CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta)

Indication: Treatment of cystic fibrosis in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator gene.

Recommendation: Reimburse with Conditions

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Single Technology

CADTH

ELEXACAFTOR/TEZACAFTOR/IVACAFTOR AND IVACAFTOR (TRIKAFTA — VERTEX PHARMACEUTICALS [CANADA] INC.)

Therapeutic Area: Cystic fibrosis, F508del CFTR mutation

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that elexacaftor/tezacaftor/ivacaftor and ivacaftor (ELX/TEZ/IVA) should be reimbursed for the treatment of patients aged 12 years and older 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.

Rationale for the Recommendation

Four double-blind randomized controlled trials (RCTs) demonstrated that treatment with ELX/TEZ/IVA resulted in added clinical benefit for patients who were heterozygous for the F508del mutation and who had one minimal function mutation (F/MF) (Study 102 [N = 405]); homozygous for the F508del mutation (F/F) (Study 103 [N = 107] and Study 109 [N = 107]); and heterozygous for the F508del mutation and a residual function mutation (F/RF) or a gating mutation (F/G) (Study 104; N = 259). Study 102 demonstrated that, compared with placebo, 24-weeks of treatment with ELX/TEZ/IVA was associated with statistically significant and clinically meaningful improvements in lung function (increase in $ppFEV_1$), nutritional status (increase in BMI), health-related quality of life (increase in CFQ-R respiratory domain scores), and a reduced rate of pulmonary exacerbations, including events that required intravenous (IV) antibiotics and/or hospitalization to manage. Studies 103, 104, and 109 demonstrated that switching to ELX/TEZ/IVA after four weeks of treatment with either TEZ/IVA or IVA was associated with statistically significant and clinically meaningful improvements in $ppFEV_1$ and CFQ-R compared with remaining on the other CFTR modulators. Given the totality of the evidence, CDEC concluded that ELX/TEZ/IVA met some of the needs identified by patients: reducing CF exacerbations, improving health-related quality of life, improving lung function, and improving digestive health allowing people to maintain a healthy body weight.

Based on 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 $1,140,840 per quality-adjusted life-year (QALY) in the F/F genotype; $1,150,105 per QALY in the F/MF genotype, $1,911,977 per QALY in the F/RF genotype, and $1,067,215 in the F/G genotype when compared with best supportive care. For the F/G genotype, ELX/TEZ/IVA was associated with an ICER $181,718 per QALY in comparison with IVA monotherapy. At these ICERs, ELX/TEZ/IVA is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for patients 12 years of age and older with CF who have at least one F508del mutation in the CFTR gene. A reduction in price of at least 90% is required for ELX/TEZ/IVA to be considered cost-effective at a $50,000 per QALY threshold.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason
Initiation	
1. Confirmed diagnosis of CF with at least one F508del mutation in the CFTR gene	Treatment with ELX/TEZ/IVA demonstrated added clinical benefit for patients with at least one F508del mutation in the CFTR gene based on 4 RCTs in patients with F/F, F/MF, F/G, and F/RF genotypes.
2. Aged 12 years and older	The indication approved by Health Canada for ELX/TEZ/IVA is limited to patients who are at least 12 years of age.
3. ppFEV1 ≤ 90%	All 4 RCTs for ELX/TEZ/IVA required patients to have ppFEV1 of ≥40% to ≤90% at the time of screening. • A subset of patients was enrolled with a baseline ppFEV1 <40% and post hoc subgroup analyses in Study 102 suggested that treatment with ELX/TEZ/IVA resulted in clinically meaningful improvements in the lung function of these patients. Patients with a ppFEV1 <40% represent a group with severe disease and significant unmet treatment needs. • There were no data available to evaluate the efficacy of ELX/TEZ/IVA in patients with a baseline $ppFEV_1$ >90%.
4. Baseline spirometry measurements of FEV_1 and FVC must be completed prior to initiation of ELX/TEZ/IVA treatment.	To establish baseline lung function and for the calculation of $ppFEV_1$.
5. Patients should be optimized with best supportive care, have stable disease, and should not have untreated infections. Patients should not be experiencing an active CF exacerbation and/or receiving oral or IV antibiotic treatment or be hospitalized for reasons related to CF at the time of initiation.	Consistent with the RCTs that were conducted with ELX/TEZ/IVA, patients should have their ppFEV1 evaluated when their functional status is optimized.
Renewal	
1. Reimbursement of treatment with ELX/TEZ/IVA should continue if, after the initial six months of treatment, there is a documented improvement in $ppFEV_1$ of at least 5% compared with the baseline measurement.	ppFEV1 improved by approximately 10% to 14% from baseline in the 24-week studies. Clinical experts noted that the magnitude of improvement in CF outcomes that would be considered clinically significant depends on the baseline status of the patient. However, for $ppFEV_1$ an improvement of at least 5% would typically be considered clinically meaningful for most patients in Canadian clinical practice.
2. Subsequent assessments for renewal of reimbursement should occur annually. Documented maintenance of ppFEV1 greater than 5% from baseline must be provided at each subsequent assessment for continued reimbursement.	The durations of the studies were not adequate to determine how long the treatment effect of ELX/TEZ/IVA would be maintained. Annual assessment for continued reimbursement provides flexibility to accommodate the practical challenges of assessing clinical response to treatment, especially the long-term effects on lung function, given the natural history of CF.
Discontinuation	
1. Patient has undergone lung transplantation	Evidence for the use of ELX/TEZ/IVA in post-lung transplant patients is limited and Canadian clinical experts indicated that the treatment should be discontinued in patients who have received lung transplantation.

Reimbursement Condition	Reason
Prescribing	
1. Prescribing of ELX/TEZ/IVA and monitoring of treatment response should be limited to CF specialists.	Care for CF patients is complex and is managed through specialized CF clinics in Canada.
2. 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. • ELX/TEZ/IVA is a combination product containing the same active components of Symdeko (TEZ/IVA) and Kalydeco (IVA). • IVA is also a component of Orkambi (LUM/IVA).
Pricing	
1. A reduction in price.	The ICER for ELX/TEZ/IVA in comparison with BSC ranged from $1,067,215 to $1,911,977 per QALY, depending on the genotype. A price reduction of at least 90% for ELX/TEZ/IVA is required for all four genotypes for ELX/TEZ/IVA to be considered cost-effective at a $50,000 per QALY WTP threshold in comparison with BSC.

BSC = best supportive care; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor and ivacaftor; ICER = incremental cost-effectiveness ratio; LUM = lumacaftor; QALY = quality adjusted life-year; WTP = willingness-to-pay.

