CADTH

CADTH COMMON DRUG REVIEW

Patient Input

LUMACAFTOR/IVACAFTOR (ORKAMBI)

Vertex Pharmaceuticals (Canada) Incorporated

Indication: Cystic Fibrosis, F508del CFTR mutation in patients 6 years and older.

CADTH received patient input for this review from:
Cystic Fibrosis Canada
Cystic Fibrosis Treatment Society

March 15, 2018

Patient Group Cystic Fibrosis Canada

1. About Your Patient Group

Established in 1960, Cystic Fibrosis Canada (CFC) is a national charitable not-for-profit corporation and is one of the world's top three charitable organizations committed to finding a cure for CF. As an internationally recognized leader in funding innovation and clinical care, we invest more in life-saving CF research and care than any other non-governmental agency in Canada. We are committed to helping people with CF to live healthy and well. Since its establishment, Cystic Fibrosis Canada has invested more than $235 million in leading research, innovation and care. As a result, Canadians with cystic fibrosis have one of the highest median survival rates in the world. As we work toward new treatments and ultimately a cure for this devastating disease, we also work to improve the services and supports people with CF need to live healthy and well.

2. Information Gathering

We gathered information for this submission through a cross-Canada survey, patient and caregiver testimonials, and CFC publications, including the 2016 Canadian CF Registry Annual Data Report. As well, information from SickKids and Genome Canada has been considered. Testimonials have been gathered through many sources since CDEC's first Orkambi review in October 2016. CFC surveyed its community from January 15 until February 12, 2018. Patients and caregivers were invited to participate through postings at CF clinics, through direct email, and Facebook. In total, 408 individuals responded to the survey. Of these respondents, 25% were adults living with CF, 53% were parents and/or caregivers of a child (including adult children) with CF, and 22% identified as none of the above and were, therefore, disqualified from the survey. Respondents included people who are currently taking Orkambi, those who were taking Orkambi and stopped (primarily due to loss of private insurance coverage), and those who have either been prescribed Orkambi or whom are believed to be good candidates for Orkambi but have not yet been prescribed it. Parents and caregivers of these individuals were also invited to share their thoughts.

Cystic Fibrosis Canada is especially concerned for people who started on Orkambi on trial or through private insurance who have lost coverage. Orkambi was working well for these people: the only thing preventing them from continuing on the drug is a lack of private insurance. As a result of lost coverage, the health of these individuals has started to decline.

3. Disease Experience

CF is the most common fatal genetic disorder in Canada. It is estimated that one in every 3,600 children born in Canada has CF. There are currently over 4,200 people with CF in Canada. The disease affects all exocrine glands of the body and results in the production of thick, sticky mucus amongst other clinical symptoms. The principal clinical impacts are on the lungs and digestive system. The most significant clinical impact is in the lungs, where patients have difficulty in clearing secretions, which in combination with aberrant inflammation leads to persistent infections with cycles of inflammation that are ineffective in clearing infections. This leads to progressive scarring of the airways and a progressive and sometimes rapid decline in lung function. This eventually leads to respiratory failure which is the main cause of death in CF. Thanks to significant progress in treatment and care, the majority of children with CF will reach adulthood. Nevertheless, of the 46 Canadian patients who died in 2016 of CF-related complications, half were under 38.9 years of age (the median age at death in 2016). The most recent data for 2016 shows the estimated median survival age to be 53.3 years of age. A demanding treatment routine combined with regular visits to specialized CF clinics, acute infections and episodic flare-ups called exacerbations that frequently lead to hospitalizations all have a significant impact on day-to-day quality of life affecting life decisions including education, career, travel, relationships, and family planning.

