

On behalf of the cystic fibrosis (CF) physicians and patients involved in the CF Canada Accelerating Clinical Trials Network (CF CanACT), we appreciate the opportunity to respond to the CADTH draft recommendations on elexacaftor/tezacaftor/ivacaftor (ETI). We are pleased to see that the recommendation is to reimburse ETI but we have major concerns regarding some of the conditions that have been included in the reimbursement recommendations. We feel it is important for us to provide our input and perspective as a group that have been involved in pivotal phase 3 clinical trials involving ETI since 2018.

Reimbursement Condition

Initiation

Item 3. ppFEV1 <90%

Response: We strongly disagree with the upper limit boundary imposed for ppFEV1. The implicit suggestion with this threshold is that people with ppFEV1>90 have insignificant lung disease to derive clinical benefit from Trikafta. This is simply not the case. There is compelling observational data that patients with ppFEV1>90 can still experience poor health outcomes including accelerated rate of lung function decline, frequent hospitalizations, poor nutritional outcomes, worse quality of life, and structural lung damage on lung imaging (1-6).

The pivotal phase 3 clinical trials evaluating elexacaftor/tezacaftor/ivacaftor (ETI) required a maximum ppFEV1 of 90% as part of their study inclusion criteria due to the concern about a “plateau effect” in FEV1 response when starting within the normal range. We do not believe there is sufficient rationale to withhold ETI in patients with “preserved” lung function based on FEV1 alone simply due to a conservative trial design.

Recently, a phase 3 clinical trial of ETI in children age 6-11 demonstrated a 10% improvement in ppFEV1, despite “preserved” lung function at baseline (mean baseline ppFEV1 89%) (7). Similarly, a phase 3 trial of ivacaftor in young adults with CF who had preserved spirometry (ppFEV1 >90%) demonstrated a ~9% improvement ppFEV1 (8). Based on this data, there is every reason to believe that adults with ppFEV1>90% would derive significant benefit from ETI.

The foundational basis of CF specialized care is focused on preventative health to improve health outcomes and prevent disease progression. This permeates all aspects of clinical practice in CF from newborn screening (to prevent failure to thrive, stunted growth, irreversible lung damage) to routine quarterly clinic visits over a lifetime (to closely monitor lung function to identify and treat exacerbations promptly before permanent lung damage has occurred and to enable the timely detection and eradication of airway pathogens such as *Pseudomonas aeruginosa*). Waiting for lung function to deteriorate will contravene our emphasis on prevention and will ignore other health outcomes which matter to patients including pulmonary exacerbations, quality of life, treatment burden, and mental health. This reimbursement condition also unjustly discriminates against children and adolescents with CF who are more likely to have preserved lung function. Based on the 2019 CF Canada Data Registry report, ~60% of children (age 6-17) have ppFEV1 >90% compared to 20% of adults (9).

Lastly, we are deeply concerned that these stipulations will create a situation in which desperate patients will inflict self-harm in order to qualify based on the ppFEV1<90 criterion. It is unethical for health policy to create a situation in which patients feel encouraged to self-sabotage in order to qualify for health care.

Item 5. Patients should be optimized with best supportive care, have stable disease, and should not have untreated infections. Patients should not be experiencing an active CF exacerbation and/or receiving oral or IV antibiotic treatment or be hospitalized for reasons related to CF at the time of initiation.

Response: We respectfully disagree with the requirement for “stable disease” (i.e. not experiencing an exacerbation) at the time of initiation. We recognize that this was part of the inclusion criteria for eligibility in the ETI clinical trial but this criterion is included in most placebo controlled randomized clinical trials to prevent confounding and to ensure safety. In CF, stability often cannot be achieved despite the best supportive care. Based on our collective experience as CF physicians, we have a number of patients who have started on ETI in hospital (received as part of a special access program) due to poor response to best supportive care (including repeated IV antibiotic regimens) and would have required lung transplant or died in hospital without being rescued by ETI. As such, this reimbursement condition will wrongfully deny access to those individuals in most desperate need. “Untreated infection” is also a complicated concept to apply in CF as many of our patients have chronic airway infection with organisms that are difficult to treat due to multi-drug antibiotic resistance and/or inability to tolerate the antibiotic regimens due to side effects.

Renewal

Item 1. Reimbursement of treatment with ELX/TEZ/IVA should continue if, after the initial six months of treatment, there is a documented improvement in ppFEV1 of at least 5% compared with the baseline measurement.

Response: We disagree with the requirement for a documented improvement in ppFEV1 of at least 5% after the initial six months of treatment. A minimal clinically important difference (MCID) has not been established for ppFEV1 and therefore a threshold of 5% is somewhat arbitrary. Furthermore, an observational study evaluating ivacaftor (a similarly effective CFTR modulator in patients with the G551D mutation) has demonstrated that short-term response to treatment (based on a ppFEV1 change at 1 month of > or <= 0%) does not predict longer-term clinical improvements (10). There was no significant difference in 2-year health outcomes including PEx rates, BMI change per year, and FEV1 decline per year post-ivacaftor between short-term response and non-response groups (10). In an observational study focused on individuals with advanced lung disease started on ETI, there was a very weak correlation observed between changes in ppFEV1 and weight during a median follow-up time of 84 days which suggests that nutritional improvements can occur without a corresponding change in ppFEV1 (11). Other clinical outcomes are also meaningful to patients and therefore terminating treatment with this arbitrary cut-off overlooks these important outcomes.