Implementation Guidance

1. CDEC noted, with clinical expert input, that patients may experience benefits from treatment with ELX/TEZ/IVA when meaningful improvement or maintenance of lung function (measured by ppFEV$_1$) is not observed. Decisions regarding continuing treatment in clinical practice settings are based on assessments of exacerbation frequency, the frequency of oral and/or IV antibiotic use, time in hospital for CF-related reasons, nutritional status (based on weight, height, and BMI), health-related quality of life, and adverse events, along with changes in lung function. Jurisdictions may want to consider additional clinical measures beyond lung function when assessing renewal of reimbursement on an individual case basis.
2. Clinically significant improvements from baseline in lung function (ppFEV1) and health-related quality of life (measured with the CFQ-R) are typically reported as at least 5% and 4 points, respectively. Validated thresholds for clinically relevant improvements in the frequency of exacerbations, total number of days in hospital for CF-related reasons, total number of days of treatment with oral and/or IV antibiotics for pulmonary exacerbations, and nutritional status were not identified. Clinical expert input indicated that the goal of therapy is to improve nutritional status (i.e., increase BMI into the healthy range for age and sex) and to reduce the frequency of exacerbations and related health care use (i.e., antibiotic use and hospitalization).
3. If a clinical measure(s) in addition to ppFEV$_1$ is (are) included for the assessment of renewal of reimbursement, then baseline measurement of the clinical measure must be completed prior to initiation of ELX/TEZ/IVA treatment. The following should be collected, as appropriate, based on the clinical measure(s) chosen: body weight, height, and BMI; total number of pulmonary exacerbations in the six months prior to starting treatment; total number of days treated with oral and/or IV antibiotics for pulmonary exacerbations in the six months prior to starting treatment; health-related quality of life using the CFQ-R.
4. Patients enrolled in three of the studies (Study 103, Study 104, and Study 109) received treatment with TEZ/IVA or IVA during the 28-day active-treatment run-in periods. Patients were subsequently randomized to receive ELX/TEZ/IVA or to remain on the active treatment administered during the run-in period. Therefore, this evidence is most relevant to patients who are switching CFTR modulator therapy. The evidence for patients who are treatment naïve comes from Study 102 and indirect treatment comparisons.
5. CADTH reanalyses estimated the incremental budget impact of reimbursing ELX/TEZ/IVA to be $1,279,931,452 over three years, which CDEC considered a potential barrier to implementation.

Discussion Points

- CF is a rare and serious disease that is life-limiting for patients. The F508del mutation in the CFTR gene is the most commonly observed mutation and, in some cases, a more severe form of CF.

- CDEC discussed the impact of CF on patients and their caregivers, noting the impact on health-related quality of life is particularly high, and as the disease progresses the limitations on daily activities grow and more time and effort are needed to manage the progressive and debilitating symptoms. In addition to experiencing a physical decline, people with CF can also suffer from psychological challenges, such as depression, anxiety, and hopelessness. Patient input highlighted the following expectations for new treatment for CF: stop or slow the progression of disease, reduce the frequency of exacerbations, reduce or avoid the development of co-morbidities and disease complications, improve digestive health (attain and maintain a healthy weight), longer life expectancy, avoid hospitalizations and reduce the need for invasive procedures, reduce the burden of daily therapy, improved quality of life (especially wellness, well-being, and the ability to contribute to society), and minimize side-effects. Given this input and the available evidence, CDEC concluded that ELX/TEZ/IVA potentially meets some very important unmet needs identified by patients.
- CDEC noted that the outcomes evaluated in the studies were clinically relevant and that statistically testing appropriately controlled for multiple comparisons, especially Study 102 which evaluated the most outcomes of interest for the review.
- The committee discussed that the evidence for patients with advanced lung disease (i.e., ppFEV1 < 40%) is limited to post-hoc subgroup analyses and observational studies, and that patients with ppFEV1 > 90% at screening were excluded from the reviewed studies. More data from high quality studies is needed to better understand the effects of ELX/TEZ/IVA in these patients with CF.
- Except for IVA, the comparators used in active controlled studies and indirect comparisons (i.e., TEZ/IVA and LUM/IVA) are not currently reimbursed by the CADTH-participating drug programs.
- CDEC noted that the included studies enrolled patients who were at least 12 years of age at screening and that this is reflected in the indication that has been approved by Health Canada. Studies investigating the efficacy and safety of ELX/TEZ/IVA in children younger than 12 years of age are currently ongoing.
- CDEC discussed variability in response to treatments with clinical experts. It was noted that those with more advanced disease may show smaller changes from baseline in commonly measured outcomes (e.g., $ppFEV_1$), but still experience clinically relevant improvements in other outcomes (i.e., health-related quality of life, frequency of exacerbations, total number of days in hospital for CF-related reasons, total number of days of treatment with oral and/or IV antibiotics for pulmonary exacerbations, and nutritional status).
- CDEC noted that the trials enrolled patients with stable disease, yet there was variation in the measurements of $ppFEV_1$ from screening to randomization. CDEC discussed with clinical experts that while ppFEV1 does not usually vary much for each patient over a shorter period of time, it would be prudent to take at least two measurements of ppFEV1 to gain a more stable value prior to starting treatment with ELX/TEZ/IVA and at the time of assessment for the renewal of reimbursement.
- A key limitation of the reviewed studies was the relatively short duration of treatment and follow up for a life-long condition. Two of the RCTs were 24 weeks long (Study 102 and Study 109), but the other two were only 4 weeks (Study 103) and 8 weeks (Study 104) in duration. Therefore, the durability of treatment effect as well as the longer-term balance between benefits and harms with ELX/TEZ/IVA are uncertain.
- The key safety concern observed with ELX/TEZ/IVA from the studies was liver toxicity. The product monograph states that treatment of patients with moderate hepatic impairment (Child-Pugh Class B) is not recommended but may be considered when there is a clear medical need, and when the benefits are expected to outweigh the risks. In such situations, the dose of ELX/TEZ/IVA should be reduced (detailed regimen in the product monograph). Patients with severe hepatic impairment (Child-Pugh Class C) should not be treated with ELX/TEZ/IVA.
- CDEC discussed the sponsor-provided indirect treatment comparison between ELX/TEZ/IVA and LUM/IVA for patients with an F/F genotype, and ELX/TEZ/IVA versus placebo for those with an F/F, F/G, or F/RF genotype. Other than Study 104 and Study 109, none of the trials used in the indirect comparisons had a run-in period, and the direction of any potential bias associated with the run-in period could not be determined. Also, randomization was stratified according to F/G or F/RF genotype in Study 104; however, randomization was not stratified according to whether or not the patient had an F508del mutation in other

included studies comparing ELX/TEX/IVA with IVA. Therefore, the selection of the F508del subgroup of patients in the placebo-controlled IVA trials would not have maintained randomization. The limitations with the indirect evidence precluded drawing concrete conclusions on the results.

Background

Trikafta consists of a fixed-dose combination tablet containing ELX 100 mg, TEZ 50 mg, and IVA 75 mg co-packaged with a tablet containing IVA 150 mg. ELX/TEZ/IVA is indicated for the treatment of CF in patients aged 12 years and older who have at least one F508del mutation in the CFTR gene. The recommended dose is two tablets (ELX 100 mg, TEZ 50 mg, and IVA 75 mg) taken in the morning and one tablet (IVA 150 mg) taken in the evening approximately 12 hours apart, with fat-containing food. Health Canada has not authorized an indication for use in children younger than 12 years of age.

