 59.5 mg (granules) (oral).

ELX-TEZ-IVA is indicated for the treatment of CF in patients aged 2 years and older who have at least one F508del mutation in the *CFTR* gene. F508del is the most common mutation in the *CFTR* gene that results in CF. The Canadian Cystic Fibrosis Registry reported that there were 4,344 people in Canada living with CF in 2019. Of these, 87.8% carried at least one F508del mutation (47.1% were homozygous and 40.7% were heterozygous).

This is the third submission to CADTH for ELX-TEZ-IVA. CADTH has previously reviewed ELX-TEZ-IVA for the treatment of CF in patients who have at least one F508del mutation in the *CFTR* gene for those aged 12 years and older (final recommendation issued in August 2021) and those aged 6 years and older (final recommendation issued in June 2022). For both of the previous reviews, CDEC recommended that ELX-TEZ-IVA be reimbursed with conditions. All of the indications for ELX-TEZ-IVA were accepted as priority reviews by Health Canada.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of a 24-week, open-label, phase III, nonrandomized, single-arm, open-label study in patients aged 2 to 5 years with at least an F/F or F/MF *CFTR* genotype
- patient perspectives gathered by a patient group, Cystic Fibrosis Canada (CF Canada)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 4 clinical specialists with expertise diagnosing and treating pediatric patients with CF
- input from 2 clinician groups, including CF Canada's Accelerating Clinical Trials Network (CF CanACT) and the CF Canada Health Care Advisory Council
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to ELX-TEZ-IVA from published literature.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical experts consulted by CADTH for the purpose of this review. The complete input received for the previous CADTH reviews of ELX-TEZ-IVA is available on the CADTH website (refer to reviews for ELX-TEZ-IVA for patients aged 6 to 11 years and aged 12 years and older).

Patient Input

One patient group, CF Canada, responded to CADTH's call for patient input for the current review of ELX-TEZ-IVA, which is focused on patients aged 2 to 5 years who have at least one F508del mutation in the *CFTR* gene.

The patient groups emphasized that CF tremendously impacts those living with the condition, their loved ones, the health systems, and society. The most significant clinical impact is in the lungs, where patients experience progressive scarring of their airways and a progressive decline in lung function. Young children who grow older with CF may suffer from pulmonary exacerbations requiring weeks to months of hospitalization and IV antibiotics. Malnutrition and low BMI are also common consequences of CF among children aged 2 to 5 years. Patients may also suffer from CF-related comorbidities, such as CF-related diabetes and CF-related liver disease. In addition, CF has a significant impact on socialization, mental health, and isolation among patients and caregivers.

The patient input stated that managing CF requires a demanding treatment routine. As the disease progresses, more time and effort, frequent clinic visits, and hospital stays are needed to manage the progressive and debilitating symptoms. This condition has a significant impact on patients' and caregivers' day-to-day activities and quality of life, in addition to a huge financial burden for families.

According to the patient group input, an ideal CF treatment would fully address the basic molecular defect in CF and restore normal chloride transport on the cell surface. Patients with CF and their loved ones are seeking treatments that can change the trajectory of the disease, reduce disease symptoms, improve sleep quality and energy levels, and improve both life expectancy and quality of life.

In the patient group input, CF CanACT emphasized the importance of early treatment of CF to prevent disease progression and irreversible damage. Extending access to ELX-TEZ-IVA to patients with CF aged 2 to 5 years would be congruent with the secondary prevention paradigm of CF care, and would decrease the long-term burden of the disease.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Unmet Needs

Similar to the input from the patient groups, the clinical experts consulted by CADTH indicated that there are significant unmet therapeutic needs for patients living with CF. There are no treatments currently available that can meet the most important goals of therapy, including: prolonging survival, preventing the need for lung transplant, slowing the decline in lung function over time, or reverse the course of the disease. In addition, the clinical experts noted that the current standard treatments for CF are burdensome for patients and their caregivers.

Place in Therapy

The clinical experts anticipate that ELX-TEZ-IVA would be used as a preventive therapy with the goal of initiating treatment before the patient develops significant lung disease. The current treatment paradigm would be significantly altered if ELX-TEZ-IVA can successfully prevent or delay progression to end organ disease (e.g., lung transplant). The clinical experts consulted by CADTH and those who responded to the call for clinician input noted that children aged between 2 years and 5 years will often have structural lung disease (e.g., bronchial wall thickening, mucus plugging, bronchiectasis), but that detection is challenging

using the tools that are available to evaluate lung function in clinical practice (i.e., spirometry) or as part of a research protocol (e.g., lung clearance index). These early stages of lung abnormalities can be visualized using CT; therefore, despite younger patients with CF often demonstrating normal lung function, the underlying disease will continue to progress.

All of the clinicians who provided input for this review recommended initiating treatment with ELX-TEZ-IVA as soon as possible. This is aligned with the previously published *Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis,* which also recommend that *CFTR* modulators be initiated at the youngest age possible with the goal of attenuating disease progression and improving clinical status. All stakeholders were in agreement that there are no data to support withholding the initiation of *CFTR* modulator treatment until clinical symptoms of CF have developed.

Patient Population

For the expanded indication (i.e., those aged 2 to 5 years), the clinical experts consulted by CADTH noted that nearly all patients would initiate therapy with ELX-TEZ-IVA as soon as possible provided it is safe to start to treatment. The clinical experts emphasized that ELX-TEZ-IVA has been a transformative and disease-modifying therapy for CF, and that it would not be appropriate to wait until the patient shows worsening symptoms, more frequent exacerbations, or a decline in lung function to initiate treatment with ELX-TEZ-IVA.

