



Cystic Fibrosis
Fibrose kystique
Canada

Submitted by: Dr. John Wallenburg, Chief Scientific Officer
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Introduction

Cystic Fibrosis Canada appreciates the opportunity to respond to the CADTH draft recommendation on elxacaftor/tezacaftor/ivacaftor (ETI).

We acknowledge the input obtained from the drug programs that participate in the CADTH reimbursement review processes and the key factors identified by the programs that could impact the implementation of a CADTH recommendation for ETI.

We were pleased to see CADTH's draft recommendation is that ETI should be reimbursed for the treatment of patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. We were also pleased to see that CADTH has acknowledged the complexity of CF care and that prescribing of ETI and monitoring of treatment response should be limited to CF specialists.

Our clinicians and our community are glad that CADTH has acknowledged the importance of considering the many benefits and outcomes that patients may experience when taking ETI. The CADTH Implementation Guidance states:

...Decisions regarding continuing treatment in clinical practice settings are based on assessments of exacerbation frequency, the frequency of oral and/or IV antibiotic use, time in hospital for CF-related reasons, nutritional status (based on weight, height, and BMI), health-related quality of life, and adverse events, along with changes in lung function. Jurisdictions may want to consider additional clinical measures beyond lung function when assessing renewal of reimbursement on an individual case basis.

We are however, concerned that these important additional clinical measures did not make it into the actual recommendation, and we are deeply concerned by several conditions for reimbursement that are in the draft recommendation itself.

Summary: Feedback on Draft Recommendations on Trikafta

We believe that the Canadian Drug Expert Committee's (CDEC's) draft recommendations are flawed in several areas and that these flaws are rooted in three fundamental errors:

- Firstly, the way in which CADTH has used population level data to make recommendations at the individual level is flawed;
- Secondly, we believe that the recommendations use a narrow interpretation of the science; and,
- Thirdly, we believe that the recommendations are flawed due to a fundamental misunderstanding of the disease and the current therapeutic paradigm that has been developed over decades of research and observation.

To address these flaws, we offer the following recommendations:

- Any reference to limiting reimbursement to patients with a ppFEV1 \leq 90% should be removed.
- The recommendation for annual assessments that continue beyond an initial determination of benefit to an individual patient should be removed.

- As per the Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis¹, discontinuation should be limited to patients who have clinically significant adverse effects that persist or recur or patients who do not meet the criteria for response to the CFTR modulator as per the guidelines or are non-adherent.
- That Canadian jurisdictions require that the manufacturer provide real-world evidence (RWE) of benefit within a pre-established term. Having post approval RWE of clinical benefit to the Canadian CF population would provide the jurisdictions with ample opportunity and solid, irrefutable evidence for discussions with the manufacturer.

Feedback: Context

Cystic Fibrosis Canada gathered information for its past patient group submission through a cross-Canada survey of patients and caregivers, to which 1455 people responded.

In that submission, we referenced Cystic Fibrosis Canada’s publications, including the 2019 Canadian CF Registry Annual Data Report. We cited the scientific literature and clinical trial data and other published studies Trikafta and its impacts, as well as a Cystic Fibrosis Canada funded study published in the fall of 2020 that projects the impact on the Canadian cystic fibrosis population of access to Trikafta. Where appropriate (in descriptions of the general impact of cystic fibrosis on life for example) we used information gathered for recently submitted CADTH submissions.

Our response to CADTH’s draft recommendation on Trikafta is informed by the work mentioned above, as well as by the work of Cystic Fibrosis Canada, the cystic fibrosis community, and cystic fibrosis physicians and researchers since that time, including development of the Canadian Clinical Consensus Guideline for Initiation, Monitoring and the Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis.

Feedback: Draft Recommendations

Initiation Criteria

We believe that the imposition of a threshold of $\leq 90\%$ ppFEV1 for reimbursement is in direct contravention of the therapeutic paradigm for cystic fibrosis that has been developed over decades of research and observation. Upon diagnosis, patients initiate an aggressive regimen of therapy aimed treating acute symptoms (when present) but more importantly, at slowing to the extent possible, disease progression. It is known that early diagnosis, and therefore early initiation of treatment leads to better health outcomes in the long run¹. That is why we have newborn screening across the country.

