



# Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis

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## Introduction

Cystic Fibrosis (CF) is the most common fatal genetic condition in Canada, affecting over 4,300 Canadians (1). CF is caused by variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that result in the absence or dysfunction of the CFTR protein, a cell-surface chloride channel that regulates salt and water absorption and secretion across cells in multiple organs. This loss of chloride transport leads to the accumulation of thick, tenacious mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration (2).

CF is a progressive, degenerative multi-system disease that mainly affects the lungs and digestive system. Given this underlying disease process, the aim of treatment is to alter the natural history, control symptoms and reduce morbidity associated with recurrent pulmonary exacerbations and hospitalizations. Percent predicted Forced Expiratory Volume in one second (pp%FEV1) is an important measure of lung function in CF (and other lung diseases)(3). Currently, approved medications work in slowing the trajectory of lung function decline and optimizing growth and nutrition. The strategy of CF care is to slow the evolving lung damage and the resultant decline in lung function that ultimately leads to respiratory failure and death.

Since 2012, CFTR modulators have been approved to tackle the underlying defect of CF. Although not a cure, they aim to restore the function of the CFTR protein at the cell surface. CFTR modulators are tailored to work to correct specific *CFTR* variants and are an example of personalized precision medicine. Consensus guidelines already include CFTR modulator therapies (4). They are recommended as an adjunct to current management, which has historically focused on treating consequences of the defect, because end-organ damage has already occurred and therefore these downstream treatments will likely remain necessary.

With the approval of a new triple therapy modulator, elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), by Health Canada and its recent recommendation by CADTH (5), it is envisaged that the bulk of Canadian patients with CF will have access to this CFTR modulator. Cystic Fibrosis Canada's Healthcare Advisory Council has developed this standardized care guideline to support CF clinics in initiating CFTR modulator therapy with the following aims:

- 1) Indications for starting CFTR modulator therapy
- 2) Assessing response to CFTR modulator therapy
- 3) Monitoring patients on CFTR modulator therapy
- 4) Assessing non-response to CFTR modulator therapy

## Current CFTR Modulator treatments

Over the last 15 years, significant research and clinical trials have been undertaken to develop CFTR modulators and to employ them in clinical care. The first modulator commercially available was ivacaftor (IVA; Kalydeco™) which is most effective in patients who have “gating” variants (4% of Canadian CF patients). For this subgroup it is a highly effective medication,

restoring CFTR function with clinical benefits of increasing lung function, reducing hospitalizations and improving nutritional status, and real-world evidence of improving survival and decreasing the need for lung transplant (6,7). In 2021, it was funded both at the 3<sup>rd</sup> party (i.e. private insurance) and provincial level.

For patients with 2 copies of the most common CF variant, *F508del* (50% of Canadian CF patients), lumacaftor/ivacaftor (LUM/IVA; Orkambi™) and tezacaftor/ivacaftor (TEZ/IVA; Symdeko™) have been developed. Studies support the efficacy of LUM/IVA and TEZ/IVA, but not to the degree achieved by IVA in patients with gating variants. Despite Health Canada approval these medications are not broadly funded provincially except through a compassionate basis or, in Quebec, through the ‘patient d’exception’ program.

The advent of a fourth CFTR modulator provides a triple combination therapy, known as elxacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA; Trikafta™). The combination of 2 correctors (TEZ and ELX) results in more effective correction of CFTR function in the *F508del* variant. Treatment with ELX/TEZ/IVA results in significant clinical improvements in people with only a single copy of the *F508del* variant (regardless of the variant on the other allele) (8). When ELX/TEZ/IVA is added to standard of care or substituted for TEZ/IVA in patients with 2 copies of *F508del*, significant improvements in lung function and sweat chloride have been observed (9). Triple combination CFTR modulator therapy will ultimately replace LUM/IVA or TEZ/IVA in most people with 2 copies of the *F508del* variant and would be indicated for all people with CF with a single *F508del* variant.

Health Canada has approved four CFTR modulator therapies that act on the CFTR protein:

1. Ivacaftor (IVA; Kalydeco™)(10–15)

IVA is effective in patients with a gating variant (Class III) or conductance variant (*R117H* 5T or 7T) (Appendix 1). It is a CFTR potentiator, and its action is to increase the amount of time that the CFTR channel is open, thus improving chloride transport.

**Indication:** CF patients with at least one gating variant or *R117H* (Appendix 1).

**Age:** 4 months or older

Product monograph link: [https://pi.vrtx.com/files/Canadapm\\_kalydeco\\_en.pdf](https://pi.vrtx.com/files/Canadapm_kalydeco_en.pdf)

2. Lumacaftor/ivacaftor (LUM/IVA; Orkambi™)(16–19)

LUM is a corrector of the *F508del* variant, modifying the conformational deformity and allowing the CFTR protein channel to move to its correct position at the cell surface (trafficking). The CFTR protein is then potentiated by IVA to keep the channel open longer, allowing chloride transport.

**Indication:** *F508del/F508del*

**Age:** 2 years or older

Product monograph link: [https://pi.vrtx.com/files/Canadapm\\_orkambi\\_en.pdf](https://pi.vrtx.com/files/Canadapm_orkambi_en.pdf)

3. Tezacaftor/ivacaftor (TEZ/IVA; Symdeko™)(20–23)

Similar to LUM, TEZ is a corrector designed to facilitate proper folding of the defective CFTR protein so it may be transported to the cell surface. It works in combination with IVA, a potentiator of the CFTR protein. TEZ/IVA has comparable efficacy to LUM/IVA, but with fewer drug interactions and fewer reported acute adverse effects.