Applicability of Existing Reimbursement Criteria to Pediatrics

In discussions with CADTH, the sponsor noted that nearly all patients in Canada aged 12 years and older who are eligible for treatment have initiated therapy with ELX-TEZ-IVA (some may have elected to discontinue, but all who are interested have been given the opportunity to access the drug). The sponsor similarly stated that nearly all patients in Canada aged 6 to 11 years who wish to initiate treatment will have initiated treatment with ELX-TEZ-IVA by the end of this calendar year. For those who have initiated treatment with ELX-TEZ-IVA, the sponsor noted that initial renewal criteria were met for all patients in Canada who started the therapy and wanted to continue (i.e., 100% of patients met the renewal criteria recommended by CADTH and/or applied by the public drug programs). The clinical experts consulted expressed general agreement with the sponsor's position, noting that rates of initial access and renewal are very high within their individual clinics. With nearly all patients who are at least 6 years of age having met the initiation and renewal criteria, newly issued CADTH reimbursement criteria focusing exclusively on those aged 2 to 5 years would effectively replace the previous criteria (i.e., although limited to those aged 2 to 5 years, all older patients would have already qualified for initiation and renewal).

The clinical experts consulted by CADTH reviewed the existing criteria that have been recommended for patients aged 6 years and older and noted the following:

- **Baseline measurements:** Regarding the baseline measurements that must be completed before initiating treatment with ELX-TEZ-IVA, the clinical experts noted that the following baseline measurements that are currently recommended by CADTH would be problematic to implement, uninformative, and/or not relevant for patients aged 2 to 5 years: baseline FEV_1 (spirometry is not performed in patients younger than 6 years of age); baseline frequency of pulmonary exacerbations

(exacerbations can be infrequent and it would be challenging establish a reliable baseline); and CFQ-R respiratory domain scores (these are not routinely obtained for patients in pediatric clinics, typically only when conducting research studies). The clinical experts noted that those aged 2 to 5 years would have growth parameters monitored in routine clinical practice. However, it was noted that a majority of patients with CF aged 2 to 5 years do not show reductions in age-standardized BMI, and that BMI percentile can fluctuate in younger patients, especially following periods of acute illness.

- **Renewal criteria:** Each of the end points are discussed subsequently, with reflection on the applicability of the existing CADTH criteria to the expanded population of patients aged 2 to 5 years:
  - **BMI and BMI z scores:** The existing criterion is "no decline in BMI (BMI z score in children) at 6 months compared with the baseline BMI assessment." The clinical experts noted that 6 months is not sufficient to accurately assess the response to treatment, and that an assessment of BMI at 12 months would be more appropriate. The longer time was suggested to account for events that could temporarily reduce BMI (e.g., increased physical activity in summer months and growth spurts). It was strongly noted that discontinuation of ELX-TEZ-IVA in such patients would not be clinically appropriate.
  - **Pulmonary exacerbations:** The existing criterion is "a decrease in the total number of days for which the patient received treatment with oral and/or IV antibiotics for pulmonary exacerbations compared with the 6-month period prior to initiating treatment OR a decrease in the total number of pulmonary exacerbations requiring oral and/or IV antibiotics compared with the 6-month period prior to initiating treatment." The clinical experts indicated that pulmonary exacerbations are less frequent in patients aged 2 to 5 years compared with adults and adolescents. The clinical experts suggested that the existing renewal criterion would be problematic for those aged 2 to 5 years. However, it was emphasized that patients who have not experienced a pulmonary exacerbation or those with a very low annual rate of pulmonary exacerbations would still benefit from the treatment. Similar to the criterion for BMI, it was noted that 12 months would be a more appropriate time frame for evaluating changes in pulmonary exacerbations.
  - **CF-related hospitalizations:** The existing criterion is "decreased number of CF-related hospitalizations at 6 months compared with the 6-month period prior to initiating ELX-TEZ-IVA treatment." The clinical experts consulted by CADTH noted that CF-related hospitalization is infrequent and highly variable in patients within the 2- to 5-year age range. As such, this would be very challenging to implement as a criterion for evaluating response to ELX-TEZ-IVA for the purposes of reimbursement.
- **Sweat chloride testing:** The previous CADTH recommendation did not include sweat chloride testing as 1 of the initiation or renewal conditions for ELX-TEZ-IVA. The sponsor has requested that "reduction in sweat chloride" be included as a reimbursement condition for ELX-TEZ-IVA in the current review. The pediatric clinical experts agreed with the prior input from the reviews of ELX-TEZ-IVA in patients aged 6 to 11 years and 12 years and older, noting that sweat chloride testing should be not used to evaluate the response to ELX-TEZ-IVA for the purposes of drug reimbursement because it is not clearly predictive of clinically important outcomes and only reflects the mechanism of action

of *CFTR* modulators like ELX-TEZ-IVA. The clinical experts also noted that access to sweat chloride testing can be challenging in some jurisdictions and that the timelines to receive the test results can fluctuate. They also raised important concerns about the capacity of the health system to accommodate repeated sweat chloride testing for all patients with at least one F508del mutation.

Clinician Group Input

Three groups of clinicians responded to CADTH's call for input: CF CanACT, the CF Canada Health Care Advisory Council, and the Canadian Cystic Fibrosis Clinician groups. The input from the clinician groups identified the same unmet medical needs for patients with CF and potential place in therapy for the drug under review as the clinical experts consulted by CADTH.

