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

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Cystic Fibrosis Fibrose kystique Canada

FURTHER

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**Conflict of interest**

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# INTRODUCTION

Cystic Fibrosis (CF) is the most common inherited 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. 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 (3). 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 (4), 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 (5,6). In 2021, it is funded both at a 3rd party 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 efficacy 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. Currently only 12% of Canadian CF patients receive CFTR modulators through these programs, participation in clinical trials or 3rd party payers.

The advent of a fourth CFTR modulator provides a triple combination therapy, known as elexacaftor/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) (7). 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 (8). 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, providing highly impactful treatment for the vast majority of Canadians with CF over 12 years of age.

Health Canada has approved four CFTR modulator therapies that act on the cystic fibrosis transmembrane conductance regulator (CFTR) pathway:

1. **Ivacaftor (Kalydeco™) (9-14)**

Ivacaftor 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:** Class III CFTR Variants: ≥12 months or older; R117H: ≥18 years or older

Health Canada Link:
https://hpr-rps.hres.ca/details.php?drugproductid=4285&query=kalydeco

### 2. Lumacaftor/ivacaftor (Orkambi™) (15-18)

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

**Indication:** F508del/F508del
**Age:** 2 years or older

Health Canada Link:
https://hpr-rps.hres.ca/query.php?drugquery=orkambi

### 3. Tezacaftor/ivacaftor (Symdeko™) (19-22)

Similar to lumacaftor, tezacaftor is a corrector designed to move the defective CFTR protein to the correct position on the cell surface. It works in combination with ivacaftor as a potentiator of CFTR. It has comparable efficacy to lumacaftor with fewer drug interactions and fewer reported acute adverse effects.
It has been trialed for patients homozygous for the F508del variant or heterozygous for the F508del variant in combination with other CFTR variants having some residual function:

**Indication:** (F508del/F508del)
Or
F508del in combination with other CFTR variants having some residual function (RF) (Appendix 1)
**Age:** 12 years or older

Health Canada Link:
https://hpr-rps.hres.ca/query.php?drugquery=symdeko

### 4. Elexacaftor/tezacaftor/ivacaftor (Trikafta™) (23-25)

This triple therapy builds on the combination of tezacaftor/ivacaftor by the addition of the next generation corrector, elexacaftor. This compound when used with tezacaftor/ivacaftor 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/Any CFTR variant (Appendix 1)
**Age:** 12 years or older

Health Canada Link:
https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=100648

### Indications for starting CFTR modulator therapy

All Canadians with a confirmed diagnosis of cystic fibrosis should have access to Health Canada approved CFTR modulators based on their variants in CFTR.

The diagnosis of CF requires:

Clinical symptoms/features or a positive newborn screen and either

- Two disease-causing Cystic Fibrosis Transmembrane Conductance Regulator (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 (8). 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 $FEV_1$

   In Canada, due to improvements in care, early-stage lung disease is increasingly being seen in adolescents and adults with CF as defined by conventional spirometry measurement. This will become common with the availability of highly effective modulator therapy (29). However, $FEV_1$ is not a useful marker in mild lung disease, in part, due to its relatively insensitivity to detection of early small airways destruction (27). This is illustrated, when CF patients with no abnormality in lung function underwent chest CT imaging. Despite a normal $FEV_1$ there was evidence of significant structural lung disease (28). Additionally, several trials have shown that in patients with normal lung function ($ppFEV_1$>90%) the addition of a CFTR modulator caused further significant gains in $ppFEV_1$ (30), illustrating improvement to be made in mild CF lung disease. The most recent data showed in children aged 6-11 years with an average $ppFEV_1$:89% of whom 45% had $ppFEV_1$>90%, the addition of ELX/TEZ/IVA produced an increase in $ppFEV_1$ of 10% (31). 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 ($ppFEV_1$<40%) or are awaiting lung transplantation also improve on treatment to the point where many no longer need transplantation (5,32). 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. The majority of patients with CF are pancreatic insufficient but some patients are not. Early introduction of CFTR modulator therapy has the potential to restore pancreatic function (33) or delay onset of pancreatic insufficiency (12,32). 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 various different Health Canada approved CFTR modulators. 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 modulator 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 $FEV_1$ rate of decline (32,34,35). These studies have shown an improvement in lung function trajectory with a slowing in the rate of $FEV_1$ decline compared to patients not on CFTR modulators. However, patients **STILL** have a decline in $FEV_1$ over time **DESPITE** the impact of CFTR modulators (32,34,36). Patients with CF have bronchiectasis with chronic infection and irreversible structural lung damage which will impact $FEV_1$ recovery and trajectory. As life expectancy improves for patients with CF it is expected that $FEV_1$ will still decline year to year due to the natural aging of the patient (37) even in the presence of CFTR modulators.

