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

Updated 2024

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Canadian CF Modulators Contributors (2024 Guideline Update)

Dr. Mark A. Chilvers
CF Clinic Director, Paediatric Cystic Fibrosis Clinic, BC Children's Hospital, Vancouver, BC

Ms. Eva Cho
Clinical Pharmacy Specialist, Paediatric Cystic Fibrosis Clinic, BC Children's Hospital, Vancouver, BC

Dr. Renée Dagenais
Clinical Pharmacy Specialist, Adult Cystic Fibrosis Clinic, St. Paul's Hospital, Vancouver, BC

Dr. Patrick Daigneault
CF Clinic Director, Paediatric Cystic Fibrosis Clinic, Centre Mère-Enfant Soleil du CHU de Québec, QC

Dr. Paul Eckford
Chief Scientific Officer, Cystic Fibrosis Canada

Ms. Jana Kocourek
Director, Healthcare Programs, Cystic Fibrosis Canada

Dr. Annick Lavoie
CF Clinic Director, Adult Cystic Fibrosis Clinic, CHUM, Montréal, QC

Dr. Nancy Morrison
Medical Director, Adult Cystic Fibrosis Clinic, QEII Health Sciences Centre, Halifax, NS

Dr. Brad Quon
Medical Director, CF CanACT, Adult Cystic Fibrosis Clinic, St. Paul's Hospital, Vancouver, BC

Dr. Felix Ratjen
Head, Division of Respiratory Medicine; Program Head, Translational Medicine; Professor, University of Toronto, The Hospital for Sick Children, ON

Dr. Julian Tam
CF Clinic Director, Adult Cystic Fibrosis Clinic, Royal University Hospital, Saskatoon, SK

Dr. Elizabeth Tullis
CF Clinic Director, Adult Cystic Fibrosis Clinic, St. Michael's Hospital, Toronto, ON

Unlisted Original Authors

Dr. Martha McKinney (former) CF Clinic Physician, Pediatric Cystic Fibrosis Clinic, Stollery Children's Hospital, Edmonton, AB

Dr. John Wallenberg (retired) Chief Scientific Officer, Cystic Fibrosis Canada

Dr. Pearce Wilcox (retired) CF Clinic Director, Adult Cystic Fibrosis Clinic, St. Paul's Hospital, Vancouver, BC

Forward

The February 2024 updated Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis has been developed as a set of concise guideline recommendations to aid Canadian CF clinicians in decision making for the initiation, continuation, monitoring and discontinuation of current CF modulators, primarily the highly effective modulators Ivacaftor (Kalydeco) and Elexacaftor/Tezacaftor/Ivacaftor and Ivacaftor (Trikafta), in Canadian patients. These guidelines are not a set of binding requirements or rigid rules. Rather they are designed to aid the clinician in best decision-making for the use of CFTR modulators in patients. No guideline document can substitute for or replace the knowledge, experience and best judgment of CF clinicians. Nor can it describe or account for every unique situation and experience of each patient. We hope that this document will be a valuable resource for most common experiences with CFTR modulators for Canadian CF patients.

We'd like to acknowledge the commitment and dedication of the original CF modulator group members who contributed to the earlier version of this document and the efforts of the revised committee to update the guideline so that it remains a valuable and relevant resource for Canadian CF Clinicians. We'd also like to acknowledge the hard work of many individuals with Cystic Fibrosis Canada who have helped support the development and publication of this guideline, without whom this document could not have been completed.

Sincerely,

Dr. Mark A. Chilvers
Chair, CF Canada Healthcare Advisory Committee
CF Clinic Director, Paediatric Cystic Fibrosis Clinic,
BC Children's Hospital, Vancouver, BC

Dr. Paul D.W. Eckford
Chief Scientific Officer,
Cystic Fibrosis Canada,
Toronto, ON

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Reviewed and Approved by Cystic Fibrosis Canada's 2023/24 Healthcare Advisory Council Members:

Co- Chair: Dr. Mark A. Chilvers
CF Clinic Director, Paediatric Cystic Fibrosis Clinic, BC Children's Hospital, Vancouver, BC

Co-chair: Ms. Jana Kocourek
Program Director of Healthcare, Cystic Fibrosis Canada

Vice-Chair: Dr. Valerie Waters
Infectious Diseases Physician, Cystic Fibrosis Clinic, The Hospital for Sick Children, Toronto, ON

Members:

Ms. Eva Cho
Pharmacist, BC Children's Hospital, Vancouver, BC

Dr. Patrick Daigneault
CF Clinic Director, Paediatric Cystic Fibrosis Clinic, Centre Mère-Enfant Soleil du CHU de Québec, QC

Ms. Karen Doyle, NP
CF Clinic Nurse Coordinator, Janeway Children's Health and Rehabilitation Centre and Health Sciences Centre, St. John's, NL

Ms. Erin Fleischer
CF Clinic Nurse Practitioner, London Health Sciences, London, ON

Ms. Ena Gaudet, RN
CF Clinic Nurse Coordinator, The Ottawa Hospital, ON

Ms. Daina Kalnins,
Dietician, SickKids- The Hospital for Sick Children, Toronto, ON

Dr. Annick Lavoie
CF Clinic Director, Adult Cystic Fibrosis Clinic, CHUM, Montréal, QC

Ms. Pat MacDiarmid
Social worker, St. Paul's Hospital, Adult, Vancouver, BC

Ms. Megan Parker, CF community member

Ms. Melissa Richmond
Physiotherapist, BC Children's Hospital, Vancouver, BC

Mr. Kenneth Wu
Physiotherapist, St. Michael's Hospital, Toronto, ON

Ms. Patti Tweed,
CF Community member (former HAC member)

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Introduction

Cystic Fibrosis (CF) is the most common fatal genetic condition in Canada, affecting 4,445 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 older children and adults with CF 3).

The strategy of CF care is to slow evolution of lung damage and 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 directly on the CFTR protein to correct the defects within the protein that are caused by 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, as end-organ damage has already occurred and therefore these treatments will likely remain necessary. For younger patients, however, accessing modulators before significant damage has occurred, is a high priority to prevent downstream consequences, with expected improvements in survival and quality of life in these patients.

With the approval of the first triple therapy modulator, elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA; marketed as “Trikafta™”), by Health Canada and its recommendation by CADTH incrementally for those over age 12 (5), over age 6 (6), and most recently over age 2 (7) that the majority of Canadian patients with CF will have access to this CFTR modulator.

Cystic Fibrosis Canada’s clinician working group has developed this standardized care guideline to support CF clinics in initiating CFTR modulator therapy in the Canadian context, with the following aims:

- Indications for starting CFTR modulator therapy
- Assessing response to CFTR modulator therapy
- Monitoring patients on CFTR modulator therapy
- Side effect management for patients on CFTR modulator therapy
- Assessing non-response to CFTR modulator therapy

Background on current CFTR Modulator treatments

Over the last 15 years, significant research and numerous 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 with "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 (8,9).