Limiting reimbursement to patients with $\leq 90\%$ ppFEV1 will discriminate against children and adolescents who predominantly have better lung function than adults. Adolescence in particular is a critical period that sets the stage for dramatic declines in health in early adulthood². Denying patients at this critical juncture would be counterproductive.

We believe that limiting reimbursement to patients with $\leq 90\%$ ppFEV1 is unethical as it will incite patients to self-harm. CADTH conducts cost-effectiveness analyses at a population level; with that

¹ Attached.

should come the understanding that patients who live with the disease will, themselves, do personal cost benefit analyses. There is no doubt that both patients and caregivers will do a calculus to determine if a short-term loss in lung function would be more than compensated for by long-term dividends in a resurgence of FEV1, accompanied benefits in terms of body mass index (BMI) and GI comfort, a reduction in pulmonary exacerbations (if they have them), reduced sinus disease, deferral of the onset or potential retreat in the symptoms of CFRD, and a decline in the rate of progression in general over time. We saw this happen with patients who desperately tried to access Trikafta through compassionate care.

Our CF clinicians and CF Canada, understanding the risks imposed by individual drug responses and that any individual patient may see no benefits at all, will always recommend against self-harm. However, we believe that patients near any ppFEV1 cut-off for access will see the overwhelmingly positive population-level response to ETI, and reasonably find the calculation to be compelling. We believe that it is unethical to impose access criteria that would incite patients, acting reasonably, to self-harm to fall within the prescribing criteria.

Furthermore, we believe that the imposition of the 90% threshold also reflects a narrow interpretation of the science. Cystic fibrosis is caused by mutations in the CF gene that lead to an absence, or significant reduction, in functional CFTR protein. The harms to the patient derive largely from the downstream consequences of having no functioning CFTR, (as opposed to its absence per se), and as these harms accumulate, the disease progresses. Although variable between patients and over time, progression is relentless, the damage irreversible, and the result fatal. The mechanism of action (MOA) of ETI, which is to correct, even imperfectly, the flawed CFTR leading to an increase in functional protein, is the same regardless of the pulmonary function of the individual.

It is not only scientifically plausible, but probable, that patients with little to no functioning CFTR and a high ppFEV1 will benefit the same as patients with little to no functioning CFTR and a low ppFEV1, even if the tool used to measure that benefit, ppFEV1, is too crude to accurately measure subtle but significant changes in the lower airways³. This is in fact supported by the evidence including a 10% increase in ppFEV1 in subjects in a phase 3 clinical trial of ETI in children aged 6-11⁴ and a phase 3 study of ivacaftor alone (ivacaftor uses the same MOA) in young adults with CF⁵.

For all of the above reasons the recommendation to limit reimbursement to patients with a ppFEV1 \leq 90% should be removed.

Renewal Criteria

We believe that the ongoing annual renewal assessments are also flawed and must be removed. The clinical trials show that each patient's response to ETI is individual, and that ETI can benefit patients in a number of clinically significant ways, including, but not limited to improvements in ppFEV1, reductions in the number and frequency of pulmonary exacerbations (PEX), improvements in BMI, and in quality of life as measured by CFQ-R. It is not currently possible to identify patients prior to starting on the drug, who will not benefit and who will, and if they respond, which clinical parameter(s) will improve for which patient. However, once an individual has been shown to respond, there is no scientific rationale to believe that they will suddenly stop benefiting.

We believe subjecting individual patients to annual reviews of response is irrational, also rooted in a narrow interpretation of the science and, considering the extreme stress that such annual re-evaluations would impose, potentially cruel.

We have unpublished, real world cases in Canada in which individuals who were on modulators that were working well for them lost their access. The physical and psychological toll of having to come off of a drug that had changed their lives, was devastating. One person said it felt like receiving a “death sentence” for the second time in their life. Similar to “Ivacaftor withdrawal syndrome” described previously⁶, stopping treatment led to rapid deterioration, at least one listing on the lung transplant list, and a near loss of life, before access was restored. In the cited cases the individuals’ health stabilized and, eventually, improved significantly once access to Trikafta was restored.

We believe that CADTH’s use of population level data from the clinical trials to set continuation criteria for individuals is flawed. CADTH does not have individual level data, the physicians do. Canadian CF physicians from across the country have developed or endorsed the attached Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis. As per those consensus guidelines, discontinuation should be limited to patients who have clinically significant adverse effects that persist or recur or patients who do not meet the criteria for response to the CFTR modulator as per the guidelines or are non-adherent.