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 (5,6). In addition, patients report an impact on respiratory symptoms, sleep quality, general well-being and physical self-esteem, and a reduced treatment burden. Patients reported renewed and unexpected physical strength, leading to greater self-confidence, autonomy and long-term planning, after treatment initiation (38).

Consideration should be given to CF related co-morbidities. Although not reported in clinical studies, patients may experience improvement in CF issues such as sinus disease, pancreatitis and CF related diabetes with the introduction of CFTR modulators (39).

Data has suggested that there may be responders and non-responders to CFTR modulator therapy (40). 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 exacerbations, provide adequate lung function data to determine improvement and stabilization of $FEV_1$ over time and monitor improvement in nutrition.

Meaningful clinical responses to be monitored include:

1. Improvement in lung function as measured by $FEV_1$ or Lung Clearance Index (LCI) (where available) obtained at a time of clinical stability
2. Reduction in the number of pulmonary exacerbations
3. Stabilization of lung function over time (i.e. attenuation of the usual decline in lung function)
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 if any CF treatments can be discontinued 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 $ppFEV_1$ 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 CFQ-R: Respiratory Domain) $\geq$ 4 points.

12 months

1) No 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 recently 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 (41). 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 every three months in the first year and then annually. For individuals with moderate or severe CF-related liver disease, recommendations for dosage adjustments are available. 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. Rare cases of delayed hypersensitivity reactions have also been reported. Few individuals required interruption or discontinuation of therapy for rash or hypersensitivity reactions. Similar occurrence 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. 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.

### iii) Drop in $FEV_1$ and respiratory symptoms

Of the available CFTR modulators, LUM/IVA has had the highest reported respiratory-related side effects. Chest tightness, dyspnea, increased sputum, and declines in $ppFEV_1$ were among the most common respiratory symptoms and tended to occur within the first few days after initiation. Bronchodilators were beneficial in mitigating symptoms of chest tightness, wheeze, and increased work of breathing in some individuals. Improvement in or resolution of symptoms occurred within 1–4 weeks following initiation, but symptoms and/or $ppFEV_1$ below baseline could persist beyond this and some patients may require a dose reduction or discontinuation 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 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) 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 to be done at baseline, 6 months and on annual basis until age 18.

## Drug-Drug interactions (Figure 1 (42))

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 different CFTR modulators.

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. 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).

## Special considerations for patients receiving IVA, LUM/IVA, TEZ/IVA CFTR Modulators

Health Canada approved ELX/TEZ/IVA in June 2021 for CFTR variants F508del/Any in patients 12 years and older. In the near future this age limit will likely be reduced to >6 years of age. 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 (8). In a study comparing patients F508del/MF 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 $FEV_1$ was observed, with significant gains in CFQ-R-Resp domain and further reduction in sweat chloride levels (43).

All patients on IVA, LUM/IVA or TEZ/IVA, should have the opportunity to transition to the triple therapy combination, ELX/TEZ/IVA.

## Pregnancy and CFTR modulators

CFTR modulators may increase fertility in women with CF due to improvement in clinical status and to their impact on the mucus in the cervix and uterus and so it is important for women on CFTR modulators to use birth control 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 CFTR indicate no impact on organogenesis at normal human doses.

Real world experience is limited but case reports and an international survey have demonstrated that CFTR modulators appear to be well tolerated during pregnancy (44). As discontinuation of CFTR modulators has been associated with significant decline in clinical status (45), the risks/benefits of CFTR therapy during pregnancy must be discussed, ideally before pregnancy. CFTR modulators are expressed in breast milk. As CFTR modulators have been associated with cataracts in children, it would be advisable that infants born to mothers taking CFTR modulators have ophthalmologic examination.