TEZ/IVA has been trialed in patients homozygous for the *F508del* variant **or** heterozygous for the *F508del* variant in combination with other *CFTR* variants having some residual function (RF):

**Indication:** *F508del/F508del*  
**or**  
*F508del* in combination with *CFTR* variants having some RF (Appendix 1)

**Age:** 12 years or older

Product monograph link: [https://pi.vrtx.com/files/Canadapm\\_symdeko\\_en.pdf](https://pi.vrtx.com/files/Canadapm_symdeko_en.pdf)

4. Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA; Trikafta™)(24–26)

This triple therapy builds on the combination of TEZ/IVA by the addition of the next generation corrector, ELX. This compound, when used with TEZ/IVA, substantially increases the amount of CFTR protein and CFTR activity at the cell surface. Clinical trials have shown important benefits in patients with at least one *F508del* variant.

**Indication** *F508del* in combination with any other *CFTR* variant (Appendix 1)

**Age:** 6 years or older

Product monograph link: [https://pi.vrtx.com/files/Canadapm\\_trikafta\\_en.pdf](https://pi.vrtx.com/files/Canadapm_trikafta_en.pdf)

## Indications for starting CFTR modulator therapy

All Canadians with a confirmed diagnosis of CF should have access to Health Canada-approved CFTR modulators based on their *CFTR* variants.

The diagnosis of CF requires:

Clinical symptoms/features or a positive newborn screen **and** either

- Two disease-causing *CFTR* variants
- or**
- Sweat chloride concentration >60 mmol/L (on 2 occasions if only one *CFTR* variant known).

To be eligible for CFTR modulator therapy, the following will apply:

1. **Mutation:** *F508del/Any CFTR variant or Gating variant/Any CFTR variant or R117H/Any CFTR variant*

These genotype recommendations are based on Phase 3 clinical trials showing substantial clinical improvement with CFTR modulators and Health Canada approval.

2. **Age:** as approved by Health Canada

CFTR modulators should be initiated at the **YOUNGEST** age possible with the goal of attenuating disease progression and improving clinical status. Data suggest that early introduction can reverse disease progression, such as restoring pancreatic function(9). There is **NO** data to support withholding CFTR modulators until significant clinical symptoms have developed or a drop in lung function occurs.

3. **Lung function:** No minimum or maximum FEV<sub>1</sub>

In Canada, due to improvements in care, early-stage lung disease in cystic fibrosis, as defined by conventional spirometry measurement, is increasingly not seen until adolescence or in young adults with CF(27). However, FEV<sub>1</sub> is not a useful marker in mild lung disease, in part due to its relatively insensitivity to detection of early small airways destruction (28). This is illustrated when CF patients with no abnormality in lung function underwent chest CT imaging; despite a normal FEV<sub>1</sub>, there was evidence of significant structural lung disease (29). Additionally, several trials have shown that in patients with normal lung function (ppFEV<sub>1</sub> >90%) the addition of a CFTR modulator caused further significant gains in ppFEV<sub>1</sub> (12), illustrating improvement to be made in mild CF lung disease. Data from 2021 showed in children aged 6-11 years with an average ppFEV<sub>1</sub> of 89% (of whom 45% had ppFEV<sub>1</sub> >90%), the addition of ELX/TEZ/IVA produced an increase in ppFEV<sub>1</sub> of 10% (24). Consequently, no upper limit of lung function should be required for eligibility as further significant gains in respiratory health can be made in CF patients with mild lung disease.



Patients with lung function that is low (ppFEV<sub>1</sub><40%) or who are awaiting lung transplantation also have the potential to improve on treatment to the point where many no longer need transplantation (6,30). Consequently, no lower limit of lung function should be required for eligibility.

**4. Pancreatic status:** Pancreatic sufficient and insufficient

Pancreatic status does not affect eligibility. Most patients with CF are pancreatic insufficient but some patients are not. Early introduction of CFTR modulator therapy has the potential to restore pancreatic function (31) or delay onset of pancreatic insufficiency (13,30). In patients with pancreatic sufficiency, CFTR modulators will likely preserve pancreatic function.

## Healthcare Advisory Council guidelines for prescribing a CFTR modulator

Table 1 summarizes the four CFTR modulators currently approved by Health Canada. The recommended *CFTR* variant, age of initiation and duration for each modulator is provided.

### Pre-modulator assessment

If a patient has not had a confirmatory sweat test and/or CF genotyping this should be undertaken. Baseline clinical assessments required are illustrated in Tables 2a and 2b. These should be obtained when the patient is clinically stable.

### Response to therapy

Clinical trials for CFTR modulators have reported improvements in lung function and weight and reduced pulmonary exacerbations requiring antibiotics. As CFTR modulators are systemic medications they impact CFTR function in the sweat glands as measured by the concentration of chloride in sweat. Although this does not have direct clinical significance at an individual level (other than reducing risk of dehydration or heat stroke), it is a biomarker of the effect of CFTR modulators and trials have shown modulator use is associated with a reduction in sweat chloride.

Longer term follow-up studies have evaluated the impact of CFTR modulators on FEV<sub>1</sub> rate of decline (30,32,33). These studies have shown an improvement in lung function trajectory with a slowing in the rate of FEV<sub>1</sub> decline compared to patients not on CFTR modulators. However, patients may **STILL** have a decline in FEV<sub>1</sub> over time **DESPITE** the impact of CFTR modulators (30,32,34). Patients with CF have bronchiectasis with chronic infection and irreversible structural lung damage that will impact FEV<sub>1</sub> recovery and trajectory. There is some evidence emerging to suggest that benefits from therapy may be sustained over time and FEV<sub>1</sub> may not decline in patients on ELX/TEZ/IVA (35,36).

In children under 12 years of age, FEV<sub>1</sub> is often in the normal range despite significant lung disease. A significant change in FEV<sub>1</sub> cannot be expected even in patients who are otherwise experiencing benefit from treatment. It is not a feasible to measure FEV<sub>1</sub> in children under the age of 6 years and efficacy is difficult to assess in this age group due to limited respiratory symptoms.