Summary of Evidence

To make their recommendation, CDEC considered the following information:

- A review of 4 of RCTs (Studies 102, 103, 104, and 109), one long-term extension phase study (Study 105), one indirect comparison submitted by the sponsor, two observational studies that evaluated the use of ELX/TEZ/IVA in patients with advanced lung disease, and one study that modelled the potential impact of ELX/TEZ/IVA on CF-related morbidity and mortality.
- Patient perspectives gathered by patient groups, Cystic Fibrosis Canada (CF Canada), the Canadian Cystic Fibrosis Treatment Society and CF Get Loud.
- Input from 5 clinical specialists with expertise diagnosing and treating patients living with CF.
- Input from 3 clinician groups, including The Canadian Cystic Fibrosis Clinic Directors, Cystic Fibrosis Canada's Accelerating Clinical Trials Network, and The Toronto Adult CF Clinic.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

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.

Patient Input

Three patient groups, Cystic Fibrosis Canada (CF Canada), the Canadian Cystic Fibrosis Treatment Society and CF Get Loud, responded to CADTH's call for patient input. Information for the CF Canada submission was based on a cross-Canada survey of patients and caregivers that was circulated through CF clinics, email, and social media (1,455 respondents). Canadian CF Treatment Society gathered information through one-on-one and group discussions with individuals with CF, parents, caregivers and treating physicians. CF Get Loud gathered information from a letter campaign that received 11,364 letters from Canadians, a town hall with CF experts and leaders, and from 20 Canadians who are currently receiving treatment ELX/TEZ/IVA.

The patient groups emphasized that CF has tremendous impact on those living with the condition, their loved ones, and on 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. Patients may suffer from pulmonary exacerbations requiring weeks of hospitalization and IV antibiotics. Malnutrition is another consequence of CF and those living with the condition are often underweight and may require a feeding tube for supplemental nutrition. Patients may also suffer from CF-related comorbidities, such as CF-related diabetes and CF-related liver disease. In addition to the decline of CF patients' physical health, many suffer from the unseen effects of CF. These include, but are not limited to, depression, anxiety, and hopelessness. The mental anguish caused by the ever-present awareness of one's mortality cannot be expressed in words and are often not quantified. Parents and caregivers have an overwhelming desire to do something to help their loved ones.

Managing CF requires a demanding treatment routine with regular visits to specialized CF clinics. As the disease progresses, even more time and effort are needed to manage the progressive and debilitating symptoms. The condition has a significant impact on day-to-day quality of life of patients and caregivers, affecting life decisions that include education, career, travel, relationships, and family planning.

Patients with CF and their loved ones are seeking treatments that can change the trajectory of the disease and improve both life expectancy and quality of life. Improved outcomes include retaining or increasing lung function, improved digestive health, better energy levels and minimizing symptoms of CF. Patients want to avoid hospital admissions, reduce the needs for invasive medical procedures and the treatment burden of daily therapies. They also wish to avoid the adverse effects of therapies, such as osteoporosis, antimicrobial resistance, and CF-related diabetes or liver dysfunction.

Clinician input

Input from clinical experts consulted by CADTH

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 transplantation, 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.

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 clinical experts noted that ELX/TEZ/IVA could be used in every patient who meets the Health Canada approved indication, regardless of their current or past treatment regimens. In clinical practice, eligible patients would be identified based on their CFTR genotype; however, there is no practical method that could be used to predict who will be most likely to respond to ELZ/TEZ/IVA. The patients who are most in need of treatment with ELX/TEZ/IVA include: patients with moderate to severe lung disease (e.g., ppFEV1 ≤ 60%), patients whose BMI is less than or equal to 20 kg/m^2, patients with frequent pulmonary exacerbations, and those experiencing a rapid decline in FEV1. However, it could be argued that all patients, including those with mild lung disease or who are pre-symptomatic, could benefit from treatment when considering the long-term outcomes and goal of preventing severe outcomes.

The clinical experts noted that the magnitude of improvement with ELX/TEZ/IVA is far greater than any other currently available treatments for CF (including all other CFTR modulators). ELX/TEZ/IVA would replace earlier CFTR modulators that the experts considered to be less effective (e.g., LUM/IVA [Orkambi] and TEZ/IVA [Symdeko]) and patients currently receiving those drugs would likely be switched to ELX/TEZ/IVA.

The following endpoints are routinely assessed in Canadian clinical practice: FEV_1, nutrition and growth (e.g., BMI or BMI z-score), hospital admissions and outpatient treatments for pulmonary exacerbations, and pulmonary exacerbation frequency per year. The magnitude of improvement in CF outcomes that would be considered clinically significant depends on the baseline status of the patient. After initiating treatment with ELX/TEZ/IVA, those with less severe disease or more advanced disease may show smaller changes from baseline in commonly measured endpoints, but still experience clinically relevant improvements (e.g., stabilization). For $ppFEV_1$ an improvement in $ppFEV_1$ of greater than or equal to 5% would typically be considered clinically meaningful for most patients in Canadian clinical practice. The experts noted that an increase in BMI should only be viewed as a goal of therapy if the patient is malnourished at the time of initiating therapy. Increasing the BMI of a patient who is in the normal range or overweight may pose challenges and should not be viewed as a desirable outcome for evaluating the response to a treatment such as ELX/TEZ/IVA.

Treatment with ELX/TEZ/IVA would most likely be interrupted or discontinued because of adverse events or progression to lung transplant. The most likely known adverse event that would result in discontinuation would be development of persistent liver enzyme abnormalities.

The clinical experts noted that ELX/TEZ/IVA should be prescribed and treatment should be monitored by an adult or pediatric CF clinic.

Clinician group input

Three groups of clinicians responded to CADTH's call for input: The Canadian Cystic Fibrosis Clinic Directors, Cystic Fibrosis Canada's Accelerating Clinical Trials Network, and The Toronto Adult CF Clinic. The input from the clinician groups identified the same unmet medical needs for CF patients and potential place in therapy for ELX/TEZ/IVA as the clinical experts consulted by CADTH. Similar to the clinical experts consulted by CADTH, the clinician groups noted that the impact of ELX/TEZ/IVA has been dramatic and life-altering for the patients who have received the treatment through Health Canada's Special Access Programme, compassionate access mechanisms, or in clinical trials (including patients who have advanced lung disease).