- *I have experienced many health crises related to cystic fibrosis leaving me with no other option but to consider a double-lung transplant. In 2011 my lung function reached an all-time low sitting at 26 percent and my family and I were faced with the difficult reality of having to make a decision. At this point I was so exhausted I couldn't even perform basic tasks.*
- *I struggled to keep up with work and university, and had to spend up to 2 hours a day on exhausting, never ending, treatments. For 20 years I had about 3 hospital admissions a year. This meant I had over 60 hospital admissions, equaling more than 3 years of my life in hospital.*
- *When two of my children were first diagnosed, the doctor told me I'd never go back to work again. It is a full-time job keeping my children healthy. From helping with their physio to clear mucus, frequent CF clinic visits, hospital stays, and on top of that ensuring our third child does not feel left out as a healthy child.*
- *My 11 year old daughter spends in excess of 26 hours a week trying to stay healthy. The fight against CF is all encompassing for the family. It requires giving up 2 to 7 hours every day for her therapies. The physical therapies take a toll on my and my wife's bodies. We both have repetitive strain injuries and arthritis in our hands, wrists and shoulder. This commitment requires scheduling all meals and everyone's activities around her therapies. We restrict our social activities to prevent passing on colds and flus. Each day that a control for cystic fibrosis is not available to her is a day that her lungs are deteriorating. All the treatments that she has access to only try to mitigate her existing health problems, none address the root cause. Without the availability of drugs that fix the basic defect in cystic fibrosis, our daughter and others like her will lose their valiant fight as they pass away while gasping for air.*
- *I lost three friends in three months, while they waited for a lung transplant. It's not right to bury your friends all under the age of 25. I've been to more funerals than weddings in my life.*

Moreover, research has shown that patients with chronic diseases (defined as a condition that persists for longer than three months) can often have anxiety and depression. It is estimated that up to one third of individuals with a serious medical condition will experience depression. Depression is one of the most common complications of chronic illness like cystic fibrosis, and it also affects caregivers.

- *On April 1st, 2011 my son and daughter were both diagnosed with Cystic Fibrosis. It remains the most devastating news I have ever received. My 9 year old son has already spend in total over 6 months of his life in the hospital. Each time he is away from school, his friends, his extra-curricular activities, his bed, his family. He is stuck in a hospital room attached to cords and tubes. He's not allowed to leave his room due to infection control. It's complete isolation. Being away from home for 2 weeks at a time affects the whole family. My daughter has developed separation anxiety.*

Limited access to the drug also creates mental health issues related to the perceived unfair access to what is potentially a life-altering drug. While patients understand and accept (albeit sometimes with difficulty) the biological differences in clinical progression and response to drugs, dealing with biased and unfair access creates additional stress.

- *In March 2015 we were offered the opportunity to participate in a CF study. There was only one spot offered, so we chose our most "sickly" child, our son, to participate. This was not easy, especially when we had to explain to our daughter why we didn't choose her. … My daughter is not on Orkambi. She is still rolling on the ground [in pain] while my son now looks on.*

Due to a serious risk of cross-infection with pathogenic bacteria people living with CF are isolated from each other. Thus in addition to suffering from increased anxiety and depression, they have limited ability to participate in support groups that are known to help other individuals living with chronic disease. Rare individuals who have survived the notorious summer camps for CF patients that were popular in the 1980s still remember those days as amongst the happiest days of their lives – because of the camaraderie and bonding with others like themselves. Now they have limited opportunities to engage with one another, save for online forums.