Modeling and real-life experience with CFTR modulator introduction have shown significant reduction in disease severity and improvement in clinical parameters in patients with significant disease burden (7,37). In addition, patients report an impact on respiratory symptoms, sleep quality, general well-being and physical self-esteem, and a reduced treatment burden. After treatment initiation patients reported renewed and unexpected physical strength leading to greater self-confidence, autonomy, and long-term planning (37).

CF-related co-morbidities should also be considered. Although not reported in clinical trials, patients may experience improvement in CF issues such as sinus disease, pancreatitis, and CF-related diabetes with the introduction of CFTR modulators (38).

Data has suggested that there may be responders and non-responders to CFTR modulator therapy (39). In order to identify responders, the recommendation is to evaluate CFTR modulator therapy for a **MINIMUM** duration of 1 year. This duration is needed to accurately assess reductions in pulmonary exacerbation frequency, provide adequate lung function data to determine improvement and stabilization of FEV<sub>1</sub> over time, and to monitor improvement in nutrition.

Meaningful clinical responses to be monitored include:

1. Improvement in lung function as measured by FEV<sub>1</sub> or Lung Clearance Index (LCI) (where available) obtained at a time of clinical stability
2. Reduction in the number of pulmonary exacerbations
3. Stabilization in lung function over time (i.e. attenuation of the usual decline in lung function in CF)
4. Reduction or stabilization of respiratory symptoms
5. Improvement in nutritional status
6. Improvement in quality-of-life scores
7. Reduction in sweat chloride.

### **Concurrent treatment**

At the present time, all patients commenced on a CFTR modulator should continue with current treatments as directed by their CF clinic (e.g. pancreatic enzymes, mucolytics, inhaled antibiotics, bronchodilators, anti-inflammatory agents). They should continue to be monitored quarterly as per CF standards of care. Ongoing clinical studies will determine what, if any, changes in CF care can be safely incorporated once patients are on CFTR modulator therapy.

The schedule of clinical assessment and monitoring is outlined in Tables 2a and 2b.

## Treatment Response

It is expected that responders will have at:

3 months

- 1) Absolute improvement in ppFEV<sub>1</sub> of  $\geq 5\%$ , measured at time of clinical stability  
**or**
- 2) A decrease in sweat chloride by 20% or 20mmol/L from baseline  
**or**
- 3) Improvement in respiratory symptoms (as measured by CF Questionnaire-Revised (CFQ-R): Respiratory Domain) by  $\geq 4$  points (i.e. the minimum clinically important difference).

12 months

- 1) No treatment-limiting adverse events or medication safety issues,  
**and** one or more of:
  - 2) Reduction in pulmonary exacerbations (IV or oral antibiotic treatment) by 20%  
**or**
  - 3) Stabilization of lung function rate of decline above baseline  
**or**
  - 4) Improvement in nutritional status with normalization of growth and nutrition  
**or**
  - 5) Radiological improvement or stability in chest CT scan.

Table 3 is a summary of changes in expected outcomes for responders to different CFTR modulators.

## Monitoring

Comprehensive monitoring of patients who are commenced on CFTR modulators is detailed in Tables 2a and 2b. Clinics should aim to follow this schedule in order to demonstrate response to therapy.

## Side effects

After initiation of CFTR modulators, it is important to focus on safety outcomes and monitor for potential adverse effects (Table 4). A systematic review of safety outcomes reported in real-world studies of the four market-available CFTR modulators has previously been published and is an excellent source of reference, but there are limited reports of longer-term real-world experience, especially with ELX/TEZ/IVA (40). Therefore, vigilant post-market monitoring for both expected and unexpected adverse effects is warranted.

Safety issues of note are:

**i) Liver enzymes and/or bilirubin**

Elevated transaminases have been observed in patients on CFTR modulators. Isolated elevation in bilirubin can also be seen in some cases. This can occur at any time during treatment, even if the modulator has been previously well tolerated. Rarely does this result in the need to interrupt therapy, reduce the dose, or discontinue the modulator. Elevated transaminases and bilirubin will need to be reviewed to further determine the need to interrupt therapy, reduce the dose, or discontinue the modulator (Table 5). It is recommended that liver enzymes should be monitored one month post-initiation and every three months in the first year, and then at least annually. For individuals with moderate or severe CF-related liver disease, recommendations for dosage adjustments are available (26). Worsening of liver function has been observed in patients with pre-existing cirrhosis and portal hypertension who have started CFTR modulators.

**ii) Rash or hypersensitivity reactions**

Rash is relatively common following initiation of CFTR modulators and has been reported in real-world studies for each of IVA, LUM/IVA, and TEZ/IVA. Similar incidence was seen in clinical trials, with cases of rash being reported for all four CFTR modulators, and serious rash or discontinuation due to rash being reported for ELX/TEZ/IVA and LUM/IVA. Rare cases of delayed hypersensitivity reactions have also been reported. The incidence of rash events appears to be higher in female CF patients, particularly those on hormonal contraceptives, and more frequent on ELX/TEZ/IVA, but the mechanism behind this is unclear.

Most cases of rash are mild and self-resolve. Few individuals require interruption or discontinuation of therapy for rash or hypersensitivity reactions. In the case that a rash or hypersensitivity reaction does warrant interruption or discontinuation of therapy, after symptoms have resolved, if deemed appropriate, the CFTR modulator may be retriaged with close monitoring. Desensitization protocols have been published (41–43), and CF centres may have alternate strategies informed by real-world practice.