In 2014, Kalydeco was funded for nine mutations it treats by some public and private drug plans. In 2015, an additional mutation was approved by Health Canada and some drug plans expanded access. By 2021, all public drug plans funded the drug for all mutations indicated, and some private plans did as well. As of 2023, the Health Canada indication is for 10 mutations in ages as young as 2 months.

For patients with 2 copies of the most common CF variant, *F508del* (approximately 50% of Canadian CF patients), lumacaftor/ivacaftor (LUM/IVA; Orkambi™) and then later tezacaftor/ivacaftor (TEZ/IVA; Symdeko™) were developed. Symdeko was approved for individuals with two copies of *F508del* or one copy of *F508del* and one of a small group of other mutations (table 1d). Studies support the efficacy of LUM/IVA and TEZ/IVA in reducing pulmonary exacerbations and improving nutritional status, but not to the degree achieved by IVA in patients with gating variants. Orkambi is funded by some public and private drug plans for those who meet age and health restrictive criteria. Symdeko is funded by some private drug plans for those who meet age and health restrictive criteria.

The advent of a second class of CFTR corrector provides a triple combination therapy, known as ELX/TEZ/IVA (Trikafta™). The combination of 2 correctors (TEZ and ELX) results in more effective correction of CFTR trafficking 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) (10). 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 (11). 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 of appropriate age with CF with a single *F508del* variant (approximately 87% of Canadian CF patients)

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

1. **Ivacaftor (IVA; Kalydeco™)(12–17))**

IVA is effective in patients with a gating variant (Class III) or conductance variant (R117H 5T or 7T). 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 of nine indicated gating variants or R117H.
Age: 2 months or older

Product monograph link: https://pi.vrtx.com/files/Canadapm_kalydeco_en.pdf

2. **Lumacaftor/ivacaftor (LUM/IVA; Orkambi™)(18-21))**

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 (2 copies)
Age: 1 year or older (to 65 as per monograph)

Product monograph link: https://pi.vrtx.com/files/Canadapm_orkambi_en.pdf

3. **Tezacaftor/ivacaftor (TEZ/IVA; Symdeko™)(22-25)**

Similar to LUM, TEZ is a corrector designed to facilitate proper folding of the defective CFTR protein so it may be trafficked 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

4. **Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA; Trikafta™)(26-28)**

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 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: 2 years or older

Product monograph link: https://pi.vrtx.com/files/Canadapm_trikafta_en.pdf

Refer to **Tables 1a- 1d** for standard dosage recommendations for the above modulators.

Modulator access for other CFTR gene variants

CFTR modulator treatments improve trafficking and/or function of the CFTR protein. These treatments may have a positive impact on other CFTR gene variants (mutations) where full length or near full length protein is produced. At the time of writing, the CFTR1 mutation database (29) includes 2114 variants, with 816 missense mutations and 269 sequence variation mutations. Not all of these variants may be clinically relevant; a subset will result in protein that has defects in trafficking and/or function and may be responsive, or partially responsive to CFTR modulation. Additionally, a few frameshift, splicing, nonsense, or large insertion/deletion variants (342, 231, 177 and 59, respectively) would be anticipated to respond to modulator therapy.

There is lack of sufficient clinical trial data on modulator use in patients with variants other than F508del or gating and conductance mutations. At least one clinical trial has been conducted by Vertex for ELX/TEZ/IVA in individuals with no F508del variant but with at least one of a short list of other variants primarily identified in in vitro laboratory data to potentially be responsive (Table 2). While at the time there were no Canadians with some of these mutations, others including A455E, D1152H, L206W and M1101K were represented in significant numbers (from 10-30+ for each variant) of Canadians. To date these results have not yet been published, however the manufacturer has stated that the cohort of the study had a 9.2 percentage point increase in ppFEV1; P<0.0001; 95% CI [7.2, 11.3] (30).

While it is important to conduct well-designed, placebo controlled double-blinded clinical trials to assess modulator effectiveness where possible, in most cases such trials are not feasible given the small numbers of patients with each potentially responsive variant. Recognizing this, the FDA approved the use of Ivacaftor (Kalydeco™) for 23 different variants based on clinical trial data and also, in vitro laboratory data on drug response of mutant CFTR protein overexpressed in the Fischer Rat Thyroid (FRT) cell line (31). Through subsequent in vitro testing, to date the US label has now been expanded for CF modulators with the following number of CFTR variants: Trikafta (177 variants; Symdeko (154 variants), and Kalydeco (96 variants) (Table 3),(32-35). This has increased patient access to modulator therapy based on safety data from F508del trials and in vitro laboratory data negating the need for clinical trials for each specific CFTR variant. Real world evidence (RWE) will ultimately support the use of highly effective modulators in patients with many of the mutations on the expanded label. .

Programs in Canada (36-39) and Europe (40 - 42) have examined patient nasal cells, or intestinal organoids (43) for response to CFTR modulator compounds to advocate for drug access for the patient. Studies of the H609R mutations in the HEK293 overexpression system (44) and in intestinal organoids (unpublished) suggest a response by this mutation to ELX/TEZ/IVA. Canadian nasal cell data for an individual with the N1303K/N1303K genotype from Israel showed the potential for a patient response to Trikafta (39). This and other data allowed access for a cohort of eight patients in

Israel with at least 1 copy of the N1303K variant and no other presumed responsive variant to ELX/TEZ/IVA and demonstrated clinical benefit of the drug (45). A trial was more recently conducted in the United States, independent of Vertex, on efficacy of ELX/TEZ/IVA in 12 individuals with at least one copy of the N1303K variant but lacking another responsive variant. Interim results show little change in sweat chloride but significant changes in both lung function (ppFEV1) and CFQ-R scores, suggesting that N1303K responds to ELX/TEZ/IVA (32).

Additionally, an RWE study conducted in France evaluated CF patients, some with non-trikafta approved variants, with severe lung disease who received treatment with ELX/TEZ/IVA through a compassionate access program. Those who demonstrated clinical benefit remained on treatment after the initial assessment period. Eighty four (84) subjects were reported, 45 (54%) showed benefit, of which 50% (22/45) were responders who had a CFTR variant not currently approved by FDA (Table 4a and 4b). These data suggest that significantly more CF patients may benefit from modulator therapy than have been approved (46). The program has now been expanded to include individuals age 6+ who do not have two variants deemed to be non-responsive (such as two nonsense mutations) and importantly the restriction to individuals with low lung function has been removed (47). Othe studies have shown that certain rare mutations respond in vivo to ELX/TEX/IVA, including c.3700A>G (48), G85E (49,50), and N1303K (51).