4. Experiences with Currently Available Treatments

Currently, Orkambi is the only disease-modifying therapy available for people with CF who have a homozygous F508del mutation; it targets and works to correct the basic defect in CF. However, there are hundreds of therapies that aid in symptom management in the categories of: antibiotics, supplemental vitamins, aerosol bronchodilators, mucolytics and pancreatic enzymes. Most CF patients take pancreatic enzymes, multi-vitamins and nutritional supplements to maintain normal growth. CF patients work tirelessly every day to improve the clearance of secretions from their lungs. This is done by performing airway clearance techniques at least twice a day for about 30-60 minutes per session. Inhaled medications are used to open the airways while inhaled antibiotic treatments are used to control infections. The total time spent on maintaining lung health is well over two hours each day. Patients frequently have periods of infection and acute inflammation called exacerbations that require a hospital stay of at least two weeks and that frequently last four weeks. The steroids that are used to reduce the inflammation and help patients recover from the exacerbation ultimately damage organs in the long-run, contributing to the development of CF related diabetes (CFRD) in 35.2% of all Canadian CF adults. Many of the other drugs that patients need to take on a regular basis also have negative side-effects. Antibiotics can cause kidney damage and total lifetime dose must be controlled, others permanently stain the teeth. Chronic use of antibiotics leads to resistance and as patients age, a need to try multiple antibiotics to find one that works. Because patients are on so many drugs, drug to drug interactions become difficult to manage and can interfere with optimum therapy. Hospitalizations interfere with school, and jobs, for both adult patients and the parents of children with CF. In 2016, there were 2,191 hospitalizations recorded which added up to almost 29,000 days spent in hospital. This does not include visits to the out-patient CF clinics. A total of 4,204 individuals with CF visited a CF clinic at least once with 3,288 (77.4%) having three or more clinic visits. Out of those reported with more than three clinic visits, 1,528 (91.7%) were children and 1,760 (68.2%) were adults. Twenty percent of CF patients travel more than 250km to their CF clinic to receive routine care, with the concomitant interruptions on day-to-day life. At home, individuals with CF had almost 1,100 courses of home IV therapy adding up to over 19,000 days on home IV antibiotics. Eventually the ongoing cycles of infection and inflammation destroy the lungs. Lung transplantation may help people with end-stage cystic fibrosis regain health. As of December 31, 2016, there were 766 individuals with CF reported as having received one or more transplants. Median age at the time of transplant was of 28.6 years. Forty-three (5.6%) have received at least two lung transplants due to transplant failure. In 2015 post-lung transplantation, 5-year survival in Canadians with CF was 67%, and 50% of patients lived over 10 years.[1]

A summary of the day in the life of one CF patient:

- *A typical day at home: **6:00-7:30 AM**: intravenous (IV) antibiotics (2x40 mins). They connect with my picc-line. It's rather tedious because of the many steps of the procedure: disinfect, flush with saline, connect the antibiotic, wait 40 minutes, flush with saline again, connect the next antibiotic, wait 40 minutes... etc. Very often, my Mum, Dad or sister will do this for me while I sleep in, so I can catch a bit more sleep. **8:00-9:00 AM**: wake-up routine; asthma meds, inhaled antibiotics and enzymes, pep-mask physiotherapy, wash all the nebulizers, prep any meds that need to be reconstituted. **9:00-10:00 AM**: breakfast; meal routine: check blood sugar, take insulin, have breakfast, morning pills (the usuals + check calendar for the ones on a variable schedule), scandishake, after-breakfast meds, if any (check calendar). 1:00-2:00 PM: lunch; repeat meal routine; **2:00-4:00 PM**: IV antibiotics (3x40 mins), (concurrent) **3:00-3:10 PM**: inhaled antibiotics. **4:00-5:00 PM**: exercise. **6:00-7:00 PM:** supper; repeat meal routine. 8:00-9:00 PM: clapping physiotherapy. **9:00-9:30 PM**: bedtime routine; asthma meds, inhaled antibiotic, bedtime meds (check calendar). **10:00-11:30 PM**: IV medications (2x40 mins) Fairly often, my Mum, Dad or sister will do this one for me too so I can go to bed a bit earlier. Juggling the timing of everything is a bit of a headache, mostly because I need to space out eating with physiotherapy (doing physio or exercise tends to give me coughing fits, which makes me throw up if I've eaten too recently). On most days I've also got a limited amount of energy, so I've got to manage my activities to make sure I don't crash before the end of the day. Other regular tasks include: keeping medical appointments (1/week or more); preparing pills in advance (it saves time at meals); speaking with my pharmacist 2-3 x a week to order meds, arrange delivery...and…staying on top of insurance reimbursements (3-4 hours / month or so).*[2]