According to the clinician group input, the treatment paradigm for CF in children aged 2 to 5 years is lifelong. All clinician groups noted that available treatments address the symptoms and complications of CF and attempt to slow down the eventual fatal progression of the disease without effectively addressing the root cause or reversing the course of the disease. They also have significant side effects and numerous drug interactions. Clinician groups emphasized that ELX-TEZ-IVA is the most effective improvement of the existing *CFTR* modulators as it addresses the underlying disease process which helps in delaying disease progression and the need for other therapies, including lung transplant. Therefore, any patient with CF who has at least 1 copy of F508del could potentially benefit from ELX-TEZ-IVA.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Are there any physiological reasons that would caution the extrapolation of data from patients with CF aged 6 years and older treated with ELX-TEZ-IVA to patients aged 2 to 5 years?	The clinical experts consulted by CADTH and those who provided input to CADTH through the call for clinician input all support starting ELX-TEZ-IVA as soon as possible. The clinical experts supported the extrapolation of efficacy data from aged children 6 years or older and noted to CDEC that the data in patients aged 2 to 5 years do not raise additional concerns regarding the safety of ELX-TEZ-IVA.
Can patients being treated with LUM-IVA (Orkambi) be switched to ELX-TEZ-IVA? If so, are there any special considerations (e.g., additional monitoring)?	The clinical experts noted to CDEC that ELX-TEZ-IVA would replace earlier *CFTR* modulators that are significantly less effective (e.g., Orkambi) and patients currently receiving those drugs would likely be switched to ELX-TEZ-IVA if they meet eligibility criteria. The clinical experts noted to CDEC that patients with CF are monitored in specialized clinics and switching from LUM-IVA to ELX-TEZ-IVA would not be anticipated to pose challenges for patients or health care providers.

Implementation issues	Response
Are there specific patient populations in which switching to ELX-TEZ-IVA is inappropriate?	The clinical experts noted to CDEC that switching would be appropriate for all patients receiving alternative *CFTR* modulators, provided they meet the eligibility and age criteria.
Considerations for initiation of therapy	
Can the clinical experts confirm that multiple breath washout tests (e.g., $LCI_{2.5}$) are only available at specialty clinics at children's hospitals and not available at all pulmonary function testing clinics?	The clinical experts noted to CDEC that this measurement is not currently used in routine Canadian clinical practice and would not be practical for the purposes of determining eligibility for ELX-TEZ-IVA reimbursement.
If children aged 2 to 5 years cannot complete an accurate spirometry (to obtain $ppFEV_1$), and the CFQ-R is not validated in this age group, are there other parameters or biomarkers that could be measured at the time of treatment initiation for the purposes of evaluating response to treatment?	The clinical experts noted to CDEC that clinically meaningful objective measures of response to ELX-TEZ-IVA are challenging to implement in clinical practice, as patients aged 2 to 5 years often do not show CF symptoms that can be objectively measured in practice using the tools and instruments that have been recommended for those aged 6 years and older. In addition, they are too young to perform spirometry measurements, and obtaining baseline measurements of pulmonary exacerbation or CF-related hospitalization is problematic due to low frequency and interpatient variability. Among the criteria currently recommended by CDEC, BMI z score is the only baseline measurement that would be captured as part of routine practice for patients aged 2 to 5 years. With respect to biomarkers, the clinical experts emphasized the following important considerations regarding sweat chloride: • Sweat chloride testing is not considered to be a clinically relevant measurement for determining if a patient is benefiting from a treatment. • If a requirement for reimbursement involves mandatory repeated sweat chloride testing as an objective validation measure for renewal, the clinical experts noted that the existing capacity for sweat chloride testing would likely be quickly overwhelmed in all provinces. There is insufficient infrastructure in place to perform repeated sweat chloride testing in all patients with CF with at least one F508del mutation.
Considerations for continuation or renewal of therapy	
Are there any clinical benefits that have not been described in the sponsor's renewal criteria or in the previous CDEC recommended renewal criteria that should be considered for use as renewal criteria?	The clinical experts emphasized that ELX-TEZ-IVA has the potential to modify the course of disease for patients with CF. When used in older patients, nearly all patients demonstrated sufficient clinical benefit to have reimbursement renewed by the public drug programs. The clinical experts noted to CDEC that, although objective measures are challenging to implement in clinical practices for those aged 2 to 5 years, these patients would likely benefit from initiating treatment. CDEC noted the opinion of Canadian clinical experts who described how subsequent renewals for ELX-TEZ-IVI can be achieved through communication that the patient is continuing to benefit from the treatment and that such an approach could be applied to younger patients, where obtaining meaningful baseline and follow-up measurements of objective criteria would be challenging.