## 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 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 (46-49).

With the introduction of TEZ/IVA/ELX, evidence is emerging of its use after lung transplant (50). Drug-drug interaction between CFTR modulators and immunosuppressants, such as calcineurin inhibitors, should be expected (51). 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 hepatoxicity.

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 3XULN of transaminases and bilirubin (>2 x 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 after clinical stability, any confounding co-morbidities have been assessed and non-adherence issues have been addressed.

## How to start CFTR Modulators

Given the large number of patients who will qualify for CFTR modulators, initiation will at first impose challenges on individual CF clinics. How this will be undertaken will be determined by individual CF centres based on the number of eligible patients, clinic resources and provincial availability. For patients who have had a significant adverse reaction to a CFTR modulator and a rechallenge is deemed appropriate, or if initiation at a reduced dose and titrating to full-dose is preferred, potential protocols are summarized in the systematic review performed by Dagenais et al (41).

## 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 and reduce mortality. All patients who are eligible should be started on therapy as soon as possible to prevent lung disease progression and 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 standard of care treatment. Follow up will be determined by their CF clinic.**

**Discontinuation of modulator therapy should be performed in patients with significant side effects or those who are deemed non-responders after 1 year of therapy. 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

<table>
<tr><th>CFTR Modulator</th><th>Indication</th><th>Approved Age</th><th>Minimum Trial Duration</th></tr>
<tr><td rowspan="2">IVA *</td><td>Gating (Class III) variant</td><td>≥1 year</td><td rowspan="2">1 year</td></tr>
<tr><td>R117H</td><td>≥ 18 years</td></tr>
<tr><td>LUM/IVA *</td><td>F508del / F508del</td><td>>2 years</td><td>1 year</td></tr>
<tr><td rowspan="2">TEZ/IVA *</td><td>F508del / F508del</td><td rowspan="2">≥12 years</td><td rowspan="2">1 year</td></tr>
<tr><td>F508del / RF variant</td></tr>
<tr><td>ELX/TEZ/IVA*</td><td>F508del / Any</td><td>≥12 years</td><td>1 year</td></tr>
<tr><td colspan="4">* Health Canada approved CFTR variants described in Appendix 1<br>RF, residual function</td></tr>
</table>

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

| **Routine Clinic Visits (Clinical Care monitoring): ≥6 years of age** | **Baseline** | **1 Month Visit** | **3 Month Visit** | **6 Month Visit** | **9 Month Visit** | **1 Year Visit** |
|---|---|---|---|---|---|---|
| Clinical assessment and review of *CFTR* genotype, initial sweat test, and past medical history (including decline in $FEV_1$ 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, ALP, bilirubin, CK, INR | X | X | X | X | X | X |
| Spirometry/LCI[a,b] | X | X | X | X | X | X |
| Sputum microbiology[c] | X | X | X | X | X | X |
| Ophthalmology exam[d] | X | | | X | | X |
| PHQ-9 and GAD-7 questionnaires[e] | X | | | X | | X |
| Safety review[f] | X | X | X | X | X | X |
| Review of prescribed therapy[g] | X | | X | X | X | X |
| Sweat chloride test | X | | X | | | X |
| CFQ-R:RD questionnaire | X | X | X | X | X | X |
| CT imaging of chest | X | | | | | X |
| Fecal elastase | X | | X | | | X |
| (orange) | Standard for CF Clinic visit &/or recommended by product monograph | | | | | |
| (red) | Clinical data needed to support CFTR modulator response | | | | | |
| (blue) | May have clinical relevance to CFTR modulator response | | | | | |

[a] LCI to be measured where available at baseline, 3 months and 12 months
[b] If $ppFEV_1$ <40%, include CPET or 6-minute exercise test at 6 and 12 months
[c] Samples obtained by sputum or cough swab
[d] For patients 6 to 18 years of age and then annually until 18 years, to exclude cataracts. May be performed by optometrist.
[e] For patients aged 12 years and older
[f] Events of special interest: rash, DIOS, pancreatitis, mental health, new organisms isolated in sputum
[g] Review of all prescribed medication including airway clearance