We are also very concerned about the safety of withdrawing therapy in patients who are experiencing clinical benefit beyond FEV1 as withdrawal of ivacaftor has been shown to lead to acute clinical deterioration (12). While experience with withdrawal of ETI is limited to date, temporary interruption during pregnancy due to concern about unknown fetal risk led to clinical deterioration such that treatment had to be restarted in 5 of 6 patients during pregnancy (13).

Item 2. Subsequent assessments for renewal of reimbursement should occur annually. Documented maintenance of ppFEV1 greater than 5% from baseline must be provided at each subsequent assessment for continued reimbursement.

Response: Based on reimbursement condition #3 in the CADTH report, it will not be possible to intervene with ETI early enough to prevent the onset of structural lung damage. As a result, lung function decline on ETI will still be expected to occur despite CFTR modulation, as occurs in other conditions leading to bronchiectasis. While there is no long-term data evaluating the rate of lung function decline in patients treated with ETI at this time, rates of decline are expected to be comparable to that observed in long-term observational studies of ivacaftor (5, 14). If baseline is used as the reference point for renewal, and assuming a rate of FEV1 decline on ETI of -0.3 to -0.9% per year as observed in the ivacaftor studies (5, 14), patients experiencing an initial 6-10% improvement in ppFEV1 will quickly find themselves ineligible for renewal within a few years of starting the drug despite deriving significant clinical benefit otherwise. Furthermore, the stress and anxiety imposed by each annual renewal visit will be excessive as our patients will feel like their life is on the line. This may lead to several mental health crises in a population with very high rates of anxiety and depression to begin with, particularly if they just fall short of the 5% threshold due to circumstances that may be outside of their control.

In conclusion, the proposed reimbursement recommendations align with the conservative inclusion criteria from clinical trials and efficacy based on population level effects. However, CF is a very heterogenous disease that affects multiple organ systems and therefore the proposed reimbursement recommendations are oversimplified and have several unintended consequences including discrimination against younger individuals with CF and are likely to put people living with CF at risk for significant harm (self-sabotage to meet eligibility criteria, stress/anxiety during the renewal process, and clinical deterioration if therapy is withdrawn).

References

1. Dasenbrook EC, Fink AK, Schechter MS, Sanders DB, Millar SJ, Pasta DJ, et al. Rapid lung function decline in adults with early-stage cystic fibrosis lung disease. *J Cyst Fibros.* 2020;19(4):527-33.
2. Mott LS, Park J, Murray CP, Gangell CL, de Klerk NH, Robinson PJ, et al. Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. *Thorax.* 2012;67(6):509-16.
3. Davies G, Stanojevic S, Raywood E, Duncan JA, Stocks J, Lum S, et al. An observational study of the lung clearance index throughout childhood in cystic fibrosis: early years matter. *Eur Respir J.* 2020;56(4).

4. Marshall H, Horsley A, Taylor CJ, Smith L, Hughes D, Horn FC, et al. Detection of early subclinical lung disease in children with cystic fibrosis by lung ventilation imaging with hyperpolarised gas MRI. *Thorax*. 2017;72(8):760-2.
5. Kawala CR, Ma X, Sykes J, Stanojevic S, Coriati A, Stephenson AL. Real-world use of ivacaftor in Canada: A retrospective analysis using the Canadian Cystic Fibrosis Registry. *J Cyst Fibros*. 2021.
6. Aurora P, Stanojevic S, Wade A, Oliver C, Kozłowska W, Lum S, et al. Lung clearance index at 4 years predicts subsequent lung function in children with cystic fibrosis. *Am J Respir Crit Care Med*. 2011;183(6):752-8.
7. Zemanick ET, Taylor-Cousar JL, Davies J, Gibson RL, Mall MA, McKone EF, et al. A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele. *Am J Respir Crit Care Med*. 2021;203(12):1522-32.
8. Davies J, Sheridan H, Bell N, Cunningham S, Davis SD, Elborn JS, et al. Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: a randomised controlled trial. *Lancet Respir Med*. 2013;1(8):630-8.
9. Cystic Fibrosis Canada. (2020). The Canadian Cystic Fibrosis Registry 2019 Annual Data Report. Toronto CCFC.
10. Heltshe SL, Rowe SM, Skalland M, Baines A, Jain M, Network GlotCFFTD. Ivacaftor-treated Patients with Cystic Fibrosis Derive Long-Term Benefit Despite No Short-Term Clinical Improvement. *Am J Respir Crit Care Med*. 2018;197(11):1483-6.
11. Burgel PR, Durieu I, Chiron R, Ramel S, Danner-Boucher I, Prevotat A, et al. Rapid Improvement after Starting Elexacaftor-Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and Advanced Pulmonary Disease. *Am J Respir Crit Care Med*. 2021;204(1):64-73.
12. Trimble AT, Donaldson SH. Ivacaftor withdrawal syndrome in cystic fibrosis patients with the G551D mutation. *J Cyst Fibros*. 2018;17(2):e13-e6.
13. Taylor-Cousar JL, Jain R. Maternal and fetal outcomes following elexacaftor-tezacaftor-ivacaftor use during pregnancy and lactation. *J Cyst Fibros*. 2021;20(3):402-6.
14. Sawicki GS, McKone EF, Pasta DJ, Millar SJ, Wagener JS, Johnson CA, et al. Sustained Benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. *Am J Respir Crit Care Med*. 2015;192(7):836-42.