**iii) Drop in ppFEV<sub>1</sub> and worsening respiratory symptoms**

Respiratory-related side effects, including chest tightness, dyspnea, and declines in ppFEV<sub>1</sub> have been reported with LUM/IVA but not the other available CFTR modulators. Bronchodilators may be beneficial in mitigating symptoms of chest tightness, wheeze, and increased work of breathing in some individuals. Improvement in or resolution of symptoms typically occurs within 1–4 weeks following initiation, but symptoms and/or ppFEV<sub>1</sub> below baseline could persist beyond this and some patients may require a dose reduction or discontinuation of LUM/IVA altogether to achieve resolution.

**iv) GI-related adverse effects**

Symptoms of abdominal pain, nausea, and vomiting have been reported in the real-world studies, but rarely prompted discontinuation of therapy. Concerns have been raised about the

potential for distal intestinal obstruction syndrome (DIOS) following initiation of highly effective CFTR modulators. Therefore, patients with chronic constipation and/or other risk factors for DIOS should have their bowel regimen optimized and constipation ruled-out prior to initiation of therapy and be closely monitored following initiation.

**v) Blood pressure elevation**

Elevations in blood pressure were reported in the phase 3 clinical trials for LUM/IVA and ELX/TEZ/IVA. For ELX/TEZ/IVA, 4% of treated subjects had systolic blood pressure >140 mmHg and 10 mmHg increase from baseline on at least two occasions. Similarly, 1% had diastolic blood pressure >90 mmHg and 5 mmHg increase from baseline on at least two occasions. The mechanism by which CFTR modulators may cause blood pressure elevations remains unclear.

**vi) Creatinine kinase**

CK elevations have been reported in clinical trials for all four CFTR modulators. Clinical context of elevations is important, as CK levels fluctuate significantly with exercise and physical activity, especially if intensive, and may take a few days to normalize thereafter. Although the clinical relevance of CK elevations is unclear, some cases may be serious enough to warrant interruption or discontinuation of therapy.

**vii) Mental health**

Cases of negative impacts on mental health (e.g. depression, anxiety) have been reported for all four market-available CFTR modulators, even in individuals without a prior history of mental health concerns, raising a signal for a potential association with CFTR modulators. Although a causal relationship has not been established and a mechanism is not clear, it is an important potential outcome to be mindful of. In addition, there are significant drug-drug interactions with LUM/IVA and antidepressant medications.

**viii) Neurological effects**

“Brain fog”, fatigue, and/or sleep disturbances have been reported by some individuals initiated on ELX/TEZ/IVA (40). In some cases, adjustments in the ELX/TEZ/IVA dosing regimen may help mitigate symptoms. A potential mechanism for these effects is not clear and a causal relationship cannot be established.

**ix) Cataracts**

Cases of non-congenital lens opacities have been reported in pediatric patients treated with IVA-containing regimens. Although other risk factors were present in some cases (such as corticosteroid use, exposure to radiation), a possible risk attributable to treatment with IVA cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with CFTR modulators: examinations should be done at baseline, 6 months, and on annual basis thereafter until the age of 18 years.

## Drug-drug interactions (Figure 1 (44))

It is important to assess for drug-drug interactions when starting or stopping medications in an individual on a CFTR modulator or when transitioning from one CFTR modulator to another. IVA, TEZ, and ELX are substrates of cytochrome P450 (CYP) enzyme CYP3A. Therefore, strong and moderate inhibitors (e.g. azole antifungals) of CYP3A can increase exposure to IVA, TEZ, and ELX, while inducers (e.g. rifampin) can decrease serum levels. Recommendations are available for how to dose-adjust modulators when taken concomitantly with moderate or strong CYP3A inhibitors, but concomitant use with inducers should be avoided(10,16,20,26). It is important to note that foods and herbal products can also affect CYP3A (food or drinks containing grapefruit can inhibit CYP3A in the gastrointestinal tract, while the herbal product St. John's wort induces CYP3A).

CFTR modulators have also been associated with inhibition or induction of enzymes. IVA and one of its metabolites weakly inhibit CYP3A and P-glycoprotein (P-gp), and potentially CYP2C9. Because of the potential impact on CYP3A and CYP2C9, the international normalized ratio (INR) should be closely monitored in individuals on warfarin who are starting or stopping a CFTR modulator. Alternatively, LUM is an inducer of CYP3A and UDP-glucuronosyltransferase (UGT) enzymes, and may increase metabolism of concomitant medications that are substrates of these enzymes (e.g. hormonal contraceptives, azole antifungals, select immunosuppressants, and psychotropic medications). This is an important consideration for patients transitioning from LUM/IVA to either TEZ/IVA or ELX/TEZ/IVA, particularly in patients taking concomitant medications that are substrates of CYP3A and/or UGT. Once LUM/IVA is discontinued and these enzymes are no longer induced, some medications that are substrates of these enzymes may require a **decrease** in dose to reduce the risk for toxicity. As well, discontinuation of LUM/IVA may broaden the number of appropriate therapeutic alternatives in cases where certain medications were to be avoided due to the inductive effects of LUM (e.g. hormonal contraceptive options for women).

### Special considerations for patients receiving IVA, LUM/IVA, or TEZ/IVA

Health Canada approved ELX/TEZ/IVA in June 2021 for CFTR variants *F508del/Any* in patients 12 years and older and in April 2022 for patients 6 years and older. A small number of children will remain on either LUM/IVA or IVA.

Data has shown that ELX/TEZ/IVA has superiority over TEZ/IVA in patients with 2 copies of *F508del* (9). In a study comparing patients with *F508del/a* minimal function or gating variant who were randomised to either continue taking TEZ/IVA or IVA or switched to ELX/TEZ/IVA, a modest incremental improvement in FEV<sub>1</sub> was observed, with significant gains in CFQ-R: Respiratory domain and further reduction in sweat chloride levels (45).

All eligible patients on IVA, LUM/IVA or TEZ/IVA, should have the opportunity to transition to the triple therapy combination, ELX/TEZ/IVA. Please see the above important consideration for drug-drug interactions in patients transitioning from LUM/IVA.