Implementation issues	Response
Can the renewal criteria for patients aged 6 years and older be used for patients aged 2 to 5 years (except for FEV_1 and/or CFQ-R)?	The clinical experts noted the following to CDEC regarding the application of the existing reimbursement criteria to patients aged 2 to 5 years: • **BMI and BMI z scores:** The clinical experts noted that 6 months is not sufficient to accurately assess the response to treatment, and that an assessment of BMI at 12 months would be more appropriate. The longer time was suggested to account for events that could temporarily reduce BMI (e.g., increased physical activity in summer months and growth spurts). It was strongly noted that discontinuation of ELX-TEZ-IVA in such patients would not be clinically appropriate. In these younger patients, who are not necessarily showing a reduction in age-standardized growth, clinicians are focused on maintaining stability and would not anticipate improvements from baseline measures. • **Pulmonary exacerbations:** Pulmonary exacerbations are less frequent in patients aged 2 to 5 years compared with adults and adolescents. The clinical experts consulted by CADTH indicated that this is reflective of clinical practice, where these events are less common in children with relatively normal lung function. The clinical experts suggested that the previously noted renewal criterion would be problematic for the use of ELX-TEZ-IVA in those aged 2 to 5 years. However, it was emphasized that patients who have not experienced a pulmonary exacerbation or those with a very low annual rate of pulmonary exacerbations would still benefit from the treatment. Similar to the criterion for BMI, it was noted that 12 months would be a more appropriate time frame for evaluating changes in pulmonary exacerbations. • **CF-related hospitalizations:** The clinical experts consulted by CADTH noted that CF-related hospitalization is infrequent and highly variable in patients within the 2- to 5-year age range. As such, this would be very challenging to implement as a criterion for evaluating response to ELX-TEZ-IVA for the purposes of reimbursement.
If a patient starts ELX-TEZ-IVA between the ages of 2 to 5 years, when they turn 6, can they just follow renewal criteria for the population of patients aged 6 years and older?	While the clinical experts noted that the application of the criteria for older patients may be challenging, as those aged 2 to 5 years would not have pretreatment baseline measurements for many of the requirements, CDEC recommended patients who start ELX-TEZ-IVA treatment between the ages of 2 and 5 years, once they turn 6 they should be subject to the discontinuation and renewal conditions in the 6 years and older recommendation. However, the baseline used should be when the patients initially started treatment with ELX-TEZ-IVA even if that was between the age of 2 and 5 years. The clinical experts noted to CDEC that for patients aged 6 years and older who started therapy when they were aged 5 years or younger, FEV_1 can be measured when they turn 6, with the caveat that children at age 6 are not yet reliably able to reproduce PFTs as they are effort-dependent tests. Therefore, FEV_1 measurements are sometimes underestimates of the true FEV_1 or are not reproducible. Reliability improves with age and practice

Implementation issues	Response
	in general and is still worth measuring. The clinical experts also noted that CF quality of life questionnaires are labour-intensive measurements that require a significant time burden to clinical teams and hence should not be required. The clinical experts also stated that renewal of therapy should not be tied to maintenance of all baseline measurements, where patients could still be experiencing response to treatment even if some measurements declined, and the possibility that the decline would be more severe without a *CFTR* modulator is real. It was also noted that the prescribing CF physician should determine if the drug should be continued or discontinued. The clinical experts indicated that treatment should be discontinued in patients with moderate to severe liver function derangements, other symptoms of concern (e.g., mental health issues, severe behavioural issues), or other clinical concerns as determined by the CF physician.
Considerations for discontinuation of therapy	
The previous CDEC recommendation for ELX-TEZ-IVA included a criterion that reimbursement should be discontinued for patients who have undergone lung transplant. Is this discontinuation criterion appropriate for patients aged 2 to 5 years?	ELX-TEZ-IVA is generally a well-tolerated treatment and patients who initiate treatment before the age of 6 years would be expected to remain on therapy for many years if they continue to benefit. Some of these patients may eventually require a lung transplant; therefore, the discontinuation criterion remains relevant for a recommendation issued for the younger patient population.
Are there other discontinuation criteria that public drug plans should consider?	The clinical experts noted to CDEC that there are no additional objective discontinuation criteria for ELX-TEZ-IVA reimbursement.
Considerations for prescribing of therapy	
Currently, there are CDEC-recommended prescribing criteria for the treatment of CF in patients aged 6 years and older who have at least one F508del mutation in the *CFTR* gene: • Prescribing of ELX-TEZ-IVA and monitoring of treatment response should be limited to CF specialists. • ELX-TEZ-IVA should not be reimbursed in combination with other *CFTR* modulators. Are the above prescribing criteria appropriate for patients aged 2 to 5 years?	The only appropriate setting for initiation and monitoring of treatment with ELX-TEZ-IVA remains an adult or pediatric CF clinic. This treatment will typically be initiated and monitored in the outpatient clinic setting, by a CF physician and the associated multidisciplinary team (e.g., specialists in respirology, infectious diseases, and gastroenterology). The experts noted that the drug may also be initiated in hospital. It would not be appropriate that a physician in a nonspecialty setting would prescribe and monitor treatment with ELX-TEZ-IVA. ELX-TEZ-IVA would not be prescribed in combination with another *CFTR* modulator.
Generalizability	
Is there a clinical desire to use ELX-TEZ-IVA in patients younger than 2 years?	CADTH noted that the scope of the current review is limited to the indication that has been approved by Health Canada and does not address usage in patients younger than 2 years.

BMI = body mass index; CDEC = CADTH Canadian Drug Expert Committee; CF = cystic fibrosis; CFQ-R = Cystic Fibrosis Questionnaire – Revised; ELX-TEZ-IVA = elexacaftor-tezacaftor-ivacaftor + ivacaftor; FEV_1 = forced expiratory volume in 1 second; $LCI_{2.5}$ = lung clearance index; LUM-IVA = lumacaftor-ivacaftor; PFTs = pulmonary function tests; $ppFEV_1$ =percent predicted forced expiratory volume in 1 second.

Clinical Evidence

Systematic Review

Description of Studies

The evidence identified in the current review of ELX-TEZ-IVA that addressed the expanded patient population (i.e., those aged 2 to 5 years) included Study 111, a 24-week, open-label, phase III, nonrandomized, single-arm, 2-part (A and B) study. Study 111 was conducted in 2 parts:

- Part A (n = 18) consisted of a 15-day treatment period conducted to evaluate the pharmacokinetics and safety and tolerability of ELX-TEZ-IVA.
- Part B (n = 75) consisted of a 24-week treatment period conducted to assess safety and tolerability (primary objective) and pharmacokinetics, pharmacodynamics, and efficacy (secondary objective).