These examples support the growing evidence for use of ELX/TEZ/IVA in patients with non-F508del CFTR variants, including those that have been shown to have in-vitro (Table 5) or ex-vivo benefit that are currently not Health Canada indicated. All current evidence, including RWE and in vitro evidence should be examined when considering off label access for individuals with mutations not currently indicated by Health Canada.

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 or Any/Any CFTR variant

These genotype recommendations are based on Phase 3 clinical trials showing substantial clinical improvement with CFTR modulators, and Health Canada approval. However, as detailed above, evidence suggests CFTR variants not approved by Health Canada may show in vitro and/or clinical response to ELX/TEZ/IVA and should be considered for modulator therapy. This should be on a case-by-case basis.

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 may reverse disease progression, such as restoring pancreatic function (11). There is NO data to support withholding CFTR modulators until significant clinical symptoms have developed or a drop in lung function occurs. This would be counter to the stated goal of preventing lung damage and functional decline.

3. **Lung function:** No minimum or maximum FEV1

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 (52). However, ppFEV1 is not a useful marker in mild lung disease, in part due to its relative insensitivity to detection of early small airways destruction (53). This is illustrated when people with CF who have no abnormality in lung function underwent chest CT imaging; despite a normal ppFEV1, there was evidence of significant structural lung disease (54). Additionally, several trials have shown that in patients with normal lung function (ppFEV1 >90%) the addition of a CFTR modulator caused further significant gains in ppFEV1 (12), illustrating improvement to be made in mild CF lung disease. Data from 2021 showed in children aged 6-11 years with an average ppFEV1 of 89% (of whom 45% had ppFEV1 >90%), the addition of ELX/TEZ/IVA produced an increase in ppFEV1 of 10% (26).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 (ppFEV1 <40%) or who are awaiting lung transplantation also have the potential to improve on treatment to the point where many no longer need transplantation (8, 55-57). Consequently, no lower limit of lung function should be required for eligibility.

As patients gain access to CFTR modulators at younger ages, standard lung function is not reliable and not routinely performed, particularly in children aged <6years. The measurement of lung clearance index, as reported in the study, is not approved for clinical use in Canada. Initiation should be independent of formal lung function testing in this age group.

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

Pancreatic status does not affect eligibility. Most patients with CF are pancreatic insufficient but some patients are pancreatic sufficient. Early introduction of CFTR modulator therapy has the potential to restore pancreatic function (47) or delay onset of pancreatic insufficiency (15,55). In patients with pancreatic sufficiency, CFTR modulators will likely help preserve or delay loss of pancreatic function.

Canadian CF clinician working group guidelines for prescribing a CFTR modulator

Pre-modulator Assessment

If a patient has not had a confirmatory sweat test or CF genotyping, ideally both should be undertaken before CFTR modulator initiation. At minimum two known disease-causing CFTR variants or one known disease-causing variant and a sweat chloride of >60 mmol/L in two independent measurements are recommended before CFTR modulator initiation. Baseline suggested clinical assessments before CFTR modulator initiation are illustrated in Tables 6a and 6b. These should be obtained when the patient is clinically stable.

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 re-challenge 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. (58).

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 (59).

For children (at 30 kgs) who transition to the adult, continuation on a lower dose may need be required, as behavioral side effects have been reported during this transition.

At age and weight dosage increases as recommended by the manufacturer, patients may experience adverse effects after initiation of the increased dose. For some patients if adverse effects outweigh benefits of increased dose, clinicians may consider stepping down to prior effective dose. If a reduced dose is continued, risk-benefit review is warranted, and if efficacy endpoints are not met, then may need to consider dose titration up towards recommended dose for age and weight.

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 generally 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 potentially reducing risk of dehydration or heat stroke), it is a biomarker of the effect of CFTR modulators and trials have shown modulator use is often associated with a

reduction in sweat chloride. There may be some exceptions to the observed effect of CFTR modulators on sweat chloride. In individuals with the N1303K, as noted above, minimal or no change sweat chloride may be observed after initiation of ELX/TEZ/IVA treatment (8,46,61). It is not currently known what other variants may show a similar response or the molecular basis of this lack of observed effect in the N1303K variant.

Longer term follow-up studies have evaluated the impact of CFTR modulators on the rate of decline in FEV1 (55,57, 62, 63). 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 may **STILL** have a decline in FEV_1 over time **DESPITE** the impact of CFTR modulators (55, 57, 62, 64). Additional longitudinal studies are required to understand the long term impacts of modulators on lung function, especially ELX-TEZ-IVA in patients for >5 years. Patients with CF have bronchiectasis with chronic infection and structural lung damage that will impact FEV_1 recovery and trajectory. There is some evidence emerging to suggest that benefits from therapy may be sustained over time. FEV_1 may not decline in patients on ELX/TEZ/IVA and radiological improvement in bronchiectasis (65,66).

In children under 12 years of age, FEV_1, which is not a sensitive measure of early lung disease, is often in the normal range despite the presence of significant lung disease, as assessed by research measures such as LCI and MRI (67). A significant change in FEV_1 cannot be expected even in patients who are otherwise experiencing benefit from treatment. It is not feasible to measure FEV1 in children under the age of 6 years and efficacy is difficult to assess in this age group due to limited respiratory symptoms. For children aged 2-5 years, objective assessment of lung function is not reliable or routinely performed and consequently can't be used as a measure of response to therapy. The measurement of lung clearance index, as reported in the study, is not approved for clinical use in Canada. Similarly, CT scans require sedation and are not recommended in routine clinical practice.

Similar to older patients, the 2-5 year cohort will likely show benefit in terms of pulmonary exacerbations, antibiotic use, weight and nutritional status, and quality of life. In clinical practice, patients have reported feeling better, having fewer symptoms such as cough or shortness of breath, having less difficulty maintaining a healthy weight, missing less work or school due to hospitalization for pulmonary exacerbations, and stabilization of the disease.

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 (7,68). 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 (68).

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 (69-73). In addition, an outcome of particular interest is recovery of pancreatic function. 95% of CF patients are pancreatic insufficient,. early modulator treatment was observed to result in recovery of some pancreatic function.

Data has suggested that there may be responders and non-responders (or more minimal responders) to CFTR modulator therapy (74). 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_1 over time, and to 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, for individuals over 6 years of age
2. Prevention and 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. No decline, or an improvement in nutritional and growth status
6. Improvement in quality-of-life scores
7. Reduction in sweat chloride.

Secondary responses observed from taking a CFTR modulator may include:

1. Minimizes and/or reverses complications of CF disease.
2. Changes to psychosocial function
3. Allows attendance at school, university and work with minimal disruption
4. Reduction in burden of care and number of therapies needed to maintain health
5. Alteration of disease trajectory

Concurrent Treatment

At the present time, all patients commenced on a CFTR modulator should continue with current standard of care 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. Any changes in routine therapy should be reviewed after 12 months of modulator therapy.