**ALT**, alanine aminotransferase; **ALP**, alkaline phosphatase; **CBC**, complete blood count; **CFQ-R**:RD, Cystic Fibrosis Questionnaire Revised; Respiratory Domain; **CK**, creatine kinase; **DIOS**, distal intestinal obstruction syndrome; **GAD-7,** General Anxiety Disorder-7; **LCI**, lung clearance index; **PHQ-9**, Patient Health Questionnaire-9

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

| **Routine Clinic Visits (Clinical Care monitoring): <6 years of age** | **Initial Visit** | **1 Month Visit** | **3 Month Visit** | **6 Month Visit** | **9 Month Visit** | **1 Year Visit** |
|---|---|---|---|---|---|---|
| Clinical assessment and review of *CFTR* 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, ALP, bilirubin, CK, INR | X | X | X | X | X | X |
| Spirometry/LCI[a] | X | X | X | X | X | X |
| Sputum microbiology[b] | X | X | X | X | X | X |
| Ophthalmology exam[c] | X | | | X | | X |
| Safety review[d] | X | X | X | X | X | X |
| Review of prescribed therapy[e] | X | | X | X | X | X |
| Sweat chloride test | X | | X | | | X |
| CFQ-R:RD questionnaire | X | X | X | X | X | X |
| Fecal elastase | X | | X | | | X |
| (orange) | Standard for CF Clinic visit &/or recommended by product monograph | | | | | |
| (pink) | Clinical data needed to support CFTR modulator response | | | | | |
| (blue) | May have clinical relevance to CFTR modulator response | | | | | |

[a] LCI to be measured where available at baseline, 3 months and 12 months
[b] Samples obtained by sputum or cough swab
[c] Done at baseline, 6 months and on annual basis
[d] Events of special interest: Rash, DIOS, pancreatitis, mental health, new organisms isolated in sputum
[e] Review of all prescribed medication including airway clearance
**ALT**, alanine aminotransferase; **ALP**, alkaline phosphatase; **CBC**, complete blood count; **CFQ-R:**RD, Cystic Fibrosis Questionnaire Revised: Respiratory Domain; **CK**, creatine kinase; **DIOS**, distal intestinal obstruction syndrome; **GAD-7,** General Anxiety Disorder-7; **LCI**, lung clearance index; **PHQ-9**, 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 >1 Year | Age >2 Years | Age >12 Years | Age >12 Years |
| Lung Function[a] | | | | |
| $FEV_1$ | | >5% predicted | | >5% predicted |
| LCI | | 15% decrease | | |
| Decrease Sweat Chloride | >20%/20mmol | >20% | >20% | >20%/20mmol |
| CFQ-R (Respiratory Domain)[b,c] | 4 Points | 4 Points | 4 Points | 4 Points |
| Pulmonary exacerbation | 20% reduction | 20% reduction | 20% reduction | 20% reduction |
| BMI/weight change[d] | Improved | Improved | Improved | Improved |

[a] Children < 3 years of age are unable to do formal lung function measurement
[b] This will be based on parents' assessment for children under 6 years of age
[c] Minimum clinically important difference is 4 points
[d] 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 $FEV_1$ | | ++ | | |
| 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 |
|---|---|---|---|---|
| **ALT** | | Repeat in 1 month | - STOP modulator<br>- Monitor AST and ALT<br>- Re-challenge modulator when AST and ALT <2x ULN* | STOP modulator |
| **AST** | | Repeat in 1 month | - STOP modulator<br>- Monitor AST and ALT<br>- Re-challenge modulator when AST and ALT <2x ULN* | STOP modulator |
| **Bilirubin** | And AST or ALT >3x ULN: STOP<br>Monitor in 2 weeks,<br>Rechallenge when Bilirubin <1x ULN* | | | |
| **ALT,** alanine aminotransferase; **AST**, aspartate aminotransferase; **ULN**, upper limit of normal | | | | |

*Rechallenge with normal dose, in first instance.