Drug program input

Input was obtained from the drug programs that participate in the CADTH reimbursement review processes. The following were identified as key factors that could impact the implementation of a CADTH recommendation for ELX/TEZ/IVA:

- Potential need for objective criteria that can be used to evaluate response to treatment
- Potential timepoints that should be used when evaluating the response to treatment
- Advice on the use of ELX/TEZ/IVA in key patient populations that were excluded from the phase 3 studies

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

There were four double-blind, phase 3, RCTs included in the CADTH systematic review: one placebo-controlled trial conducted in patients who were heterozygous for the F508del mutation and who had one minimal function mutation (F/MF) (Study 102 [N = 405]); two active-controlled trials in patients who were homozygous for the F508del mutation (F/F) (Study 103 [N = 107] and Study 109 [N = 107]); and one active-controlled trial in patients who were heterozygous for the F508del mutation and a residual function mutation (F/RF) or a gating mutation (F/G) (Study 104; N = 259).

The double-blind treatment periods were 24 weeks in Study 102 and Study 109, 8 weeks in Study 104, and 4 weeks in Study 103. Studies 103, 104, and 109 all included a 28-day active-treatment run-in period where all patients with either an F/F or F/RF genotype received treatment with TEZ/IVA plus IVA (Studies 103, 109, and the F/RF subgroup of patients in Study 104) and patients with an F/G genotype received treatment with ivacaftor (IVA) (F/G subgroup of patients in Study 104). Patients were subsequently randomized to receive ELX/TEZ/IVA or to remain on the active treatment administered during the run-in period. All the studies included a screening phase (up to 28 days) and a safety follow-up phase (approximately four weeks or entry into an open-label extension phase study).

The inclusion and exclusion criteria for the included RCTs were similar except for the CFTR genotypes (i.e., F/MF, F/F, F/G, or F/RF). Patients were required to have stable CF disease in the opinion of the investigator and a $ppFEV_1$ of ≥40% and ≤90% at the time of screening. The trials 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, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within four weeks before first dose of study drug. Patients with a history of solid organ or hematological transplantation were excluded, as were patients with abnormal laboratory values (e.g., hemoglobin < 10 g/dL [< 100 g/L]), abnormal liver function, or abnormal renal function.

Efficacy Results

Patients with F/MF Genotype (Study 102)

Treatment with ELX/TEZ/IVA was associated with a statistically significant absolute increase from baseline in $ppFEV_1$ compared with placebo at 4 weeks (least squares mean difference [LSMD]: 13.8% [95% CI, 12.1 to 15.4]; P < 0.0001) and 24 weeks (LSMD: 14.3%

[95% CI, 12.7 to 15.8]; P < 0.0001). Improvements in ppFEV$_1$ with ELX/TEZ/IVA were observed at the time of the first post-baseline assessment (i.e., day 15) and were higher at all time points throughout the study. Results for change from baseline in ppFEV$_1$ were generally consistent across all subgroup analyses, including those based on age (12 to <18 years or ≥18 years) and ppFEV$_1$ at screening (<70% or ≥70%). The sponsor conducted an additional post hoc subgroup analysis for the subset of patients with a ppFEV$_1$ below 40% at baseline (16/203 [7.9%] in the placebo group and 18/200 [9.0%] in the ELX/TEZ/IVA group), in which the absolute difference in ppFEV$_1$ with ELX/TEZ/IVA versus placebo was 15.2% (95% CI, 7.3 to 23.1) at 4 weeks and 18.4% (95% CI, 11.5 to 25.3) at 24 weeks.

Treatment with ELX/TEZ/IVA was associated with a lower rate of pulmonary exacerbations compared with placebo (rate ratio 0.37 [95% CI, 0.25 to 0.55]). Similarly, treatment with ELX/TEZ/IVA was associated with lower rates of pulmonary exacerbations requiring hospitalization (rate ratio 0.29 [95% CI, 0.14 to 0.61]) and pulmonary exacerbations requiring IV antibiotic therapy (rate ratio 0.22 [95% CI, 0.11 to 0.43]). Hazard ratios (HR) favoured ELX/TEZ/IVA over placebo for time-to-first pulmonary exacerbation (HR: 0.34 [95% CI, 0.22 to 0.52]), time-to-first pulmonary exacerbation requiring hospitalization (HR: 0.25 [95% CI, 0.11 to 0.58]), and time-to-first pulmonary exacerbation requiring IV antibiotics (HR: 0.19 [95% CI, 0.09 to 0.39]).

Treatment with ELX/TEZ/IVA was associated with a statistically significant improvement in BMI at 24 weeks compared with placebo (LSMD: 1.04 kg/m^2 [95% CI, 0.85 to 1.23]; P <0.0001). In patients less than 20 years of age (n = 145), those treated with ELX/TEZ/IVA demonstrated improvements in BMI z-score compared with placebo (LSMD: 0.30 [95% CI, 0.17 to 0.43]). Similarly, the ELX/TEZ/IVA group demonstrated greater improvement in body weight at 24 weeks compared with the placebo group (LSMD: 2.9 kg [95% CI, 2.3 to 3.4]).

Treatment with ELX/TEZ/IVA was associated with a statistically significant and clinically meaningful improvement in Cystic Fibrosis Questionnaire – Revised (CFQ-R) respiratory domain score from baseline compared with placebo through 24 weeks (LSMD: 20.2 [95% CI, 17.5 to 23.0]).

The ELX/TEZ/IVA group demonstrated statistically significant reductions in sweat chloride compared with the placebo group at 4 weeks (LSMD: -41.2 mmol/l [95% CI, -44.0 to -38.5]) and 24 weeks (LSMD: -41.8 [95% CI, -44.4 to -39.3]).

The Treatment Satisfaction Questionnaire for Medication (TSQM) was included as an exploratory endpoint for patients between the ages of 12 and 17 years. The difference in change from baseline favoured ELX/TEZ/IVA compared with placebo in the domains for global satisfaction (LSMD: 11.9 [95% CI, 1.8 to 22.0]) and effectiveness (LSMD: 14.4 [95% CI, 3.5 to 25.4]). The TSQM was not included as an endpoint in Study 109.

Patients with F/F Genotype (Study 103 and Study 109)

In Study 103, treatment with ELX/TEZ/IVA was associated with a statistically significant and clinically meaningful increase from baseline in ppFEV1 compared with TEZ/IVA at 4 weeks (LSMD: 10.0% [95% CI, 7.4 to 12.6]; P < 0.0001). Improvements in ppFEV1 with ELX/TEZ/IVA were observed at the time of the first post-baseline assessment (i.e., day 15) and were higher at all time points throughout the study. The results for change from baseline in ppFEV1 were generally consistent across all subgroup analyses. A post-hoc subgroup analysis from Study 103 suggested that the magnitude of the observed treatment effect (LS mean: 7.8% [95% CI, 4.8 to 10.8]) for CFTR-modulator experienced patients is less than that for CFTR-modulator naïve patients (LS mean: 13.2% [95% CI, 8.5 to 17.9]). In Study 109, treatment with ELX/TEZ/IVA was associated with a statistically significant absolute increase from baseline in ppFEV1 compared with TEZ/IVA through 24 weeks (LSMD: 10.2% [95% CI, 8.2 to 12.1]; P < 0.0001).