The schedule of recommended clinical assessment and monitoring for patients prescribed CFTR modulator therapies is outlined in Tables 6a and 6b.

Treatment Response

It is expected that responders age 6 or older will have at:

3 months

Absolute improvement in $ppFEV_1$ of $\geq$5%, measured at time of clinical stability

or

A decrease in sweat chloride by 20% or 20mmol/L from baseline

or

Improvement in respiratory symptoms (as measured by CF Questionnaire-Revised (CFQ-R): Respiratory Domain) by ≥4 points (i.e. the minimum clinically important difference).

12 months

No treatment-limiting adverse events or medication safety issues, **and** one or more of:

Reduction in pulmonary exacerbations (IV or oral antibiotic treatment) by 20%

or

Stabilization of lung function rate of decline above baseline

or

No decline, or an improvement in nutritional status with normalization of growth and nutrition

or

Radiological improvement or stability in chest CT scan.

For children aged 2-5 years, given the challenges in obtaining objective clinical data, response to therapy should be determined by the treating CF clinician. This may be supported by the age-appropriate routine CF clinical assessments completed as part of standard care.

Table 7 is a summary of changes in expected outcomes for responders to CFTR modulators.

Monitoring

Comprehensive monitoring of patients who are commenced on CFTR modulators is detailed in Tables 6a and 6b. Clinics should aim to follow this schedule to demonstrate response to therapy.

Side Effects

After initiation of CFTR modulators and with age/weight dependent dosage increases, it is important to focus on safety and monitor for potential adverse effects (Table 8). 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 (75). Therefore, vigilant post-market monitoring for both expected and unexpected adverse effects is warranted.

Safety Issues of Note:

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 modulators have been previously well-tolerated. Rarely does this result in the need to change modulator therapy but it is still prudent to monitor routinely. The degree of elevation of transaminases and bilirubin will determine the need to interrupt modulator therapy, reduce the dose, or discontinue the modulator (Table 9). It is recommended that liver enzymes be monitored one-month post-initiation and every three months in the first year (and as needed), and then at least annually thereafter (it is suggested to monitor more frequently for patients who have had elevations). For individuals with moderate or severe CF-related liver disease,

recommendations for empiric dosage adjustments are available (28) observed in patients with pre-existing cirrhosis and portal hypertension who have started CFTR modulators. However, real world data show that variations in transaminases with modulator therapy rarely led to liver injury (76, 9) and can be managed with dose interruption or adjustment.

ii) Rash or hypersensitivity (dermatological) 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 in clinical trials was reportedly 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 resolve without intervention. 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 and if deemed appropriate, the CFTR modulator may be retried with close monitoring (JCF 2024). Desensitization protocols have been published (77-80) and CF clinics may have alternate strategies informed by real-world practice.

iii) Drop in ppFEV$_1$ and worsening respiratory symptoms

Respiratory-related side effects, including chest tightness, dyspnea, and declines in ppFEV$_1$ 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$_1$ 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, diarrhea, constipation, 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. Several reports have suggested, there may be an increased risk of pancreatitis in patients on CFTR modulators of which some recovered pancreatic function as determined by fecal elastase (81).

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 (34).

More recently, there have been reports of benign intracranial hypertension in patients on modulator therapy, which, in some cases, may have been associated with hypervitaminosis A. Dose interruption was needed in some, whereas in others symptoms resolved with reduction of vitamin supplementation (73).

vi) Creatinine kinase (CK)

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) Neuropsychiatric/mental health adverse effects

There has been increasing attention to mental health in the CF community, given the high prevalence in people with CF compared to the general population (82,83). Cases of negative impacts on mental health 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. Neuropsychiatric impacts range from mood alterations, anxiety, sleep, neurocognition disturbance (Brain Fogg) to suicidality 47, (84-86).

Results from a recent study indicated no causal relationships between ELX/TEX/IVA and depression related events and suicidal ideation/attempts. Additional long terms studies and clinical observations are necessary. It is critical to observe and be mindful of changes in mental health including potential behavioral implications and increases in anxiety as recently observed in some CF patients.

In Europe, a labelling change was recently made to the ELX/TEZ/IVA product monograph to include depression as an adverse effect (87). Usually this is within 3 months of initiation or if there is a history of psychiatric illness. Mental health screening is recommended to take place three times during the first year of modulator administration and annual screening thereafter (table 2a).

One Canadian CF clinic has published their experience with a protocol developed for how to manage and monitor patients who experience worsening mental health following ELX/TEZ/IVA initiation and require a dose adjustment (84,85). There are also notable drug-drug interactions with LUM/IVA and some psychotropic medications (e.g. antidepressants, anti-anxiety medications, antipsychotics, mood stabilizers) that should be evaluated in patients taking one or more of these therapies before or after LUM/IVA initiation (82).

viii) Cataracts

Cases of non-congenital lens opacities and cataracts have been reported in pediatric patients treated with IVA-containing regimens (35). 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 (refer to Table 6a and 6b)

Discontinuation of CFTR modulator

Health care professionals and patients often face a balance in wishing to resolve/minimize side effects without losing benefits of continued CFTR modulation or a significant worsening in clinical status on drug discontinuation. These patients may require CFTR modulation dose reduction, interruption, or even permanent discontinuation. This has been the case particularly with skin, liver, and neurocognitive side effects as detailed above.

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 and should be on a case-by-case basis. Suggested dose interruptions are detailed in table 10. In addition, measurement of sweat chloride may be useful to assess degree of CFTR modulation on the reduced dose (52).

When re-challenging CFTR modulator therapy, in some cases, medication may need to be re-initiated at a reduced dose with slow incremental increases. Close monitoring for recurrence of adverse effects and risk-benefit should be assessed prior to each increment. There may be cases where the indicated dose for age/weight may not be achievable, and patients may need to remain on a reduced modulator dosage. Decisions to continue with treatment at the tolerated dose, while balancing efficacy endpoints and adverse effects will need to be reviewed on an individualized basis by the prescribing physician.

Examples of these reactions may include:

1. Elevation of transaminates (Table 5) beyond the higher range of fluctuations observed in patients with CF (>8X ULN) OR 3X ULN of transaminases as well as bilirubin (2X ULN)
2. Allergic reactions to treatment and failed desensitization challenges
3. Mental health or neuropsychiatric adverse effects

Ultimately, the risk-benefit of discontinuing treatment should be considered 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 and/or required follow-up monitoring. This decision to discontinue therapy should be done at the discretion of the prescribing physician, when the patient is clinically stable, after a wholistic examination of all clinical evidence, and after any confounding co-morbidities have been assessed and non-adherence issues have been addressed.

Drug-drug interactions

It is important to assess for drug-drug interactions (figure 1) (88) 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 (34). 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(12,18,22,28). 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 (Pgp), and potentially CYP2C9. Due to 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. 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

The Health Canada approval of ELX/TEZ/IVA for CFTR variants *F508del*/Any, in patients 2 years of age or older means some children will remain on either LUM/IVA or IVA, and some adults will remain on IVA.