## **Pregnancy/lactation and CFTR modulators**

CFTR modulators may increase fertility in women with CF (46,47) due to improvement in clinical status and to their impact on the mucus in the cervix and uterus; therefore, it is important for women who currently on or who are planning to initiate a CFTR modulator to use reliable contraception to prevent unplanned pregnancies. The clinical trials of CFTR modulators excluded women who were not using effective contraception, so the effect of these drugs on a developing human fetus is unknown. Animal studies of the individual drugs IVA, LUM, TEZ and ELX indicate no impact on organogenesis at normal human doses.

CFTR modulators cross the placenta (48) and are expressed in breast milk (49). The potential risks and benefits of taking CFTR therapy during pregnancy and during breast-feeding must be discussed, ideally before pregnancy. Real-world experience is limited, but case reports/series and an international survey have demonstrated that CFTR modulators appear to be well tolerated during pregnancy (50,51). Discontinuation of CFTR modulators has been associated with significant decline in clinical status (52), sometimes warranting re-initiation of therapy in pregnant women who stopped their CFTR modulator during the pregnancy (51). As CFTR modulators have been associated with cataracts in children, it would be advisable that infants born to, and/or breast-fed by, mothers taking CFTR modulators have ophthalmologic examination. A 2021 report reveals the potential for infants with CF born to mothers taking CFTR modulators to falsely test negative for CF in newborn screens. CFTR mutation testing for all infants born to mothers who are on a CFTR modulator during their pregnancies is recommended (53).

## **CF Patients who have received a lung transplantation**

Lung transplant is a treatment option for people with CF with end-stage lung disease. While CFTR modulators would not be expected to directly improve lung graft function, they have the potential to alleviate extrapulmonary manifestations of CF such as chronic rhinosinusitis and gastrointestinal disease. Of note, paranasal sinuses may act as a reservoir for pathogens following transplantation, therefore treatment of chronic rhinosinusitis with CFTR modulators may reduce respiratory infectious complications after lung transplantation (54–57).

With the introduction of ELX/TEZ/IVA, evidence is emerging of its use after lung transplant (58–60). Drug-drug interactions between CFTR modulators and immunosuppressants, such as calcineurin inhibitors, should be expected (61). In addition, liver injury secondary to use of CFTR modulators may complicate management of a lung transplant recipient prescribed antimicrobials and immune suppressing medications associated with hepatotoxicity.

The general recommendations on response to CFTR modulator therapy following initiation would not be applicable to the lung transplant population. It is recommended that a CF specialist be involved in the initiation of CFTR modulators and subsequent monitoring of a CF patient who has undergone lung transplant and commenced on a CFTR modulator.



## **Discontinuation**

Discontinuation (or dose reduction) of CFTR modulator therapy should be considered in patients who have clinically significant adverse effects that persist or recur despite a decrease in dose (if appropriate) and/or stopping and re-challenge.

Examples of these reactions may include:

1. Elevation of transaminases (Table 5) beyond the higher range of fluctuations observed in patients with CF (>8x ULN) or 3x ULN of transaminases and bilirubin (>2x ULN)
2. Allergic reactions to treatment and failed desensitisation challenges

However, the risk-benefit of discontinuing treatment should be considered on a case-by-case basis depending on the severity of the adverse event and risk of stopping treatment.

Therapy should be discontinued in patients who, as assessed by the CF team, do not meet criteria for response to the CFTR modulator or are non-adherent to the CFTR modulator. This decision to discontinue therapy should be done when the patient is clinically stable, and after any confounding co-morbidities have been assessed and non-adherence issues have been addressed.

## **How to start CFTR modulators**

Prior to initiation of a CFTR modulator, it is recommended that patients (and caregivers) receive detailed education and counselling about the therapy as well as all necessary follow-up and monitoring. The appropriate modulator dose based on patients' age, liver function, and drug-drug interactions should be confirmed prior to initiation (and reassessed, should any of these parameters change). For patients who have had a significant adverse reaction to a CFTR modulator and a rechallenge is deemed appropriate, or if initiating patients at a reduced dose and titrating to full-dose is preferred, potential protocols are summarized in the systematic review performed by Dagenais et al. (40).

No titration or cross-tapering is necessary for patients who are transitioning from one CFTR modulator to ELX/TEZ/IVA. Patients will take the last evening dose of their baseline modulator, then the first dose of ELX/TEZ/IVA the following morning and continue with ELX/TEZ/IVA thereafter. When transitioning from LUM/IVA it may take up to 2 weeks for ELX/TEZ/IVA to have an effect (62).

## Summary

The approval of CFTR modulators by Health Canada is a milestone in CF care and is the first time that a CF treatment has targeted the basic defect and not the consequences of the disease. Real-world evidence suggests that CFTR modulators will slow the progression of disease, reduce mortality and improve quality of life. All patients who are eligible should be started on therapy as soon as possible to prevent progression of lung disease and other CF-related co-morbidities.

Patients should be started on an age-appropriate, *CFTR* variant-specific modulator with a recommended duration of at least 1 year. Response to therapy and safety should be monitored. If response to therapy is seen, then patients will continue indefinitely on the CFTR modulator therapy and other standard of care treatments. Follow up will be determined by their CF clinic. Discontinuation of modulator therapy should be performed in patients who experience significant side effects, are deemed non-responders after 1 year of therapy, or are unable to adhere to therapy and/or the necessary follow-up monitoring despite all available support strategies. Efficacy data should be collected as part of the Canadian Cystic Fibrosis Registry or as part of a prospective study.