The recommendation for annual assessments that continue beyond an initial determination of benefit to an individual patient should be removed.

Pricing Criteria

We agree that a reduction in price is probably in order although we believe that requiring a reduction of 90% is excessive. This would put ETI on, or near, par with other CF medicines⁷ over which ETI provides a clearly superior clinical benefit^{8,9}. We are nonetheless confident that the pCPA and the manufacturer, having already negotiated mutually acceptable terms for the previous generation modulators, ivacaftor and lumacaftor + ivacaftor should have no problems negotiating an agreement for ETI.

Feedback: Implementation Guidance

We are sensitive to the factors identified by the drug programs that participate in the CADTH reimbursement review processes that could impact the implementation of a CADTH recommendation for ETI. The potential need for objective criteria that can be used to evaluate response to treatment, potential timepoints that should be used when evaluating the response to treatment, and advice on the use of ETI in key patient populations that were excluded from the phase 3 studies were all identified as key factors.

We understand the desire for objective criteria that can be used to evaluate response to treatment as this relates to cost-effectiveness and believe that this can best be accomplished using population level real-world evidence (RWE) compared to the population level data from the clinical trials. The above referenced Consensus Guidelines call for baseline clinical assessments prior to initiating CFTR modulator therapy. Many of the listed parameters are tracked in the Canadian CF registry as part of routine clinic visits. We believe that a recommendation, that Canadian jurisdictions require that the manufacturer provide RWE of benefit within a pre-established term, is readily achievable and would provide the jurisdictions with a more accurate assessment of actual benefits derived from the drug, while not

negatively impacting patients at the individual level. ETI's patent will not expire until the mid-2030's. Having 5-yr post approval RWE of clinical benefit to the Canadian CF population would provide the jurisdictions with ample opportunity and solid, irrefutable evidence for discussions with the manufacturer.

We applaud CADTH for acknowledging the complex nature of CF care which is managed through specialized CF clinics in Canada and limiting the prescribing of ETI and monitoring of treatment response to CF specialists. We recommend that CADTH fully exploit that Canadian expertise in CF clinic care. Canada's CF physicians recently developed the aforementioned Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis. Those guidelines include objective criteria to evaluate response on an individual basis and timepoints that should be used with evaluating the response, and some patient populations excluded from the phase 3 trials (e.g. during pregnancy). We believe that CADTH should recommend that Canada's CF physicians use those Consensus Guidelines as the authoritative guide for the initiation, monitoring and discontinuation of ETI in Canada.

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

July 2021

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Conflict of interest

Some authors have served as clinical trial leads or consultants to Vertex, and may have received grants, unrelated to the development of these Guidelines

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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 FEV₁

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, FEV₁ 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 FEV₁ there was evidence of significant structural lung disease (28). 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 (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 ppFEV₁:89% of whom 45% had ppFEV₁>90%, the addition of ELX/TEZ/IVA produced an increase in ppFEV₁ 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 (ppFEV₁<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 FEV₁ rate of decline (32,34,35). These studies have shown an improvement in lung function trajectory with a slowing in the rate of FEV₁ decline compared to patients not on CFTR modulators. However, patients **STILL** have a decline in FEV₁ 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 FEV₁ recovery and trajectory. As life expectancy improves for patients with CF it is expected that FEV₁ 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 FEV₁ over time and monitor improvement in nutrition.

Meaningful clinical responses to be monitored include:

1. Improvement in lung function as measured by FEV₁ 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 ppFEV₁ 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) ≥ 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 FEV₁ 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 ppFEV₁ 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 ppFEV₁ 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 FEV₁ 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 hepatotoxicity.