Data has shown that ELX/TEZ/IVA has superiority over TEZ/IVA in patients with 2 copies of *F508del* (11). In a study comparing patients with *F508del*/a minimal function or gating variant who were randomized 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: Respiratory domain and further reduction in sweat chloride levels (89). It is anticipated that patients on LUM/IVA will see a similar improvement in FEV_1 to those who switched from TEZ/IVA.

All eligible patients on IVA, LUM/IVA or TEZ/IVA, should have the opportunity to transition to the triple therapy combination, ELX/TEZ/IVA. The 10 mutations indicated for IVA in Canada are among the list of 177 mutations responsive to ELX/TEZ/IVA in the US FDA indication, and patients transitioning from IVA to ELX/TEZ/IVA may see additional clinical benefits from the triple combination modulator. Please see the above important considerations for drug-drug interactions in patients transitioning from LUM/IVA.

Pregnancy/lactation and CFTR modulators

CFTR modulators may increase fertility in women with CF (90,91) 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 are 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 (92) and can be detected in the breast milk of mothers on modulator therapy (93).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, case reports/series and an international survey have demonstrated that CFTR modulators appear to be well tolerated during pregnancy (94,95). Discontinuation of CFTR modulators has been associated with significant decline in clinical status of the mother sometimes warranting re-initiation of therapy in pregnant women who stopped their CFTR modulator during the pregnancy (95).

However, most clinicians are comfortable continuing modulator therapy (84) with some mothers holding modulator therapy until the 2nd trimester. The decision to continue or withhold modulatory therapy during pregnancy should be made considering the risks for the mother and the baby (84).

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 on the schedule detailed in table 6a for the time frame in which they are exposed to CFTR modulators.

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 (63,64,).

Recent Canadian clinical recommendations were developed for the follow up of pregnancies and newborns of mothers who are receiving CFTR modulators (96, 97) These provide advice on infant bloodwork, newborn screen and ophthalmology follow up.

CF Patients who have received a lung transplantation

Lung transplant may be 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 (98). 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 (99-102).

With the introduction of ELX/TEZ/IVA, evidence is emerging of its use after lung transplant (103-106). Drug-drug interactions between CFTR modulators and immunosuppressants, such as calcineurin

inhibitors, should be expected (107). 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 pulmonary response to CFTR modulator therapy following initiation would not be applicable to the lung transplant population, however extrapulmonary impacts may be relevant. It is recommended that a CF specialist be involved in the initiation of CFTR modulators and subsequent monitoring in CF patients who have undergone lung transplant.

Patients who have received a liver transplantation

Liver transplant may be a treatment option for people with end-stage CF-related liver disease. Limited data exists for the use of CFTR modulators post-liver transplantation.Important considerations for use of CFTR modulators in this population are the potential for liver injury and potential drug-drug interactions with immunosuppressants.

The majority of evidence available for use of CFTR modulators post-liver transplantation is with ELX/TEZ/IVA. Based on available evidence, many patients who are post-liver transplant tolerate therapy without liver toxicity. If liver function tests do rise after initiation of a CFTR modulator, these may be mild and eventually stabilize. Dose Interruption or reduction of modulator may effectively manage more concerning liver function test elevations. However, some patients may require discontinuation of therapy. Doses of immunosuppressant medications may need to be adjusted after initiation of CFTR modulator therapy to maintain target therapeutic concentrations.

Consideration can be made to initiate a CFTR modulator in patients who are post-liver transplant at a full or reduced dose, with close monitoring of liver function tests and therapeutic drug monitoring of immunosuppressants, with close collaboration between the patients' CF and Liver Transplant teams. (108-112)

Additional considerations

Medical criteria/drug coverage

For the most part, public and private drug plans use the medical criteria recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH) and, in Quebec, the National Institute of Excellence in Health and Social Services (INESSS). These criteria are generally updated when changes to the Health Canada indication are made. While the medical criteria are generally aligned across public and private drug plans, the level and duration of coverage varies by plan. It is therefore recommended that health care providers work with their patients to determine the level of coverage that is available to them, and for how long this coverage may be available. Patients may be required to pay a deductible, premium and/or co-pay to access modulators.

Off-label use of CFTR modulator therapies for non-indicated variants

Given the established safety profile of the currently approved CF modulators, based on both clinical trials for the current Health Canada indications, and real-world evidence (RWE) from patients on

modulators for several years, in conjunction with laboratory data, clinical trial data and RWE for many non-*F508del* variants/mutations, it is reasonable to consider off-label use of CF modulators in individuals with mutations/variants not currently indicated in Canada.

It is unclear whether public and private plans will provide access to those with rare mutations that may respond to therapy without a Health Canada indication and Health Technology Assessment (HTA). This is especially true for those who may respond to Trikafta who carry a mutation that is not on the list of 177 mutations regulated by the FDA. Canada's public and private drug plans rely heavily on the recommendations that Canada's HTA bodies – CADTH and INESSS – make. CADTH's recommendations are non-binding: Canada's public and private drug plans can choose to provide broad access. More advocacy is needed.

The matter of broad access may be further complicated by a lack of clinical trial or in vitro evidence. It is estimated that this leaves approximately 70 Canadians with ultra-rare mutations, mutations not yet fully characterized in their ELX/TEZ/IVA response and individuals without two identified variants, without a regulatory pathway to access. It is therefore necessary for health care practitioners to advocate for individual patient access through public and private drug plans. The Program for Individualized Cystic Fibrosis Therapy (CFIT) is a resource that can be used to demonstrate individual patient response to therapy, which may assist in gaining access for some of these patients.

Summary

The continued approval of CFTR modulators by Health Canada is a milestone in Canadian 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 at the youngest age 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. Dosing strategies to minimize side effects should be pursued and measurement of sweat chloride may be useful to determine efficacy of CFTR modulation. 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 Ultimately the decision to continue on modulator therapy is determined by patient preference and clinical guidance. Efficacy data should be collected as part of the Canadian Cystic Fibrosis Registry or as part of a prospective study.

Consideration should be given to patients with rare CFTR variants who may benefit from a therapeutic trial of modulator therapy.

Tables and Figures

Tables 1a-d- Dosage recommendations for Modulators based on weight and age

Table 1a- Elexacaftor/Tezacaftor/Ivacaftor (Trikafta®)

Age	Weight	Standard Dosing
2 years to < 6 years	< 14 kg	1 packet (elexacaftor 80 mg/tezacaftor 40mg /ivacaftor 60 mg granules) po qAM AND 1 packet (ivacaftor 59.5 mg granules) po qPM
	≥ 14 kg	1 packet (elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg granules) po qAM AND 1 packet (ivacaftor 75 mg granules) po qPM
6 years to < 12 years	< 30 kg	2 tablets (elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg tablet) po qAM AND 1 tablet (ivacaftor 75 mg tablet) po qPM
	≥ 30 kg	2 tablets (elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg tablet) po qAM AND 1 tablet (ivacaftor 150 mg tablet) po qPM
12 years and older	none	2 tablets (elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg tablet) po qAM AND 1 tablet (ivacaftor 150 mg tablet) po qPM

** Indication *F508del* / Any

Elexacaftor/Tezacaftor/Ivacaftor (Trikafta™)

People with cystic fibrosis (CF) aged 2 years and older who have at least one copy of the F508del CFTR variant.