Patients were eligible to be included in Study 111 if they had received a diagnosis of CF and were aged 2 to 5 years (inclusive). All patients had an F508del *CFTR* mutation that was either F/MF (69.3%) or F/F (30.7%). Patients were excluded from the study if they had any comorbidities that could impact treatment outcomes, or if they had received a prior hematological or solid organ transplant. The trial excluded patients with a history of colonization with *Burkholderia cenocepacia*, *Burkholderia dolosa*, and/or *Mycobacterium abscessus*. Patients were also considered to be ineligible if they reported an acute upper or lower respiratory infection, a pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before the first dose of the study drug. Patients with a history of solid organ or hematological transplant were excluded, as were patients with abnormal laboratory values (e.g., hemoglobin < 10 g/dL), abnormal liver function, or abnormal renal function.

Safety and tolerability were the primary end points in Study 111. Secondary end points were absolute change from baseline in sweat chloride through 24 weeks and absolute change from baseline in $LCI_{2.5}$. Changes from baseline in growth parameters (BMI, BMI z score, weight, weight z score, height, and height z score) were evaluated as additional efficacy end points, but no statistical analyses were conducted. Descriptive statistics were provided for pulmonary exacerbations and CF-related hospitalizations in Study 111. $LCI_{2.5}$ was only evaluated in patients who were at least 3 years of age at the time of screening (n = 50).

Efficacy Results

Treatment with ELX-TEZ-IVA resulted in a within-group improvement (reduction) in sweat chloride from baseline through 24 weeks (least squares [LS] mean absolute change was −57.9 mmol [95% confidence interval (CI), −61.3 to −54.6]; nominal P < 0.0001). The reduction from baseline was observed at all postbaseline assessments (i.e., weeks 4, 12, and 24). Results for the subgroup analyses based on *CFTR* genotype were−70.0 mmol/L (95% CI, −75.4 to −64.5) in the F/F group and −52.6 mmol/L (95% CI, −56.9 to −48.4) in the F/MF group.

Among those patients who were assessed, treatment with ELX-TEZ-IVA resulted in an improvement (reduction) in $LCI_{2.5}$ through 24 weeks (within-group LS mean absolute change from baseline −0.83 [95% CI, −1.01 to −0.66]; nominal P < 0.0001). The reduction from baseline was observed at all postbaseline

assessments (i.e., weeks 4, 12, and 24). The results were similar in the F/F and F/MF genotype subgroups (LS mean change: −0.89 [95% CI, −1.15 to −0.63] and −0.82 [95% CI, −1.06 to −0.57], respectively).

Sixteen percent of patients experienced a pulmonary exacerbation event through 24 weeks (each patient experience 1 event), with an annualized event rate of 0.32 per year. One patient experienced a pulmonary exacerbation that required hospitalization. There were no CF-related hospitalizations in Study 111.

The absolute changes from baseline in growth end points at 24 weeks were: 0.10 (95% CI, 0.00 to 0.20) for BMI z score; 0.02 (95% CI, −0.04 to 0.09) for body weight z score; and −0.06 (95% CI, −0.11 to 0.00) for height z score.

Harms Results

The overall percentage of patients who experienced at least 1 adverse event (AE) was 98.7% (nearly all were mild [62.7%] or moderate [36.0%] in severity). These AEs included cough (61.3%), increased alanine transaminase (ALT)(10.7%), rhinorrhea (33.3%), increased aspartate aminotransferase (AST) (5.3%), rash (16.0%), pyrexia (34.7%), vomiting (28.0%), COVID-19 (18.7%), nasal congestion (17.3%), upper respiratory tract infection (14.7%), decreased appetite (12.0%), and infective pulmonary exacerbation of CF (10.7%). Two patients (2.7%) experienced serious adverse events (SAEs): 1 patient with anal incontinence, urinary incontinence, and abnormal behaviour [wording from original source]); and 1 patient with an infective pulmonary exacerbation of CF. One patient (1.3%) discontinued treatment due to an SAE and 5 patients (6.7%) had AEs leading to treatment interruption. For AEs of special interest, 8 patients (10.7%) experienced elevated transaminase events and 15 patients (20.0%) experienced rash events (all events were mild or moderate in severity). Two patients experienced rash events leading to treatment interruption. There were no study discontinuations due to rash events or elevated transaminase events.

Critical Appraisal

Internal Validity

Study 111 was conducted in a manner similar to all other pivotal studies for the use of *CFTR* modulators in patients aged 2 to 5 years (i.e., expansion of approval indications for Orkambi and Kalydeco). Each of these studies was conducted in 2 parts, with part A involving a small number of patients (n = 18 for Study 111) with a primary objective of evaluating pharmacokinetics, and part B enrolling more patients (n = 75 for Study 111) with the primary objective of evaluating safety and tolerability. As with the other trials for *CFTR* modulators in patients aged 2 to 5 years, ELX-TEZ-IVA was administered in an open-label manner in Study 111 and there was no comparator group for either part A or part B. The limited number of secondary efficacy end points evaluated in the study were objective and unlikely to be influenced by the open-label administration of a *CFTR* modulator (i.e., change from baseline in sweat chloride concentration and change from baseline in $LCI_{2.5}$).