**Table 1:** Summary of Health Canada-approved CFTR modulators and CF Canada Healthcare Advisory Council’s recommended trial duration

<b>CFTR Modulator</b>	<b>Indication</b>	<b>Approved Age</b>	<b>Minimum Trial Duration</b>
IVA *	Gating (Class III) variant	≥4 months	1 year
	<i>R117H</i>	≥4 months	
LUM/IVA *	<i>F508del / F508del</i>	≥2 years	1 year
TEZ/IVA *	<i>F508del / F508del</i>	≥12 years	1 year
	<i>F508del / RF variant</i>		
ELX/TEZ/IVA*	<i>F508del / Any</i>	≥6 years	1 year
* Health Canada approved CFTR variants described in Appendix 1 <b>RF</b> , residual function			

**Table 2a:** Schedule for baseline evaluation and monitoring of patients aged 6 years and older who commence on CFTR modulators

<b>Routine Clinic Visits (Clinical Care monitoring): ≥6 years of age</b>	<b>Baseline</b>	<b>1 Month Visit</b>	<b>3 Month Visit</b>	<b>6 Month Visit</b>	<b>9 Month Visit</b>	<b>1 Year Visit</b>
Clinical assessment and review of <i>CFTR</i> genotype, initial sweat test, and past medical history (including decline in FEV <sub>1</sub> and frequency of pulmonary exacerbations over past 2 years)	X					
Height, weight, and blood pressure	X	X	X	X	X	X
Blood for CBC, ALT, AST, ALP, GGT, bilirubin, CK, INR	X	X	X	X	X	X
Spirometry/LCI <sup>a,b</sup>	X	X	X	X	X	X
Sputum microbiology <sup>c</sup>	X	X	X	X	X	X
Ophthalmology exam <sup>d</sup>	X			X		X
PHQ-9 and GAD-7 questionnaires <sup>e</sup>	X			X		X
Safety review <sup>f</sup>	X	X	X	X	X	X
Review of prescribed therapy <sup>g</sup>	X		X	X	X	X
Sweat chloride test	X		X			X
CFQ-R: Respiratory Domain	X	X	X	X	X	X
CT imaging of chest	X					X
Fecal elastase	X		X			X
	Standard for CF Clinic visit &/or recommended by product monograph					
	Clinical data needed to support CFTR modulator response					
	May have clinical relevance to CFTR modulator response					
<p><sup>a</sup> LCI to be measured where available at baseline, 3 months and 12 months</p> <p><sup>b</sup> If ppFEV<sub>1</sub> &lt;40%, include CPET or 6-minute exercise test at 6 and 12 months</p> <p><sup>c</sup> Samples obtained by sputum or cough swab</p> <p><sup>d</sup> For patients 6 to 18 years of age and then annually until 18 years, to exclude cataracts. May be performed by optometrist.</p> <p><sup>e</sup> For patients aged 12 years and older</p> <p><sup>f</sup> Events of special interest: rash, DIOS, pancreatitis, mental health, new organisms isolated in sputum</p> <p><sup>g</sup> Review of all prescribed medication including airway clearance</p> <p><b>ALT</b>, alanine aminotransferase; <b>AST</b>, aspartate aminotransferase; <b>ALP</b>, alkaline phosphatase; <b>GGT</b>, gamma glutamyl transferase; <b>CBC</b>, complete blood count; <b>CFQ-R</b>, Cystic Fibrosis Questionnaire-Revised; <b>CK</b>, creatine kinase; <b>DIOS</b>, distal intestinal obstruction syndrome; <b>GAD-7</b>, General Anxiety Disorder-7; <b>LCI</b>, lung clearance index; <b>PHQ-9</b>, Patient Health Questionnaire-9</p>						

**Table 2b:** Schedule for baseline evaluation and monitoring of patients under 6 years of age who commence on CFTR modulators

<b>Routine Clinic Visits (Clinical Care monitoring): &lt;6 years of age</b>	<b>Initial Visit</b>	<b>1 Month Visit</b>	<b>3 Month Visit</b>	<b>6 Month Visit</b>	<b>9 Month Visit</b>	<b>1 Year Visit</b>
Clinical assessment and review of <i>CFTR</i> genotype, initial sweat test, past medical history (including frequency of pulmonary exacerbations over past 2 years)	X					
Height, weight, and blood pressure	X	X	X	X	X	X
Blood for CBC, ALT, AST, ALP, GGT, bilirubin, CK, INR	X	X	X	X	X	X
Spirometry/LCI <sup>a</sup>	X	X	X	X	X	X
Sputum microbiology <sup>b</sup>	X	X	X	X	X	X
Ophthalmology exam <sup>c</sup>	X			X		X
Safety review <sup>d</sup>	X	X	X	X	X	X
Review of prescribed therapy <sup>e</sup>	X		X	X	X	X
Sweat chloride test	X		X			X
CFQ-R: Respiratory Domain	X	X	X	X	X	X
Fecal elastase	X		X			X
	Standard for CF Clinic visit &/or recommended by product monograph					
	Clinical data needed to support CFTR modulator response					
	May have clinical relevance to CFTR modulator response					
<sup>a</sup> LCI to be measured where available at baseline, 3 months and 12 months <sup>b</sup> Samples obtained by sputum or cough swab <sup>c</sup> Done at baseline, 6 months and on annual basis <sup>d</sup> Events of special interest: Rash, DIOS, pancreatitis, mental health, new organisms isolated in sputum <sup>e</sup> Review of all prescribed medication including airway clearance <b>ALT</b> , alanine aminotransferase; <b>AST</b> , aspartate aminotransferase; <b>ALP</b> , alkaline phosphatase; <b>GGT</b> , gamma glutamyl transferase; <b>CBC</b> , complete blood count; <b>CFQ-R</b> , Cystic Fibrosis Questionnaire-Revised; <b>CK</b> , creatine kinase; <b>DIOS</b> , distal intestinal obstruction syndrome; <b>GAD-7</b> , General Anxiety Disorder-7; <b>LCI</b> , lung clearance index; <b>PHQ-9</b> , Patient Health Questionnaire-9						