Table 1b- Ivacaftor (Kalydeco®)

Age	Weight	Standard Dosing
2 months to < 4 months	≥ 3 kg	1 packet (ivacaftor 13.4 mg granules) po BID
4 to < 6 months	≥ 5 kg	1 packet (ivacaftor 25 mg granules) po BID
6 months and older	≥ 5 kg to < 7 kg	1 packet (ivacaftor 25 mg granules) po BID
	≥ 7 kg to < 14 kg	1 packet (ivacaftor 50 mg granules) po BID
	≥ 14 kg to < 25 kg	1 packet (ivacaftor 75 mg granules) po BID
6 years and older	≥ 25 kg	1 tablet (ivacaftor 150 mg tablet) po BID

**Indication Gating (Class III) variant, R117H

Ivacaftor (Kalydeco™)

People with cystic fibrosis (CF) aged 2 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*
	R117H		

Table 1c- Lumacaftor/Ivacaftor (Orkambi®)

Age	Weight	Standard Dosing
1 year to < 2 years	7 kg to < 9 kg	1 packet (lumacaftor 75 mg/ivacaftor 94 mg granules) po BID
	9 kg to < 14 kg	1 packet (lumacaftor 100 mg/ivacaftor 125 mg granules) po BID
	≥ 14 kg	1 packet (lumacaftor 150 mg/ivacaftor 188 mg granules) po BID
2 years to 5 years	< 14 kg	1 packet (lumacaftor 100 mg/ivacaftor 125 mg granules) po BID
	≥ 14 kg	1 packet (lumacaftor 150 mg/ivacaftor 188 mg granules) po BID
6 years to 11 years	None	2 tablets (lumacaftor 100 mg/ivacaftor 125 mg tablet) po BID
12 years and older	None	2 tablets (lumacaftor 200 mg/ivacaftor 125 mg tablet) po BID

** Indication *F508del / F508del*

Lumacaftor/Ivacaftor (Orkambi™)

People with cystic fibrosis (CF) who are homozygous for the *F508del* variant in the (*CFTR*) gene.

Table 1d- Tezacaftor/Ivacaftor (Symdeko®)

Age	Standard Dosing
12 years and older	1 tablet (tezacaftor 100 mg/ivacaftor 150 mg tablet) po qAM AND 1 tablet (ivacaftor 150 mg tablet) po qPM

** Indication *F508del / F508del, F508del* / RF variant

Tezacaftor/Ivacaftor (Symdeko™)

People with cystic fibrosis (CF) who are homozygous for the *F508del* variant in the *CFTR* gene
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*

Table 2: Vertex rare mutation clinical trial variants (with no F508del variant)
By Variant Analysis Showed Consistency Across Variants [a]

		ppFEV1 Mean Change (SD) (percentage points)		Sweat Chloride Mean Change (SD) (mmol/L)		CFQ-R RD Score Mean Change (SD) (points)
	n	ELX/TEZIVA	n	ELX/TEZIVA	n	ELX/TEZIVA
3849+10KBC>T[b]	30	11.6 (8.8)	30	-16.4 (9.6)	30	17.7 (19.4)
2789+5G>A[b]	26	5.8 (7.9)	25	-16.4 (13.3)	26	17.5 (18.7)
3272-26A>G[b]	23	8.8 (8.9)	25	-13.1 (7.8)	25	18.1 (20.6)
D1152H	18	3.4 (5.1)	18	-9.3 (7.3)	19	12.7 (18.8)
R347P	17	9.8 (9.9)	18	-38.5 (15.2)	18	13.6 (17.9)
L206W	13	3.9 (5.6)	15	-43.5 (18.0)	14	11.7 (18.9)
A455E	12	8.6 (9.2)	14	-33.3 (11.2)	14	19.5 (15.7)
R1066H	6	4.6 (7.4)	6	-59.2 (14.6)	6	10.4 (13.8)
G85E	29	12.4 (11.9)	33	-37.3 (17.6)	32	23.4 (20.2)
M1101K	8	12.0 (9.5)	8	-49.2 (19.0)	8	31.4 (17.8)
R347H	5	5.7 (6.1)	5	-21.3 (4.5)	5	8.1 (23.2)
L1077P	5	17.3 (10.0)	<5	--	<5	--

[a]Results shown where at least 5 participants had that variant in the active treatment arm
[b]Non-canonical splice variants
CFQ-R RD: Cystic fibrosis Questionnaire-Revised Respiratory Domain; **ppFEV1,** percent predicted forced expiratory volume in 1 second; **SD:** standard deviation

Table 3: US FDA approved variants for reference

Modulator type	Link to FDA approved variant
Elexacaftor/Tezacaftor/Ivacaftor (Trikafta™)	https://www.cff.org/sites/default/files/2022-02/Trikafta-Approved-Mutations.pdf
Tezacaftor/Ivacaftor (Symdeko™)	https://www.cff.org/sites/default/files/2022-02/Symdeko-Approved-Mutations.pdf
Ivacaftor (Kalydeco™)	https://www.cff.org/sites/default/files/2022-02/Kalydeco-Approved-Mutations.pdf

Table 4a: French compassionate program evidence for ETI response in FDA and non- FDA mutations

FDA mutations	non-FDA mutations
S364P	N1303K
R347P	R334W
H1085R	R1066C
G85E	A561E
I601F	3041-15T>G
M1101K	T1086I
S492F	Q552P
R74W;V201M;D1270N	1341G>A
D1152H	4374+1G>A
S549N	1717-1G>A
S977F	2789+5G>A
I601F	3849+10kb C>T
S549N	
G551D	
D1152H	

Source: (49)

Table 4b: French compassionate program non-responders

Allele 1	Allele 2
2789+5G>A	3120+1G>A
2789+5G>A	2789+5G>A
2789+5G>A	K710X
1811+1.6kb A>G	1811+1.6kb A>G
4096-3C>G	4096-3C>G
L558S	2183 AA>G
c.2989-313A>T	2942 insT
I507del	711+1G>T
I507del	R553X
K464N	3659delC
1717-1G>A	3659delC
M1T	M1T
357delC	357delC
c.3469-2880_3717+2150del	c.3469-2880_3717+2150del
711+1G>T	711+1G>T
1525-1G>A	1525-1G>A
2183AA>G	2183AA>G
3120+1G>A	3120+1G>A
Q493X	2183AA>G
G542X	2183AA>G
G542X	4271delC
G542X	1717-1G>A
G542X	G542X
R553X	394delTT
R553X	1717-1G>A
R553X	4374+1G>T
R1162X	3129delAATT
W846X	4374+1G>A/3170delA
W846X	3791delC
W1282X	1078delT
W1282X	W1282X
Y122X	Y122X