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

Discontinuation

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

Examples of these reactions may include:

1. Elevation of transaminases (Table 5) beyond the higher range of fluctuations observed in patients with CF (>8X ULN) or 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

CFTR Modulator	Indication	Approved Age	Minimum Trial Duration
IVA *	Gating (Class III) variant	≥1 year	1 year
	<i>R117H</i>	≥ 18 years	
LUM/IVA *	<i>F508del / F508del</i>	>2 years	1 year
TEZ/IVA *	<i>F508del / F508del</i>	≥12 years	1 year
	<i>F508del / RF variant</i>		
ELX/TEZ/IVA*	<i>F508del / Any</i>	≥12 years	1 year
* Health Canada approved CFTR variants described in Appendix 1 RF , residual function			

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 <i>CFTR</i> 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
	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 ^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 <i>CFTR</i> genotype, initial sweat test, past medical history (including frequency of pulmonary exacerbations over past 2 years)	X					
Height, weight, and blood pressure	X	X	X	X	X	X
Blood for CBC, ALT, 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
	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 ^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; 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 LCI		>5% predicted 15% decrease		>5% predicted
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 - 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
Bilirubin	And AST or ALT >3x ULN: STOP Monitor in 2 weeks, Rechallenge when Bilirubin <1x ULN*			

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

*Rechallenge with normal dose, in first instance.

Figure 1:

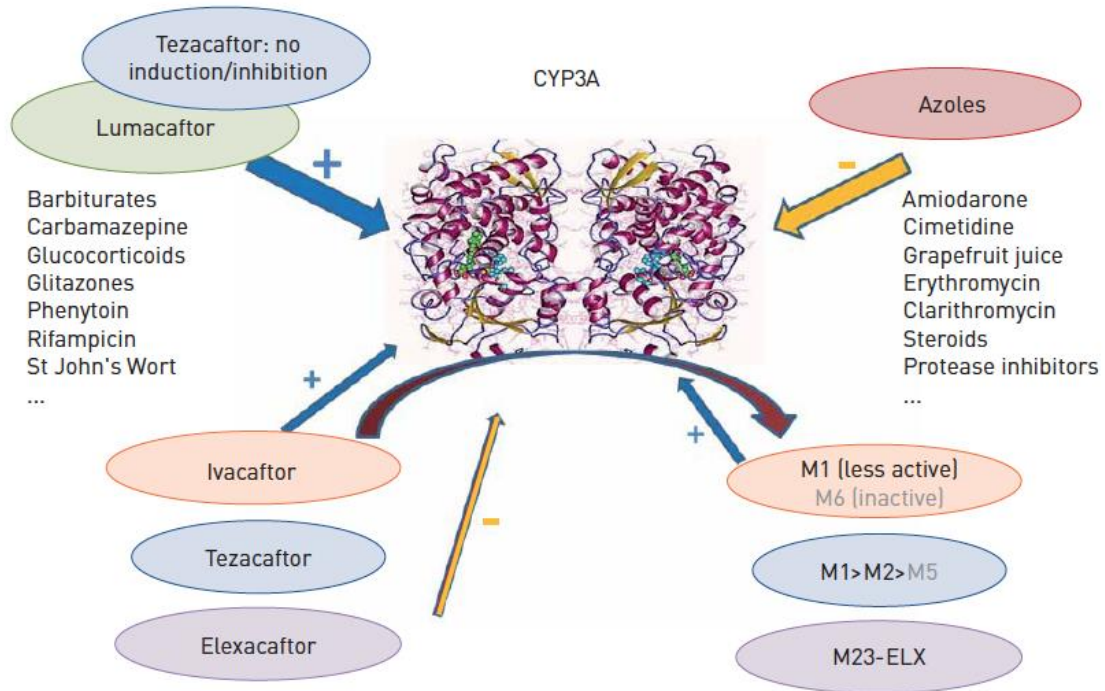


FIGURE 1 A summary of interactions between cystic fibrosis transmembrane regulator modulators and other drugs/compounds and cytochrome P450 3A4 (CYP3A). Blue arrows: induction of the cytochrome; yellow arrow: inhibition of the cytochrome; curved arrow: metabolism of a drug by the cytochrome. Adapted 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	<i>G551D</i>	<i>G178R</i>	<i>S1255P</i>
	<i>G1244E</i>	<i>G551S</i>	<i>S549N</i>
	<i>G1349D</i>	<i>S1251N</i>	<i>S549R</i>

OR

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

Lumacaftor/Ivacaftor (Orkambi™)

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

Tezacaftor/Ivacaftor (Symdeko™)

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

OR

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

Trikafta™

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

For Reference Only: List of minimal function variants (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
<hr/>				
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		
<hr/>				
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
CFTR50kdel	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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