**Table 3:** Summary of objective outcomes for patients initiated on Health Canada-approved CFTR modulators

Outcome	IVA	LUM/IVA	TEZ/IVA	ELX/TEZ/IVA
	Age ≥4 Months	Age ≥2 Years	Age ≥12 Years	Age ≥6 Years
Lung Function <sup>a</sup>	FEV <sub>1</sub> LCI	<u>&gt;5% predicted</u>	<u>15% decrease</u>	<u>&gt;5% predicted</u>
Decrease Sweat Chloride	>20%/20mmol	>20%	>20%	>20%/20mmol
CFQ-R (Respiratory Domain) <sup>b,c</sup>	4 Points	4 Points	4 Points	4 Points
Pulmonary exacerbation	20% reduction	20% reduction	20% reduction	20% reduction
BMI/weight change <sup>d</sup>	Improved	Improved	Improved	Improved

<sup>a</sup> Children < 6 years of age are unable to do formal lung function measurement  
<sup>b</sup> This will be based on parents' assessment for children under 6 years of age  
<sup>c</sup> Minimum clinically important difference is 4 points  
<sup>d</sup> As assessed by CF Clinic  
**BMI**, body mass index; **CFQ-R**, Cystic Fibrosis Questionnaire-Revised; **LCI**, lung clearance index

**Table 4:** Frequency of adverse events reported in clinical trials for all Health Canada-approved CFTR modulators.

Adverse event	IVA	LUM/IVA	TEZ/IVA	ELX/TEZ/IVA
Increase cough, chest tightness		++		+
Drop in FEV <sub>1</sub>		++		
Elevated blood pressure		+		+
Elevated transaminases	++	++	+	+
Elevated CK	+	+	+	++
Rash	++	++	+	++
Cataracts	+	+	+	+
Neurological symptoms, depression, or anxiety	+	+	+	+
Abdominal pain	++	++		+
Nausea and vomiting	+	++	+	
Distal intestinal obstruction syndrome				+

( ++:Common (>10%), +:Uncommon)

This summary does not capture all reported side effects. Reference should be made to the product monograph for each CFTR modulator.

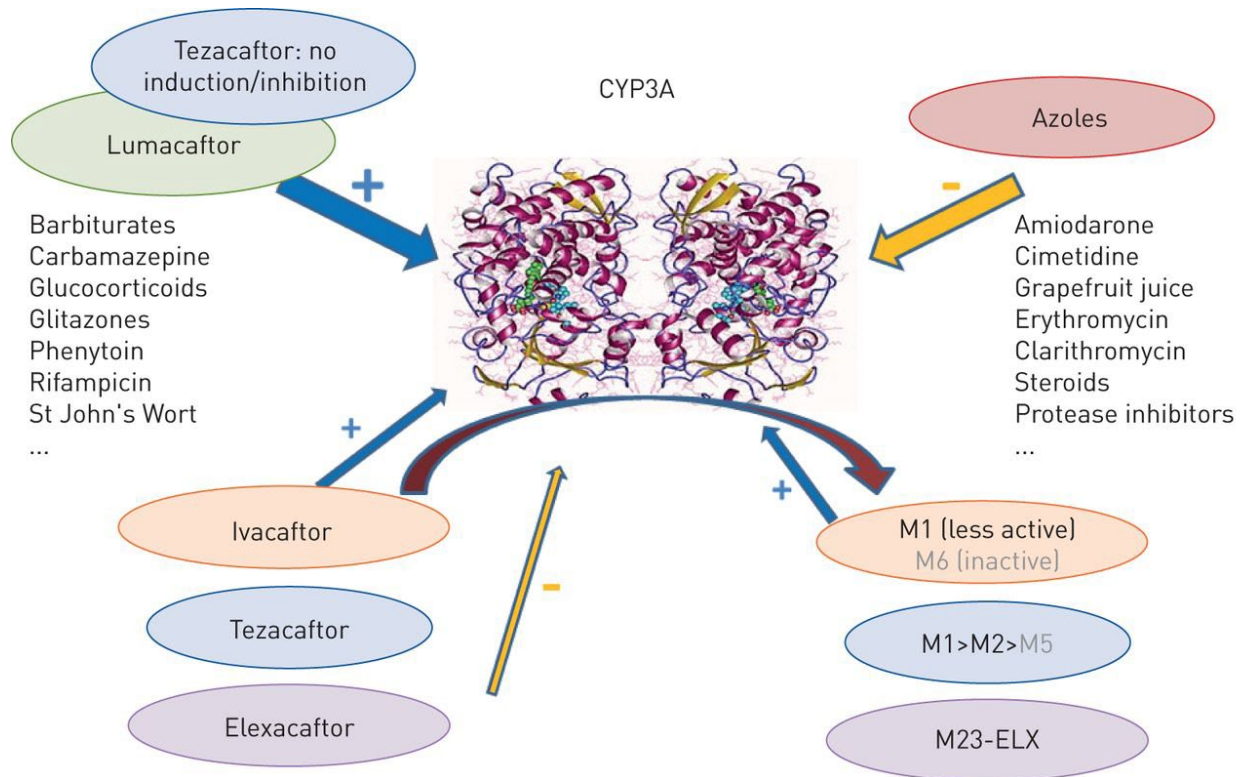
**Table 5:** Liver transaminase and bilirubin elevation monitoring and recommended action

Lab parameter	>2x ULN	>3x ULN	>5x ULN	>8x ULN
<b>ALT</b>		Repeat in 1 month	- STOP modulator - Monitor AST and ALT - Re-challenge modulator when AST and ALT <2x ULN*	STOP modulator
<b>AST</b>		Repeat in 1 month	- STOP modulator - Monitor AST and ALT - Re-challenge modulator when AST and ALT <2x ULN*	STOP modulator
<b>Bilirubin</b>	And AST or ALT >3x ULN: STOP Monitor in 2 weeks, Rechallenge when Bilirubin <1x ULN*			

**ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **ULN**, upper limit of normal

\*Rechallenge with half dose, in first instance.