Pulmonary exacerbations were only captured as adverse events in Study 103 and Study 109. The percentage of patients with at least one pulmonary exacerbation was greater in the TEZ/IVA compared with the ELX/TEZ/IVA group in both studies.

Compared with TEZ/IVA, treatment with ELX/TEZ/IVA was associated with improvements in BMI at 4 weeks in Study 103 (LSMD: 0.60 kg/m2 [95% CI, 0.41 to 0.79]) and body weight at 4 weeks (LSMD: 1.6 kg [95% CI, 1.0 to 2.1]). Changes from baseline in BMI and body weight were not investigated in Study 109.

Treatment with ELX/TEZ/IVA was associated with a statistically significant and clinically meaningful improvement in CFQ-R respiratory domain score from baseline compared with TEZ/IVA at 4 weeks in Study 103 (LSMD: 17.4 [95% CI, 11.8 to 23.0]) and through 24 weeks in Study 109 (LSMD: 15.9 [95% CI, 11.7 to 20.1]).

The ELX/TEZ/IVA group demonstrated statistically significant reductions in sweat chloride compared with the TEZ/IVA group at 4 weeks (LSMD: -45.1 mmol/l [95% CI, -50.1 to -40.1]) in Study 103 and through 24 weeks in Study 109 (LSMD: -42.8 [95% CI, -46.2 to -39.3]; P < 0.0001).

The TSQM was included as an exploratory endpoint in Study 103 for patients between the ages of 12 and 17 years. The ELX/TEZ/IVA group demonstrated improvements compared with the TEZ/IVA group in the domains for global satisfaction (LSMD: 11.9 [95% CI, 1.8 to 22.0]) and effectiveness (LSMD: 14.4 [95% CI, 3.5 to 25.4]). The TSQM was not included as an endpoint in Study 109.

Patients with F/G and F/RF Genotypes (Study 104)

Treatment with ELX/TEZ/IVA was associated with a statistically significant within-group improvement in ppFEV1 through 8 weeks (LS mean change: 3.7% [redacted]. Treatment with ELX/TEZ/IVA was associated with a statistically significant improvement in ppFEV1 compared to the control group (LSMD: 3.5% [redacted]; P < 0.0001). [redacted].

Pulmonary exacerbations were only captured as adverse events. Compared with the pooled control group (TEZ/IVA and IVA), fewer ELX/TEZ/IVA-treated patients reported at least one pulmonary exacerbation ([redacted]).

[redacted].

[redacted]

The ELX/TEZ/IVA group demonstrated a statistically significant decrease in sweat chloride from baseline (LS mean -22.3 mmol/l [redacted]; P < 0.0001). Treatment with ELX/TEZ/IVA also resulted in a decrease in sweat chloride from baseline compared to the pooled control group (LSMD: -23.1 mmol/l [redacted]; P < 0.0001).

Harms Results

Patients with F/MF Genotype (Study 102)

The overall percentage of patients who experienced at least one adverse event was 96.0% in the placebo group and 93.1% in the ELX/TEZ/IVA group. The percentage of patients who experienced at least one serious adverse event (SAE) was 20.9% in the placebo group and 17.3% in ELX/TEZ/IVA. Pulmonary exacerbations were the most reported SAE and were more frequent in the placebo group compared with the ELX/TEZ/IVA group (17.9% versus 6.4%). There were few other SAEs that were reported for more than one patient in each treatment group. There were two withdrawals due to adverse events (WDAEs) reported in the ELX/TEZ/IVA group (1.0%) and none in the placebo group. The reasons for discontinuation from the ELX/TEZ/IVA group included portal hypertension (0.5.%) and rash (0.5%).

Patients with F/F Genotype (Study 103 and 109)

The overall percentage of patients who experienced at least one adverse event in Study 103 and Study 109 was 63.5% and 88.5% in the TEZ/IVA groups (respectively) compared with 58.2% and 92.0% in the ELX/TEZ/IVA groups (respectively). The percentage of patients who experienced at least one SAE was 15.9% in the TEZ/IVA group compared with 5.7% in the ELX/TEZ/IVA group of Study 109. The difference between the groups was due to a greater percentage of patients in the TEZ/IVA group who experienced a pulmonary exacerbation compared with the ELX/TEZ/IVA group (11.4% versus 1.1%). SAEs were rare in the 4-week Study 103 and only reported for one patient in the TEZ/IVA group (pulmonary exacerbation) and two patients in the ELX/TEZ/IVA group (pulmonary

exacerbation and rash) (1.9% versus 3.6%). There were no WDAEs reported in either the TEZ/IVA or ELX/TEZ/IVA groups in Study 103. In Study 109, WDAEs were reported for 2 patients (2.3%) in the TEZ/IVA group (compulsive disorder and psychotic disorder) and 1 patient (1.1%) in the ELX/TEZ/IVA group (anxiety and depression).

Patients with F/G and F/RF Genotypes (Study 104)

The overall percentage of patients who experienced at least one adverse event was 66.7% in the ELX/TEZ/IVA group and 65.9% in the control group. The percentage of patients who experienced at least one SAE was 8.7% in the control group compared with 3.8% in the ELX/TEZ/IVA group. The difference between the groups was due to a greater percentage of patients in the control group who experienced a pulmonary exacerbation that was classified as an SAE compared with the ELXTEZ/IVA group (5.6% versus 1.5%). There were two WDAEs from the control group (1.6%; pulmonary exacerbation, and anxiety and depression) and one in the ELX/TEZ/IVA group (0.8%; elevated alanine transaminase [ALT] and aspartate transaminase [AST] levels).

Critical Appraisal

Randomization was stratified based on relevant prognostic factors (i.e., age, sex, baseline ppFEV$_1$, and prior CFTR modulator use [in Study 104]). Baseline and demographic characteristics were generally well-balanced across the treatment groups in each of the included studies. Study treatments were administered in a double-blind manner with all groups issued the same number of tablets each day. The adverse event profile of ELX/TEZ/IVA and the comparators was unlikely to compromise blinding in any of the included trials. There were few patients who discontinued the trials (completion rate ranged from 96.8% to 100%), although the studies were relatively short in duration which may in part explain the high percentage of patients who completed. Adherence with the study treatments was reported to be over 99% across all treatment groups in the included trials. In accordance with the study protocols, the use of concomitant medications remained stable throughout the treatment period for all treatment groups. The only exceptions were the lower usage of some antibiotics for pulmonary exacerbations in the ELX/TEZ/IVA group relative to the placebo group in Study 102 (this difference was attributable to the efficacy of ELX/TEZ/IVA for reducing pulmonary exacerbations relative to placebo). The primary and key secondary endpoints were analyzed with statistical testing procedures that controlled the type 1 error rate and all endpoints within the statistical testing hierarchies were statistically significant.