Pulmonary exacerbations were only evaluated with descriptive statistics and there were no prebaseline or postbaseline comparisons of event rates. In response to an inquiry from CADTH regarding why pulmonary exacerbations were not included as an efficacy end point, the sponsor reported that, similar to the pediatric trial for patients aged 6 to 11 years, exacerbations occur less frequently in younger patients relative to older patients. As Study 111 was a single-arm trial without a defined pretreatment evaluation period, together with

the low pulmonary exacerbation rates in the study population, comparison to a pretreatment event rate was not possible.

External Validity

Eligibility and diagnostic criteria used to screen patients for Study 111 were similar to those used in the other phases of the ELX-TEZ-IVA clinical development program (e.g., Studies 106 and 116 for patients aged 6 to 11 years, and Studies 102, 103, 104, and 109 for patients aged 12 years and older). As noted in the previous CADTH review of ELX-TEZ-IVA, these criteria are generally consistent with Canadian clinical practice for diagnosing patients with CF. As all Canadian provinces and territories have instituted newborn screening, diagnosis of CF and confirmation of genotyping would typically occur early in the child's life (e.g., an average of 1 month after birth). As such, there would be no changes in diagnostic testing requirements to establish patient eligibility based on CF diagnosis and genotype for the revised age range for ELX-TEZ-IVA.

The clinical experts consulted by CADTH noted that the baseline growth parameters for the patients in Study 111 offered a reasonable reflection of the typical patient in Canadian practice.

Change from baseline in lung function was evaluated as a secondary efficacy end point in Study 111 using $LCI_{2.5}$. This is reflective of regulatory guidance, which has noted that spirometry may not be sensitive enough to detect treatment differences in children with cystic fibrosis. In addition, spirometry is not typically performed in patients younger than 6 years in Canada, and FEV_1 has not been used as a clinical trial end point in any *CFTR* modulator studies for those younger than 6 years. LCI is used in CF clinical trials as it may be more sensitive in identifying early underlying structural deficiencies within the lungs of patients with CF that cannot be detected using spirometry. Similar to spirometry assessments, the LCI test can be challenging to perform accurately with young children. In Study 111, the sponsor noted that LCI was only performed with patients who were aged at least 3 years at the time of screening. Although LCI is used as an end point in clinical studies, as noted previously, it is not routinely used in Canadian clinical practice and the clinical relevance of differences in this end point have not been characterized. The clinical experts consulted by CADTH indicated that LCI is not reliably correlated with FEV_1. A literature review conducted by CADTH found that variable correlation was observed between FEV_1 and LCI in children.

ELX-TEZ-IVA was added to the existing therapeutic regimens used by patients, which is reflective of how ELX-TEZ-IVA would be administered in clinical practice. The clinical experts consulted by CADTH indicated that the background therapies used in Study 111 were similar to what would be anticipated in Canadian clinical practice, with the following exacerbations: all patients in Canadian practice would be supplementing with vitamins, and the use of mucolytics (i.e., dornase alfa and inhaled hypertonic saline) could be slightly lower for patients aged 2 to 5 years in Canada.

The 24-week study treatment periods were sufficient for observing change from baseline in sweat chloride and $LCI_{2.5}$ in Study 111; however, the clinical experts consulted by CADTH suggested that 24 weeks is unlikely to be enough time to observe meaningful changes in BMI for a younger patient population that is relatively healthy. In addition, the absence of a control group in Study 111 limits the ability to interpret the results of change from baseline in the growth parameters.

Long-Term Extension Studies

Patients who completed Study 111 were eligible to enrol in an open-label extension study. However, the sponsor reported that the interim results of the extension study were not available at the time of filing the application with CADTH.

Indirect Comparisons

Feasibility of ITC in Patients Aged 2 to 5 Years

The sponsor conducted an indirect treatment comparison (ITC) to compare the clinical efficacy of ELX-TEZ-IVA in Study 111 with other *CFTR* modulators in patients with F/F and F/MF mutations to generate inputs needed for the cost-effectiveness analysis. A meta-analysis approach via mixed-effects model for repeated measures (MMRM) was used with individual patient-level data from relevant trials, with data from all comparators being included in 1 model for each genotype. The sponsor concluded that the ITC was not feasible due to the small number of patients in this age group, which reduced the power to detect differences between ELX-TEZ-IVA, LUM-IVA, and/or placebo. As such, the sponsor did not include the ITC comparison in their submission to CADTH and used estimates from the previous CADTH submission for patients aged 6 to 11 years to use as assumptions within their economic model.

ITCs in Patients Aged 6 to 11 Years and 12 Years and Older

To inform the pharmacoeconomic model, the sponsor submitted estimates of clinical efficacy of ELX-TEZ-IVA compared to placebo derived from ITCs that were previously conducted for patients aged 6 to 11 years and 12 years and older, using individual patient data from relevant phase III randomized controlled clinical trials.

The sponsor conducted a single indirect comparison for patients aged 6 to 11 years with an F/F genotype to derive relative estimates of clinical efficacy for: ELX-TEZ-IVA versus LUM-IVA, ELX-TEZ-IVA versus placebo, and ELX-TEZ-IVA versus TEZ-IVA. TEZ-IVA is not currently approved by Health Canada or reimbursed by the Canadian public drug programs for use in patients aged 6 to 11 years. To conduct the primary indirect comparisons, the sponsor extracted 24-week individual patient data for those with an F/F genotype from the following studies: Study 106B for ELX-TEZ-IVA (N = 29), pooled data from Study 809-109 and Study 809-011B for LUM-IVA (N = 160), and Study 661-113B (N = 61) for TEZ-IVA. Additional sensitivity analyses were performed using 8-week data. The sponsor reported the following indirect estimate of effect for ELX-TEZ-IVA compared with placebo for absolute change from baseline through 24 weeks: [redacted] for $ppFEV_1$. The primary limitation of the ITC was the difference in study design across the included studies (Studies 106B, 809-011B, and 661-113B were single-arm, open-label trials; and Studies 809-109 and 661-115 were double-blind, placebo-controlled trials) and differences in baseline characteristics.