Figure 1:



**FIGURE 1**

A summary of interactions between cystic fibrosis transmembrane regulator modulators and other drugs/compounds and cytochrome P450 3A4 (CYP3A). Blue arrows: induction of the cytochrome; yellow arrow: inhibition of the cytochrome; curved arrow: metabolism of a drug by the cytochrome.

Taken from (42) <https://doi.org/10.1183/16000617.0112-2019>



## Appendix 1

List of Variants approved by Health Canada taken from references: 9,15,19,25

### Ivacaftor (Kalydeco™)

Cystic fibrosis (CF) patients aged 12 months and older who have at least one copy of a CFTR variant listed:

<b>Named Variants</b>	<i>G551D</i>	<i>G178R</i>	<i>S1255P</i>
	<i>G1244E</i>	<i>G551S</i>	<i>S549N</i>
	<i>G1349D</i>	<i>S1251N</i>	<i>S549R</i>

OR

Cystic fibrosis (CF) patients aged 18 years and older who have at least one copy R117H

### Lumacaftor/Ivacaftor (Orkambi™)

Cystic fibrosis (CF) patients who are homozygous for the *F508del* variant in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.

### Tezacaftor/Ivacaftor (Symdeko™)

Cystic fibrosis (CF) in patients who are homozygous for the *F508del* variant

OR

<b>Named Residual Function Variants</b>	<b>Heterozygous for F508del and:</b>		
	<i>P67L</i>	<i>A455E</i>	<i>R1070W</i>
	<i>D110H</i>	<i>D579G</i>	<i>D1152H</i>
	<i>R117C</i>	<i>711+3A→G</i>	<i>2789+5G→A</i>
	<i>L206W</i>	<i>S945L</i>	<i>3272-26A→G</i>
	<i>R352Q</i>	<i>S977F</i>	<i>3849+10kbC→T</i>

### Trikafta™

Cystic fibrosis (CF) patients aged 12 years and older who have at least one copy of the *F508del* CFTR variant and another CFTR variant on the opposite allele.

**For Reference Only:**

**List of minimal function variants<sup>1</sup>**

Q2X	L218X	Q525X	R792X	E1104X
S4X	Q220X	G542X	E822X	W1145X
W19X	Y275X	G550X	W882X	R1158X
G27X	C276X	Q552X	W846X	R1162X
Q39X	Q290X	R553X	Y849X	S1196X
W57X	G330X	E585X	R851X	W1204X
E60X	W401X	G673X	Q890X	L1254X
R75X	Q414X	Q685X	S912X	S1255X
L88X	S434X	R709X	Y913X	W1282X
E92X	S466X	K710X	Q1042X	Q1313X
Q98X	S489X	Q715X	W1089X	Q1330X
Y122X	Q493X	L732X	Y1092X	E1371X
E193X	W496X	R764X	W1098X	Q1382X
W216X	C524X	R785X	R1102X	Q1411X
185+1G>T	711+5G>A	1717-8G>A	2622+1G>A	3121-1G>A
296+1G>A	712-1G>T	1717-1G>A	2790-1G>C	3500-2A>G
296+1G>T	1248+1G>A	1811+1G>C	3040G>C (G970R)	3600+2insT
405+1G>A	1249-1G>A	1811+1.6kbA>G		3850-1G>A
405+3A>C	1341+1G>A	1811+1643G>T	3120G>A	4005+1G>A
406-1G>A	1525-2A>G	1812-1G>A	3120+1G>A	4374+1G>T
621+1G>T	1525-1G>A	1898+1G>A	3121-2A>G	
711+1G>T		1898+1G>C		
182delT	1119delA	1782delA	2732insA	3791delC
306insA	1138insG	1824delA	2869insG	3821delT
365-366insT	1154insTC	1833delT	2896insAG	3876delA
394delTT	1161delC	2043delG	2942insT	3878delG
442delA	1213delT	2143delT	2957delT	3905insT
444delA	1259insA	2183AA>G <sup>a</sup>	3007delG	4016insT
457TAT>G	1288insTA	2184delA	3028delA	4021dupT
541delC	1343delG	2184insA	3171delC	4022insT
574delA	1471delA	2307insA	3171insC	4040delA
663delT	1497delGG	2347delG	3271delGG	4279insA
849delG	1548delG	2585delT	3349insT	4326delTC
935delA	1609del CA	2594delGT	3659delC	
1078delT	1677delTA	2711delT	3737delA	
A46D	V520F	Y569D	N1303K	
G85E	A559T	L1065P		
R347P	R560T	R1066C		
L467P	R560S	L1077P		
I507del	A561E	M1101K		

<sup>1</sup> (from <https://www.cff.org/sites/default/files/2021-12/Study-VX18-445-106-Eligible-Mutations-June-2019.pdf>)

CFTRdele1		
	CFTRdele16-17b	991del5
CFTRdele2	CFTRdele17a,17b	1461ins4
CFTRdele2,3	CFTRdele17a-18	1924del7
CFTRdele2-4	CFTRdele19	2055del9>A
CFTRdele3-10,14b-10,14b-16	CFTRdele19-21	2105-2117del13insAGAAA
CFTRdele4-7	CFTRdele21	2372del8
CFTRdele4-11	CFTRdele22-24	2721del11
CFTR50kdel	CFTRdele22,23	2991del32
CFTRdup6b-10	124del23bp	3121-977_3499+248del2515
CFTRdele11	306delTAGA	3667ins4
CFTRdele13,14a	602del14	4010del4
CFTRdele14b-17b	852del22	4209TGTT>AA

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