The diagnostic criteria used in Study 103 and Study 109 were consistent with Canadian clinical practice for identifying patients with CF who are homozygous for the F508del-CFTR mutation. The gating and residual function mutations that were used to select patients for inclusion in Study 104 were consistent with the approved indications for TEZ/IVA and IVA in Canada. There were no widely accepted criteria for defining minimal function mutations in the CFTR gene; therefore, the identification of patients with minimal function mutations in Study 102 relied on a novel approach designed by the sponsor (i.e., in vitro response to TEZ, IVA, or TEZ/IVA). The clinical experts consulted by CADTH noted that terms ‘residual function’ and ‘minimal function’ are not currently used in Canadian clinical practice. Patients with CF with more severe lung disease (e.g., ppFEV$_1$ < 40% at screening) or a normal ppFEV$_1$ at screening (≥ 90%) were excluded from the studies; therefore, the results of the included studies are primarily applicable to patients with moderate (i.e., FEV$_1$ 40% to 69%) to mild (i.e., FEV$_1$ 70% to 89%) lung disease. As patients with advanced lung disease are an important subgroup with a high level of unmet medical need, CADTH supplemented this review with additional evidence from observational studies to address this important gap in the RCT evidence.

Study 103, Study 104, and Study 109 included an open-label 4-week active-treatment period with TEZ/IVA or IVA prior to randomization. As such, these trials were essentially investigating switching to ELX/TEZ/IVA from either TEZ/IVA or IVA compared with remaining on TEZ/IVA for patients with an F/F or F/RF genotype or remaining on IVA for patients with an F/G genotype. As TEZ/IVA is not widely reimbursed in Canada, the switching design limits the generalizability of the studies directly to the Canadian setting. To address this potential gap in the evidence, the sponsor submitted indirect comparisons with CADTH to provide an estimate of ELX/TEZ/IVA versus placebo for those with an F/F or F/RF genotype.

Indirect Comparisons

Description of studies

The sponsor conducted indirect comparisons to derive relative estimates of the clinical efficacy for ELX/TEZ/IVA compared to local standard of care in the F/F, F/RF and F/G populations, given the absence of RCTs. Although head-to-head trials were conducted for ELX/TEZ/IVA versus TEZ/IVA (for patients with F/F or F/RF genotypes) and IVA (for patients with an F/G genotype), the sponsor

conducted indirect comparisons to derive estimates of effect for: (1) ELX/TEZ/IVA versus LUM/IVA for patients with an F/F genotype; and (2) ELX/TEZ/IVA versus placebo for those an F/F, F/G, or F/RF genotype. A literature search conducted by CADTH did not identify any additional published indirect comparisons that included the patients, interventions, and outcomes identified in the protocol for CADTH's review of ELX/TEZ/IVA.

All the sponsor's indirect comparisons were conducted using Bucher's method for continuous endpoints. The sponsor stated that Bucher's method was considered the most appropriate approach for these indirect comparisons because of the 4-week active-treatment run-in periods in the ELX/TEZ/IVA trials. As the studies for TEZ/IVA, LUM/IVA, and IVA all enrolled patients who were naïve to CFTR-modulator treatment, the baselines were not considered to be sufficiently comparable to the ELX/TEZ/IVA studies to conduct an individual patient data meta-analysis.

Efficacy Results

For patients with an F/F genotype, indirect comparisons were performed for (1) ELX/TEZ/IVA versus placebo; and (2) ELX/TEZ/IVA versus LUM/IVA. The direct evidence for ELX/TEZ/IVA versus TEZ/IVA was from Study 104, the direct estimate for TEZ/IVA versus placebo was from the EVOLVE trial; and the direct estimate for LUM/IVA versus placebo was derived from a meta-analysis of the TRAFFIC and TRANSPORT trials. The sponsor reported the following indirect estimates of effect for ELX/TEZ/IVA compared with placebo for absolute change from baseline through 24 weeks: [redacted] for $ppFEV_1$; [redacted] for BMI; and [redacted] for the CFQ-R respiratory domain.

For patients with an F/G genotype, indirect comparisons were performed for ELX/TEZ/IVA versus placebo. The direct evidence for ELX/TEZ/IVA versus IVA was derived from a subgroup analysis of Study 104 and the estimates for IVA versus placebo were derived from a meta-analysis of subgroup data from three studies STRIVE, KONNECTION, and KONDUCT. The sponsor reported the following indirect estimates of effect for ELX/TEZ/IVA compared with placebo for absolute change from baseline through 8 weeks: [redacted] for $ppFEV_1$; [redacted] for BMI; and [redacted] for the CFQ-R respiratory domain.

For patients with an F/RF genotype, indirect comparisons were performed for ELX/TEZ/IVA versus placebo. The direct evidence for ELX/TEZ/IVA versus TEZ/IVA was derived from a subgroup analysis of Study 104 and the estimates for TEZ/IVA versus placebo were from the EXPAND trial. The sponsor reported the following indirect estimates of effect for ELX/TEZ/IVA compared with placebo for absolute change from baseline through 8 weeks: [redacted] for $ppFEV_1$; [redacted] for BMI; and [redacted] for the CFQ-R respiratory domain.

Harms Results

The indirect comparison filed by the sponsor did not include any comparisons for adverse events.

Critical Appraisal

The primary limitation of the indirect comparisons was the difference in study design across the included studies. The ELX/TEZ/IVA studies (i.e., Study 104 and Study 109) included the open-label 4-week active-treatment period with TEZ/IVA or IVA prior to randomization. None of the other trials used in the indirect comparisons had a similar run-in period; therefore, the study designs, baseline values, and the endpoint values for the common comparator were different. As both the ELX/TEZ/IVA and the comparator groups of Study 104 and Study 109 received 4 weeks of treatment with a CFTR modulator, the direction of any potential bias associated with the run-in period is uncertain.

Other Relevant Evidence

Long-term extension study

Study 105 is an ongoing, open-label uncontrolled trial that enrolled patients who had completed Study 102 or 103 (i.e., patients with either an F/MF or an F/F genotype). Interim results were reported for 24 weeks of follow-up for Study 102 patients and 36 weeks for Study 103 patients (data cut-off October 2019). A total of 507 patients were enrolled in the extension study (n = 400 from Study 102 and n = 107 from Study 103).

Efficacy Results

Among patients previously enrolled in Study 102, the absolute change from baseline to week 24 in $ppFEV_1$ was similar for patients who switched from placebo to ELX/TEZ/IVA (14.9% [95% CI, 13.5 to 16.3) and for those who remained on ELX/TEZ/IVA (14.3% [95% CI 12.9% to 15.7%]) during the extension study. Patients previously enrolled in Study 103 reported an absolute change from baseline to week 36 in $ppFEV_1$ of 12.8% (95% CI, 10.1 to 15.4) and 11.9% (95% CI, 9.3 to 14.5) during the extension study, for patients previously treated with TEZ/IVA and ELX/TEZ/IVA, respectively.