Source: (49)

Table 5: ETI-responsive based on in vitro data approved by the US FDA

Invitro trial variants	Invitro trial variants	In vitro trial variants	Invitro trial variants
3141del9	G1349D	L453S	R75Q
546insCTA	G178E	L967S	R792G
A1006E	G178R	L997F	R933G
A1067T	G194R	M1101K	S1159F
A120T	G194V	M152V	S1159P
A234D	G27R	M265R	S1251N
A349V	G314E	M952I	S1255P
A455E	G463V	M952T	S13F
A46D	G480C	P205S	S341P
A554E	G551D	P574H	S364P
D110E	G551S	P5L	S492F
D110H	G576A	P67L	S549N
D1152H	G576A;R668C†	Q1291R	S549R
D1270N	G622D	Q237E	S589N
D192G	G628R	Q237H	S737F
D443Y	G85E	Q359R	S912L
D443Y;G576A;R668C†	G970D	Q98R	S945L
D579G	H1054D	R1066H	S977F
D614G	H1085P	R1070Q	T1036N
D836Y	H1085R	R1070W	T1053I
D924N	H1375P	R1162L	T338I
D979V	H139R	R117C	V1153E
E116K	H199Y	R117G	V1240G
E193K	H939R	R117H	V1293G
E403D	I1027T	R117L	V201M
E474K	I1139V	R117P	V232D
E56K	I1269N	R1283M	V456A
E588V	I1366N	R1283S	V456F
E60K	I148T	R170H	V562I
E822K	I175V	R258G	V754M

Invitro trial variants	Invitro trial variants	In vitro trial variants	Invitro trial variants
E92K	I336K	R31L	W1098C
F1016S	I502T	R334L	W1282R
F1052V	I601F	R334Q	W361R
F1074L	I618T	R347H	Y1014C
F1099L	I807M	R347L	Y1032C
F191V	I980K	R347P	Y109N
F311del	K1060T	R352Q	Y161D
F311L	L1077P	R352W	Y161S
F508C	L1324P	R553Q	Y563N
F508C;S1251N†	L1335P	R668C	
F575Y	L1480P	R74Q	
G1061R	L15P	R74W	
G1069R	L165S	R74W;D1270N†	
G1244E	L206W	R74W;V201M;D1270N†	
G1249R	L320V	R74W;V201M†	
G126D	L346P	R751L	

† Complex/compound mutations where a single allele of the CFTR gene has multiple mutations; these exist independent of the presence of mutations on the other allele.
Source: https://pi.vrtx.com/files/uspi_elexacaftor_tezacaftor_ivacaftor.pdf

Table 6a: 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

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
Blood for CBC, ALT, AST, ALP, GGT, bilirubin,CK	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[h]	X		X	X	X	X
Sweat chloride test	X		X			X
CFQ-R: Respiratory Domain[g]	X	X	X	X	X	X
Spirometry/LCI[a,b]	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					

[a] LCI to be measured where available at baseline, 3 months and 12 months (clinical research tool used only in clinics with research capacity)
[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] PHQ-9 and GAD-7 for patients aged 12 years and older every six months (however, if scores abnormal, review every 3 months)
[f] Events of special interest: rash, Distal Intestinal Obstructive Syndrome, pancreatitis, mental health, new organisms isolated in sputum
[g] CFQ-R can be completed at various times, but often it's BL and when renewing provincial insurance
[h] Review of all therapies (including prescribed medication and airway clearance)
ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **ALP**, alkaline phosphatase; **GGT**, gamma glutamyl transferase; **CBC**, complete blood count; **CFQ-R**, Cystic Fibrosis Questionnaire-Revised; **CK**, creatine

kinase; **GAD-7,** General Anxiety Disorder-7; **LCI**, lung clearance index; **PHQ-9**, Patient Health Questionnaire-9

Table 6b: Schedule for suggested 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, AST, ALP, GGT, bilirubin, CK, INR	X	X	X	X	X	X
Sputum microbiology[a]	X	X	X	X	X	X
Ophthalmology exam[b]	X			X		X
Safety review[c]	X	X	X	X	X	X
Review of prescribed therapy[d]	X		X	X	X	X
Sweat chloride test	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					

[a] Samples obtained by sputum or cough swab
[b] Done at baseline, 6 months and on annual basis
[c] Events of special interest: Rash, DIOS, pancreatitis, mental health, new organisms isolated in sputum
[d] Review of all prescribed therapies (including medication and airway clearance)
ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **ALP**, alkaline phosphatase; **GGT**, gamma glutamyl transferase; **CBC**, complete blood count; **CBC**, complete blood count; **CK**, creatine kinase; **DIOS**, distal intestinal obstruction syndrome;

Table 7: Summary of objective outcomes for patients initiated on Health Canada-approved CFTR modulators

Outcome	IVA	LUM/IVA	TEZ/IVA	ELX/TEZ/IVA
	Age ≥2 Months	Age ≥2 Years	Age ≥12 Years	Age ≥2 Years
Lung Function [a]FEV1				>5% predicted, if >6 years of age
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 OR weight change[d]	Improved	Improved	Improved	Improved

[a] Children < 6 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; **CFTR**, cystic fibrosis transmembrane conductance modulator; **ELX**, elexacaftor; **FEV_1**, forced expiratory volume in 1 second; **IVA**, ivacaftor; **LCI**, lung clearance index; **LUM**, lumacaftor; **TEZ**, tezacaftor

Adapted from Enberink EO, Ratjen F, Davis SD, Retsch-Bogart G, Amin R, and Stanojevic S. Inter-test reproducibility of the lung clearance index measured by multiple breath washout. Eur Respir J. 2017:Oct 5;50(4):1700433. doi: 10.1183/13993003.00433-2017

Table 8: 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
Headache	++	++	++	++
Upper respiratory tract infection	++			++
Rhinitis	++			
Nasal congestion	++			
Arthralgia	++			
Bacteria in sputum	++			
Increase cough, chest tightness		++		+
Drop in FEV1		++		
Elevated blood pressure		+		+
Elevated transaminases	++	++	+	+
Elevated CK	+	+	+	++
Diarrhea		++		++
Dyspnea		++		
Nasopharyngitis		++	++	
Rash	++	++	+	++
Influenza				++
Cataracts	+	+	+	+
Neurological symptoms, depression, or anxiety	+	+	+	+
Abdominal pain	++	++		+
Nausea and vomiting	++	++	+	
Distal intestinal obstruction syndrome			++	+