Studies Addressing Gaps in the Evidence From the Systematic Review

The sponsor did not include any additional studies to address gaps in the pivotal trial evidence.

Ethical Considerations

Patient group, clinical expert, and drug program input gathered during this CADTH review, as well as relevant literature, were reviewed to identify ethical considerations relevant to the use of ELX-TEZ-IVA for the treatment of CF in patients aged 2 to 5 years who have at least one F508del mutation in the *CFTR* gene.

Ethical considerations identified in this review included those related to the following.

- **Diagnosis, treatment, and experiences of CF:** Ethical considerations in the context of CF highlighted the physical and psychosocial burden of CF on patients, families, and caregivers.
- **Evidence and evaluation of ELX-TEZ-IVA in patients aged 2 to 5 years:** Clinical trial evidence indicated that ELX-TEZ-IVA was well-tolerated in study participants aged 2 to 5 years, with few SAEs, and with the recommendation for ongoing monitoring of liver enzymes. However, as the trial was not primarily designed to assess efficacy, the determination of efficacy in patients aged 2 to 5 years for the purposes of regulatory approval was extrapolated from studies conducted in older patients with CF. Extrapolation may offer benefits such as avoiding exposing vulnerable patients, such as children, to unnecessary research and extending access to therapy in patient populations that may be difficult to study or cannot be studied in clinical trials. However, extrapolation also presents potential risks if efficacy is not generalizable and thus overestimates or underestimates real-world effectiveness across different populations. Long-term monitoring is required to understand long-term safety, efficacy, and comparative effectiveness of ELX-TEZ-IVA in patients aged 2 to 5 years. The lack of long-term efficacy and comparative effectiveness data limits the ability to accurately model and assess the cost-effectiveness of ELX-TEZ-IVA for use in patients aged 2 to 5 years.
- **The use of ELX-TEZ-IVA in patients aged 2 to 5 years:** Clinical experts noted that, given the efficacy data in patients aged 6 years and older, they expected ELX-TEZ-IVA to benefit patients aged 2 to 5 years who have at least one F508del mutation in the *CFTR* gene. As a result, they suggested that they would recommend prescribing ELX-TEZ-IVA for children aged 2 to 5 years, given the expected benefits of preventive treatment to prevent structural lung damage, the lack of effective alternatives, and the generally favourable safety and tolerability profile in this age group. As an orally administered medication, ELX-TEZ-IVA is relatively accessible and easy to administer for patients or their caregivers, including relative to alternate therapies.
- **Health systems considerations:** Expensive drugs for rare diseases, such as ELX-TEZ-IVA, raise ethical considerations related to distributive justice and equitable access, the sustainability of health care budgets and consideration of opportunity costs, and fair pricing of pharmaceuticals. As a highly expensive medication, the cost of ELX-TEZ-IVA could present challenges for provincial drug budgets where the reimbursement of ELX-TEZ-IVA may have a disproportionately large budget impact. There is a need to address potential inequities in access due to inconsistent reimbursement and/or insurance coverage across and within jurisdictions in Canada.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Microsimulation
Target population	Patients with CF aged 2 to 5 years who have at least one F508del *CFTR* mutation in the *CFTR* gene, represented by the following 4 genotypes: • Homozygous for F508del *CFTR* (F/F) • Heterozygous for F508del *CFTR* with minimal function mutation (F/MF) • Heterozygous for F508del *CFTR* with a gating mutation (F/Gating), inclusive of the R117H mutation • Heterozygous for F508del *CFTR* with residual function mutation (F/RF)
Treatment	ELX-TEZ-IVA[a] with background BSC
Dose regimen	Based on patient weight, 1 granule packet containing elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg or elexacaftor 80 mg, tezacaftor 40 mg, and ivacaftor 60 mg granules in the morning; and 1 granule packet of ivacaftor 59.5 mg or ivacaftor 75 mg in the evening
Submitted price	ELX-TEZ-IVA (Trikafta), 100 mg/50 mg/75 mg plus 75 mg, or 80 mg/40 mg/60 mg plus 59.5 mg granules: $840 per daily dose
Treatment cost	$306,810 annually per patient, regardless of strength
Comparators	• F/F genotype: LUM-IVA with BSC, BSC alone • F/MF, F/RF, or F/Gating mutations: BSC alone • BSC for all genotypes consisted of recommended medications (such as mucolytics, inhaled and oral antibiotics, inhaled hypertonic saline, nutritional supplements, enteral tube feeding, pancreatic enzymes, antifungal agents, and corticosteroids) and physiotherapy.
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (97 years)
Key data sources	• Baseline patient characteristics were derived for each genotype separately from a number of trials of *CFTR* modulators in these populations. • Baseline mortality hazard was estimated based on an age-specific mortality from a CF population survival curve derived from the literature. This survival was adjusted for changes in patient characteristics using a Cox proportional hazards model. • The sponsor submitted an ITC to inform placebo-adjusted estimates for acute change in $ppFEV_1$ and mean change in weight-for-age z scores in the F/F population for patients on *CFTR* modulators. Data for the F/MF population were based on Study 116, where patients were aged 6 to 11 years, while the data for the F/RF and F/Gating populations were extrapolated from trial data for the population aged 12 years and older. Patients on BSC were assumed not to experience any improvement in either outcome. In the absence of clinical data for patients aged 2 to 5 years, patients in the model were assumed to experience gains in efficacy as indicated by the ITC upon turning 6. • The impact of treatment on long-term reduction in $ppFEV_1$ decline, beyond 192 weeks, was based on a propensity score matched analysis of F/F and F/MF patients aged 12 years on ELX-TEZ-IVA (for up to 120 weeks) in Study 105-IA3 to untreated control patients from the US Cystic Fibrosis Foundation Patient Registry. The value from F/MF patients (89.7%) was assumed to be a suitable proxy for F/RF and F/Gating patients in the absence of published long-term rate of change data on these genotypes.