During treatment with ELX/TEZ/IVA, the annual event rate for pulmonary exacerbations was 0.27 (95% CI, 0.19 to 0.39) for those previously treated with placebo and 0.32 (95% CI, 0.24 to 0.44) for those previously treated with ELX/TEZ/IVA in Study 102, and 0.30 (95% CI, 0.20 to 0.45) for those previously enrolled in Study 103.

The LS mean change from baseline to week 24 for the CFQ-R respiratory domain was 19.2 (95% CI, 16.7 to 21.7) for those switched from placebo to ELX/TEZ/IVA (Study 102), and 20.1 (95% CI, 17.6 to 22.6) for those who received ongoing ELX/TEZ/IVA treatment. The LS mean change was 13.8 (95% CI, 8.9 to 18.8) and 14.3 (95% CI, 9.5 to 19.2) for patients from Study 103, respectively, who were switched from TEZ/IVA to ELX/TEZ/IVA, and those treated with ELX/TEZ/IVA in both study periods.

The absolute change in BMI from baseline to week 24 (Study 102) or week 36 (Study 103) ranged from LS mean of 1.2 kg/m^2 to 1.3 kg/m^2. The change from baseline in BMI z-score was reported for patients who were 20 years of age or younger at the start of the parent studies. The point estimate for the LS mean change from baseline in z-scores ranged from 0.30 to 0.43 across the different treatment populations.

Harms Results

Most patients (93%) reported at least one adverse event during the extension study. The most reported adverse events were infective pulmonary exacerbation of CF (25%), cough (23%), oropharyngeal pain (15%) and nasopharyngitis (14%). Seven patients (1.4%) stopped treatment due to adverse events and 80 patients (16%) experienced at least one serious adverse event.

Critical Appraisal

Study 105 is an ongoing, uncontrolled, open-label trial that enrolled patients who had completed Study 102 or Study 103. As this was an unblinded study, patient's expectations of treatment could potentially have biased the reporting of subjective outcomes, such as respiratory symptoms (as measured by the CFQ-R), or harms. Extension studies are often limited by selection bias, as only patients who are tolerant to treatment and complete the parent studies are eligible to enroll. For Study 105 the risk of selection bias may be low given that only [redacted] patients ([redacted]%) out of the [redacted] randomized in the parent studies, were not enrolled or treated in the extension study. During the first 24 weeks of follow-up, discontinuation of treatment was also low ([redacted] patients, [redacted]%), however the frequency of missing data was higher for some outcomes relative to others. Issues with the generalizability of these data are the same as for the parent double-blind studies.

Observational Studies in Patients with Advanced Lung Disease

Two observational studies provided short-term data on the efficacy and safety of ELX/TEZ/IVA in patients with CF and who had advanced pulmonary disease ($ppFEV_1$ <40% or under evaluation for lung transplantation). All patients had at least one F508del CFTR mutation.

Irish Cohort

The retrospective chart review by O'Shea et al. (2021) reported data for 14 patients who were followed for a mean duration of 4.9 months after starting ELX/TEZ/IVA. Statistically significant improvements were reported for: mean $ppFEV_1$ (increased from 27% [SD 7.3] at baseline to 36% [SD 16.5] after a mean follow-up of 26 days); mean BMI (increased from 20.7 kg/m^2 [SD 3.6] to 22.1 kg/m^2 [SD 3.4)]) and mean sweat chloride (reduced from 105 mmol/L [SD 15] to 54 mmol/L [SD 23]) after an average of 62 days of follow-up. The rate of infective pulmonary exacerbations requiring hospitalization was 0.28 events per month (SD 0.17) in the 12 months prior to ELX/TEZ/IVA, and 0.04 events per month (SD 0.07) during the 4.9 month follow up period ($P < 0.001$).

French Cohort

The prospective cohort study by Burgel et al. (2021) reported data for 245 patients who were followed for a median of 84 days after initiating treatment with ELX/TEZ/IVA. The mean change from baseline in the ppFEV$_1$ was 15.1% (95% CI, 13.8 to 16.4) and the change from baseline in weight was 4.2 kg (95% CI, 3.9 to 4.6), based on pooled data from 1- and 3-month assessments. The authors reported statistically significant reductions in the percentage of patients receiving long-term oxygen (43% at baseline versus 23% at 3 months), non-invasive ventilation (28% at baseline versus 20% at 3 months); and enteral tube feeding (18% at baseline versus 10% at 3 months). Data were missing for 31% of patients at the 3-month visits with no imputation in the analyses. Prior to the initiation of ELX/TEZ/IVA, 16 patients were waiting for a lung transplant and 37 were under consideration for inclusion as transplant candidates in the next three months (total of 53 patients; 22%). At the end of follow up, 5 patients (2%) were on the transplant list or being considered for transplant, 2 patients had received a transplant (0.8%), and 1 patient died while waiting for transplant (0.4%).

Critical Appraisal

The two observational studies provided descriptive data on the effects of ELX/TEZ/IVA in CF patients with advanced lung disease. The short-term results showed acute increases in ppFEV$_1$ and weight that were comparable to those observed in the clinical trials; but should be interpreted with caution given the limitations of the open-label, uncontrolled, observational study designs, and the small sample size for the Irish cohort (N = 14). Both studies had a limited follow-up duration, and the monitoring and reporting of patient outcomes were impacted by the COVID-19 pandemic and lockdown measures. The large amount of missing data for some outcomes makes it challenging to interpret and generalize the results of these studies.

Simulation Study for Morbidity and Mortality

Stanojevic et al. (2020) used a microsimulation model to estimate the impact of treatment with ELX/TEZ/IVA in eligible patients in Canada. The model forecasted an increase in median survival and a reduction in pulmonary exacerbations with the introduction of ELX/TEZ/IVA. The outcomes from these simulations are contingent on the validity of several assumptions that were required to build the model and extrapolate the impacts out to 10 years. There is uncertainty in the extrapolation of short-term effects of ELX/TEZ/IVA in a subset of patients with CF, to the broader population in the longer-term, and in the generalizability of observational data with IVA on the rate of decline in ppFEV$_1$ to patients treated with ELX/TEZ/IVA. Moreover, the model likely overestimates the proportion of CF patients who may receive ELX/TEZ/IVA and impact of treatment on pulmonary exacerbations.