Adverse event	IVA	LUM/IVA	TEZ/IVA	ELX/TEZ/IVA
Increased hepatic enzymes	+			
Hypoglycemia	+			
Pneumonia*		+		
Hemoptysis*		+		
Cough*		+		
Increased blood creatine phosphokinase*		+		
Transaminase elevations*		+		
Cholestatic hepatitis*		+		
Hepatic encephalopathy*		+		

(++:Common (>10%), +:Uncommon)
*These reactions occurred in 1% or less of patients.
This summary does not capture all reported side effects. Reference should be made to the product monograph for each CFTR modulator.
CK, creatine kinase; **ELX**, elexacaftor; **FEV_1**, forced expiratory volume in 1 second; **IVA**, ivacaftor; **LUM**, lumacaftor; **TEZ**, tezacaftor

Table 9: 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 Monitor AST and ALT Re-challenge modulator when AST and ALT <2x ULN*	STOP modulator
AST		Repeat in 1 month	STOP modulator Monitor AST and ALT Re-challenge modulator when AST and ALT <2x ULN*	STOP modulator

Lab parameter	>2x ULN	>3x ULN	>5x ULN	>8x ULN
Bilirubin	And AST or ALT >3x ULN: STOP Monitor in 2 weeks, Re-challenge when Bilirubin <1x ULN*			
ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **ULN**, upper limit of normal				

*Re-challenge with reduced dose, in first instance,

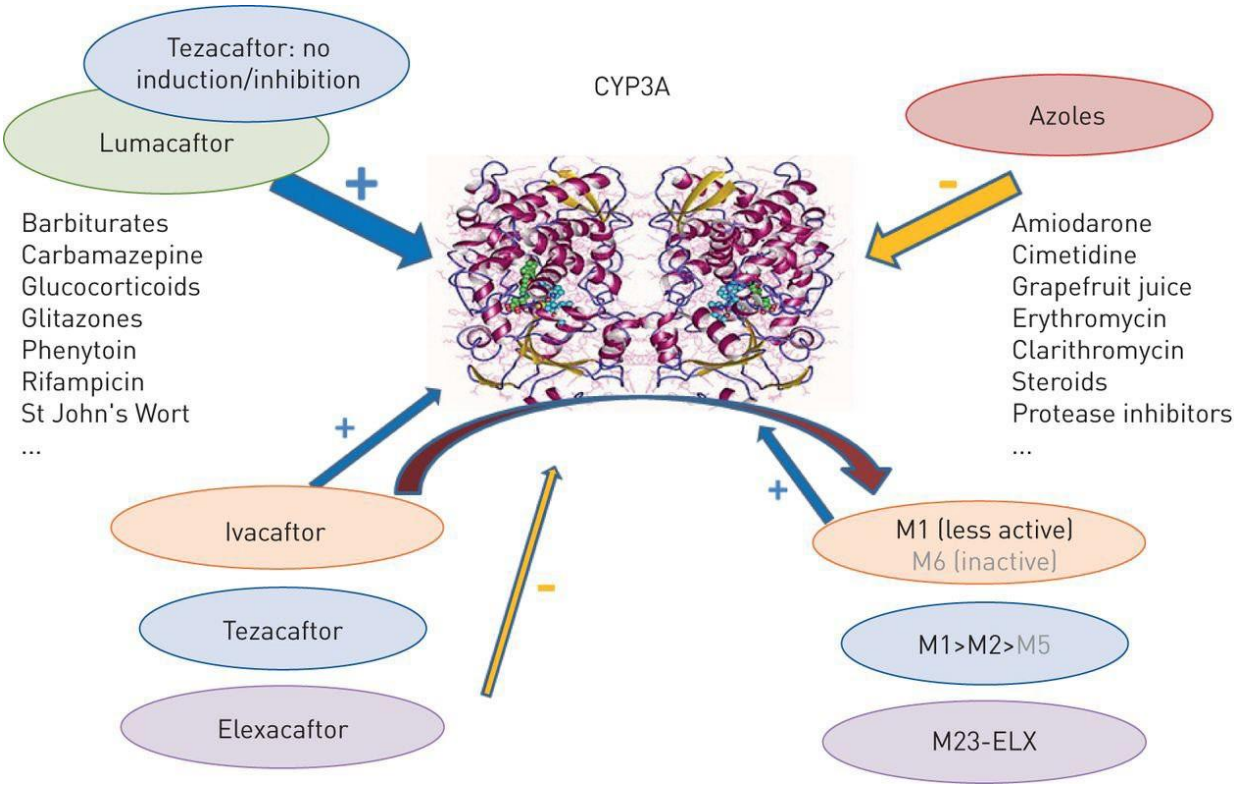
Table 10: Suggested dose adjustment for ELX/TEZ/IVA due to side effect

Event	Severity	Dose Adjustment	Re-introduction	Other actions
Rash	Mild Severe	Continue standard dose Stop	N/A Once symptoms resolve, restart at full dose, or start desensitization process	Treat with antihistamines, topical steroids Treat with antihistamines, topical steroids
	>3 X ULN >5 X ULN >8 X ULN	Continue standard dose Dose reduction Stop	N/A Re-introduce at reduced dose Titrate dose with clinical response +- sweat chloride Re-introduce at reduced dose Titrate dose with clinical response +- sweat chloride	Repeat LFTs monthly Repeat LFTs after 2 weeks Repeat LFTs 1-2 weekly
Pre-existing liver disease	Moderate hepatic impairment: VST treatment if clear medical need and benefits outweigh risks	Dose reduction	Re-introduce at reduced dose Titrate dose with clinical response +- sweat chloride	

Event	Severity	Dose Adjustment	Re-introduction	Other actions
Insomnia /daytime fatigue	Moderate	Standard dose	Consider switching am/pm dosing times	
Neuro-psychiatric, mood or anxiety symptoms	Moderate Severe	Dose reduction Stop	12 weeks after symptoms resolve, increase dose Titrate dose with clinical response +- sweat chloride Once symptoms resolve, consider re-introduction with reduced dose or alternate drug Titrate dose with clinical response +- sweat chloride	Consider initiation or dose adjustment of psychopharmacologic therapy Consider initiation or dose adjustment of psychopharmacologic therapy
Pregnancy		Standard dose or stop VST to 2nd trimester		Review with obstetrician CF clinic
Abbreviations: LFTs= Liver Function Tests, ULN= upper limit of normal, VST= variant specific therapy				

Table obtained from Spoletini G, Gillgrass L, Pollard K, Shaw N, Williams E, Etherington C, Clifton IJ, Peckham DG. Dose adjustments of elexacaftor/tezacaftor/ivacaftor in response to mental health side effects in adults with cystic fibrosis. J Cyst Fibros. 2022;21:1061-65. (85)

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.



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