**Figure 1:**

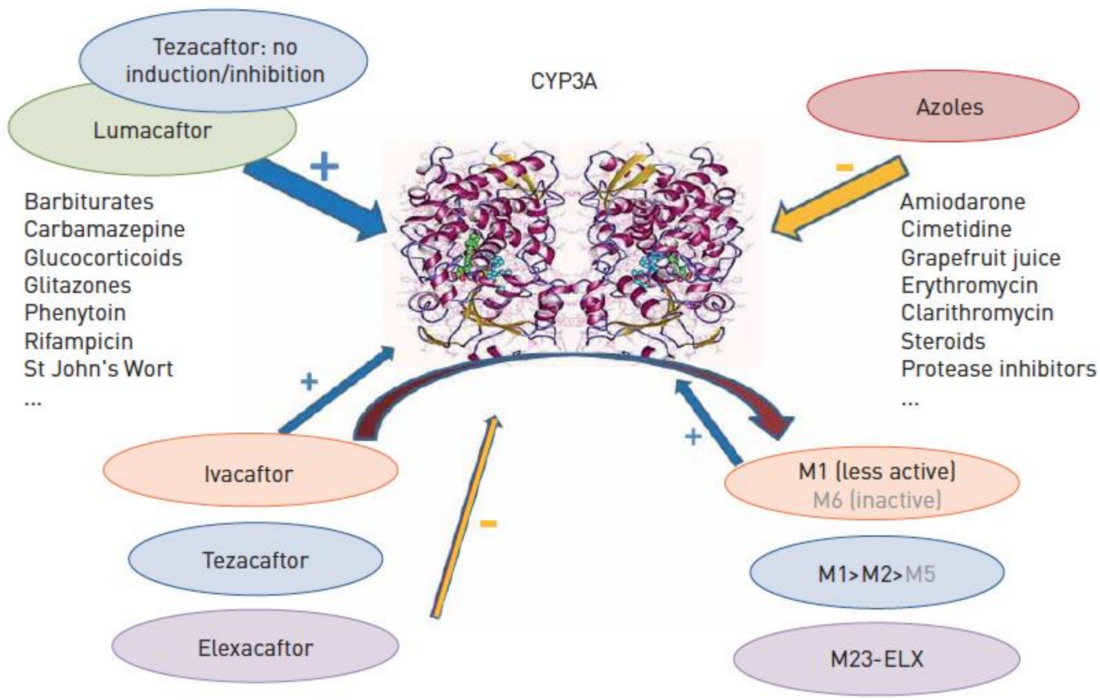


FIGURE 1 A summary of interactions between cystic fibrosis transmembrane regulator modulators and other drugs/compounds and cytochrome P450 3A4 (CYP3A). Blue arrows: induction of the cytochrome; yellow arrow: inhibition of the cytochrome; curved arrow: metabolism of a drug by the cytochrome. Adapted from [28–32].

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:

| **Named Variants** | *G551D* | *G178R* | *S1255P* |
|---|---|---|---|
| | *G1244E* | *G551S* | *S549N* |
| | *G1349D* | *S1251N* | *S549R* |

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

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

**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 (adapted from ref:52)

| | | | | |
|---|---|---|---|---|
| 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 [a] | 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 | |

| | | |
|---|---|---|
| CFTRdele1 | CFTRdele16-17b | 991del5 |
| CFTRdele2 | CFTRdele17a,17b | 1461ins4 |
| CFTRdele2,3 | CFTRdele17a-18 | 1924del7 |
| CFTRdele2-4 | CFTRdele19 | 2055del9>A |
| CFTRdele3-10,14b-16 | CFTRdele19-21 | 2105-2117del13insAGAAA |
| CFTRdele4-7 | CFTRdele21 | 2372del8 |
| CFTRdele4-11 | CFTRdele22-24 | 2721del11 |
| CFTR50kbdel | CFTRdele22,23 | 2991del32 |
| CFTRdup6b-10 | 124del23bp | 3121-977_3499+248del2515 |
| CFTRdele11 | 306delTAGA | 3667ins4 |
| CFTRdele13,14a | 602del14 | 4010del4 |
| CFTRdele14b-17b | 852del22 | 4209TGTT>AA |

| | | | |
|---|---|---|---|
| A46D | V520F | Y569D | N1303K |
| G85E | A559T | L1065P | |
| R347P | R560T | R1066C | |
| L467P | R560S | L1077P | |
| I507del | A561E | M1101K | |

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