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Microsimulation
Target population	Patients with CF aged 12 years and older who have at least one F508del mutation in the CFTR gene, represented by the following four genotypes considered in separate analyses: 1. Homozygous for F508del-CFTR (F/F) 2. Heterozygous for F508del-CFTR with a minimal function mutation (F/MF) 3. Heterozygous for F508del-CFTR with a residual mutation (F/RF) 4. Heterozygous for F508del-CFTR with a gating mutation (F/Gating), inclusive of R117H
Treatment	ELX/TEZ/IVA, with background best supportive care (BSC)
Submitted drug price	elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta),100 mg/ 50 mg/ 75 mg and 150 mg tablets: $280 per tablet, $840 per daily dose
Annual cost	At the recommended dose of two tablets of ELX 100 mg/ TEZ 50 mg/ IVA 75 mg taken in the morning and one tablet of IVA 150 mg taken in the evening, the annual cost is $306,600 per patient (or $840 daily).
Comparators	BSC for all genotypes, consisting 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. Ivacaftor in patients heterozygous for F508 del-CFTR with a gating mutation, or the R117H mutation, on the second allele only, in combination with BSC.
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, Life Years
Time horizon	Lifetime (approximately 65 years)
Key data sources	• A number of trials in CFTR modulator naïve patients to inform baseline patient characteristics for each genotype. • Literature to determine the impact of patient characteristics on mortality, as well as baseline rates of pulmonary exacerbations. • The sponsor commissioned multiple indirect treatment comparisons to inform placebo-adjusted rates for acute change in $ppFEV_1$ and mean change in weight-for-age z-score for each genotype from baseline for patients on CFTR modulators with the F/F, F/RF and F/Gating genotypes. Study 102 was used to directly inform these values in the F/MF genotype. Patients on BSC were assumed to not experience any increase in either outcome. • Impact of treatment on long-term reduction in $ppFEV_1$ decline was based on non-comparative literature and not specific to ELX/TEZ/IVA. Impact of CFTR modulator use on pulmonary exacerbations beyond the influences of changes in $ppFEV_1$ to pulmonary exacerbation rates was based on an adjustment factor calculated by the sponsor.
Submitted results	1. Homozygous for F508del-CFTR (F/F) ICER vs. BSC = $358,763 per QALY (incremental costs: $4,638,324; incremental QALYs: 12.93) 2. Heterozygous for F508del-CFTR with an MF mutation (F/MF) ICER vs. BSC = $358,597 per QALY (incremental costs: $4,526,116; incremental QALYs: 12.59) 3. Heterozygous for F508del-CFTR with an RF mutation (F/RF) ICER vs. BSC = $531,195 per QALY (incremental costs: $3,782,240; incremental QALYs: 7.12) 4. Heterozygous for F508del-CFTR with a gating mutation (F/Gating), inclusive of R117H ICER vs. BSC = $353,239 per QALY (incremental costs: $4,184,761; incremental QALYs: 11.85) ICER vs. IVA = $256,956 per QALY (incremental costs: $1,082,149; incremental QALYs: 4.21)
Key limitations	• There is no evidence of the long-term impact of ELX/TEZ/IVA on the rate of decline in $ppFEV_1$ or on pulmonary exacerbations, in comparison with BSC or IVA. This leads to substantial uncertainty with the cost-effectiveness of ELX/TEZ/IVA. • There is uncertainty associated with the magnitude of benefit with ELX/TEZ/IVA and IVA with regards to acute increases in $ppFEV_1$ and weight for age z-score as determined by the sponsor submitted ITC due to ELX/TEZ/IVA trials, as there were key differences in the designs of the trials included in the ITC.

Component	Description
	• The sponsor incorporated dynamic pricing of ELX/TEZ/IVA and IVA based on an assumption of generic entry. This assumption is associated with considerable uncertainty, and likely underestimates the total costs associated with ELX/TEZ/IVA and IVA. • Drug acquisition costs were adjusted for patient compliance, while treatment efficacy was not. While drug wastage may occur, they will be dispensed and paid for by public drug plans. This underestimated the total drug costs associated with ELX/TEZ/IVA and IVA. • Health care costs incurred by the health care system for the period for which ELX/TEZ/IVA is associated with a survival benefit in comparison with BSC were excluded, which underestimates the total costs associated with ELX/TEZ/IVA. • The sponsor included a treatment specific utility increment to account for the impact of treatment with ELX/TEZ/IVA beyond its impact mediated via $ppFEV_1$ and pulmonary exacerbations. The increment calculated by the sponsor was adjusted for $ppFEV_1$ but not for pulmonary exacerbations, and thus likely leads to double counting of benefits with ELX/TEZ/IVA.
CADTH reanalysis results	CADTH conducted re-analyses which included the removal of an additional benefit of ELX/TEZ/IVA and IVA on the long-term rate of decline in ppFEV1 and pulmonary exacerbations; the removal of dynamic pricing of ELX/TEZ/IVA and IVA; the inclusion of costs for ELX/TEZ/IVA in the period for which it achieved a survival benefit in comparison with BSC; the removal of an adjustment to drug acquisition costs by patient compliance; and, the removal of a treatment specific utility increment for patients on ELX/TEZ/IVA. 1. Homozygous for F508del-CFTR (F/F) ICER vs. BSC = $1,140,840 per QALY 2. Heterozygous for F508del-CFTR with an MF mutation (F/MF) ICER vs. BSC = $1,150,105 per QALY 3. Heterozygous for F508del-CFTR with an RF mutation (F/RF) ICER vs. BSC = $1,911,977 per QALY 4. Heterozygous for F508del-CFTR with a gating mutation (F/Gating), inclusive of R117H ICER vs. BSC = $1,067,215 per QALY ICER vs. IVA = $181,718 per QALY ELX/TEZ/IVA was not cost-effective at a willingness to pay threshold of $50,000 per QALY in any scenario conducted by CADTH. A price reduction in excess of 90% for ELX/TEZ/IVA is required for all four genotypes in order for ELX/TEZ/IVA to be considered cost-effective at a willingness to pay threshold of $50,000 per QALY in comparison with BSC.

Budget Impact

CADTH identified key limitations with the sponsor's analysis, which included: The anticipated market uptake of ELX/TEZ/IVA was substantially underestimated, drug acquisition costs were adjusted by patient compliance, which is not appropriate, several assumptions around patients eligible for IVA and the likelihood of switching did not align with expectations, and there is uncertainty with the proportion of patients who would be eligible for public coverage of ELX/TEZ/IVA. The CADTH re-analysis included: increasing the market uptake of ELX/TEZ/IVA in all three years of the time horizon, removing the adjustment of costs for patient compliance, altering the proportion of patients currently receiving IVA to align with the submitted pharmacoeconomic model, and assuming a proportion of patients eligible for IVA but not receiving it would elect to receive ELX/TEZ/IVA. Based on CADTH reanalyses, the budget impact of introducing ELX/TEZ/IVA is expected to be $419,553,709 in Year 1, $426,604,322 in Year 2, and $433,773,421 in Year 3, for a three-year total budget impact of $1,279,931,452. The model is sensitive to the proportion of patients eligible for public drug coverage, as well as the anticipated market uptake and price of ELX/TEZ/IVA. Uncertainty remains with regards to the proportion of patients with public drug coverage who would be eligible for ELX/TEZ/IVA. Changes in this parameter would lead to substantial changes in the estimated budget impact.

CDEC Members

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

June 16, 2021 Meeting

Regrets

One member did not attend.

Conflicts of Interest

None

CADTH

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