Component	Description
Key limitations	• The long-term impact of treatment with *CFTR* modulators on $ppFEV_1$ rate of decline and PEx rates in comparison with BSC is uncertain due to a lack of evidence beyond the trial periods for any genotype or age group. This results in substantial uncertainty with the cost-effectiveness of ELX-TEZ-IVA. • The sponsor incorporated dynamic pricing for *CFTR* modulators based on an assumption of generic entry. This assumption is associated with uncertainty and likely underestimates the total costs associated with ELX-TEZ-IVA. • Drug acquisition costs were adjusted for patient compliance, while treatment efficacy was not. While drug wastage may occur, drugs will still be dispensed and paid for by public drug plans. This underestimated the total drug costs associated with ELX-TEZ-IVA. • Costs incurred by the health care system for the period for which ELX-TEZ-IVA extends survival in comparison with BSC were excluded, which underestimates the total costs associated with ELX-TEZ-IVA. • The sponsor adjusted disease-management costs for hospital visits and pharmacotherapy for patients receiving *CFTR* modulators, but the cited studies did not indicate whether results were controlled for patient $ppFEV_1$. Therefore, the magnitude of potential cost savings is uncertain and may have been double-counted. • The sponsor included a treatment-specific utility increment to account for the benefit of treatment with ELX-TEZ-IVA beyond its impact driven by $ppFEV_1$ and PEx. The increment calculated by the sponsor was adjusted for $ppFEV_1$ but not for PEx, likely leading to double counting of QALY benefits with ELX-TEZ-IVA. • The survival benefit predicted in the model for ELX-TEZ-IVA was overestimated and did not meet face validity.

CADTH reanalysis results	CADTH conducted a reanalysis that included: the removal of the additional benefit of *CFTR* modulators on the long-term rate of decline in ppFEV1 and PEx; the removal of dynamic pricing; inclusion of health care costs across the entire model time horizon; the removal of an adjustment to drug acquisition costs by patient compliance; assuming equal hospital and pharmacotherapy costs according to $ppFEV_1$ between treatments; and the removal of a treatment-specific utility increment for patients on ELX-TEZ-IVA.
	Results of the CADTH reanalysis are as follows.
	• F/F genotype:
	  ◦ ICER vs. BSC = $1,283,744 per QALY gained (inc. costs = $10,287,657; inc. QALYs = 8.0)
	  ◦ ICER vs. LUM-IVA = $850,053 per QALY gained (inc. costs = $5,142,458; inc. QALYs = 6.0)
	• F/MF genotype:
	  ◦ ICER vs. BSC = $1,311,755 per QALY gained (inc. costs = $10,387,273; inc. QALYs = 7.9)
	• F/Gating genotype:
	  ◦ ICER vs. BSC = $1,204,386 per QALY gained (inc. costs = $10,387,077; inc. QALYs = 8.6)
	• F/RF genotype:
	  ◦ ICER vs. BSC = $1,437,829 per QALY gained (inc. costs = $10,971,100; inc. QALYs = 7.3)
	ELX-TEZ-IVA was not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained in any scenario conducted by CADTH. A price reduction in excess of 94% for ELX-TEZ-IVA (for both granules and tablets) is required for ELX-TEZ-IVA to be considered cost-effective at a willingness-to-pay threshold of $50,000 in any of the genotypes when compared with BSC.

BSC = best supportive care; CF = cystic fibrosis; ELX-TEZ-IVA = elexacaftor-tezacaftor-ivacaftor and ivacaftor; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LUM-IVA = lumacaftor-ivacaftor; LY = life-year; PEx = pulmonary exacerbation; QALY = quality-adjusted life-year; vs. = versus.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the sponsor's adjustment of drug costs by a compliance rate for patients underestimates drug costs and the resulting budget impact, the sponsor's estimate of the proportion of patients switching treatments from LUM-IVA to ELX-TEZ-IVA upon ELX-TEZ-IVA reimbursement may be underestimated, and there is uncertainty regarding the proportion of patients with public drug coverage. The CADTH reanalysis assumed 100% compliance for all drugs. In the CADTH base case, the reimbursement of ELX-TEZ-IVA for the treatment of CF in patients aged 2 to 5 years with at least one F508del *CFTR* mutation is expected to be $42,404,017 in year 1, $46,295,984 in year 2, and $48,029,320 in year 3. Therefore, the 3-year total is $136,729,321. A CADTH scenario analysis found the budget impact to be sensitive to assumptions around the proportion of patients with public drug coverage.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

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Regrets: None

Conflicts of interest: None

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