5. Improved Outcomes

When asked about what improved outcomes and trade-offs should be considered when evaluating new therapies, patients, families and caregivers said:

- *I expect (disease modifying therapies) to prolong my life and continually give me quality of life. I expect (them) to allow me to work full time instead of being on income assistance. I expect to plan my life without fearing hospital time. In terms of well-being, I expect my life will give me years not just as a patient, but as meaningful and valued member of my friends, family, and community at large.*
- *Fewer hospitalizations, fewer polyp removal surgeries, less time missing school, less time missing his sports and time with friends, less pain from the infections he experiences and the emotional stress of enduring the increase in his medical treatments while he is ill.*
- *Taking antibiotics, and inhalers, and IVs are good band aids, but the underlying problems must be fixed before you can expect the band aids to fix anything. You can't keep fixing the symptoms and not the disease and expect some miracle to happen.*
- *5% increase in lung function can make a HUGE difference and I would be able to be a more productive member of society.*
- *All drugs and treatments have potential side effects. They effect each person differently, and for different durations. I am willing to experience potential side effects because I believe the potential benefits to my health far outweigh the possibility of some side effects which may be temporary in nature.*
- *I do not wish to die at a young age and leave my wife behind. The side effects (of a medication) are nothing compared to the thought of making my wife a widow.*

6. Experience with Drug Under Review

Patients have accessed Orkambi through clinical trials, private insurance, the manufacturer's compassionate care program. Some Quebec residents have accessed it through the patient d'exception program, the only public insurance program that covers Orkambi for those who need it. In terms of access, respondents to CFC's survey noted:

- *I was not part of a clinical trial, my doctor prescribed Orkambi, I had private insurance which I lost, am now currently on Orkambi through community raised funds.*
- *I was not part of the trial but my doctor prescribed it and I accessed for 18 months before my private benefits cut me off due to the cost.*
- *I was not part of a clinical trial but my doctor prescribed ORKAMBI and I now access ORKAMBI partially through private insurance and partially through Compassionate Access (the portion not covered by my private insurance is covered by Vertex because my lung function is below 40%).*
- *I was not part of a clinical trial but my doctor prescribed ORKAMBI and my father came out of retirement to go back to work so I now access ORKAMBI through his private insurance as an adult disabled dependant.*
- *I was not part of a clinical trial and my doctor has not prescribed ORKAMBI because of access issues although he thinks I would benefit from it.*

Among respondents to CFC's survey, when asked which symptoms Orkambi manages better than existing therapies: 70% of adults and 71% of children reported to be on Orkambi experienced improved lung function; 67% of adults and 74% of children experienced a reduced the rate of pulmonary exacerbations; 42% of adults and 85% of children benefited from improved nutritional status. When it comes to ease of use, 82% of adults noted that Orkambi is easier to use than existing

therapies, while 87% of parents of children with CF said it was easier to use. Ease of use is often correlated with increased efficacy.

- *2 small pills, 2x per day. Very simple, and not simply another inhalation treatment that adds to an already challenging day managing the burdensome treatment needs that people with CF endure.*
- *My little girl hasn't missed a day of school since she has been on Orkambi. She is able to participate in all sports and activates and overall her quality of life is amazing.*
- *For the first time in her life she has had a sustained and genuine appetite. Small thing we non-CF'ers no doubt take for granted. But as a CF dad, that one benefit alone is truly priceless... made one well up in gratitude. And that's not even the BIG positive impact*
- *I went from being on a year and a half long roller coaster of numerous hospital stays with IV treatments, 2 partial pneumonia thoraces to being stable with more energy. I am able to look after my home and my family and do not fall into bed every night knowing I will not have any energy the next day. My daughter can have a friend over for a play date and I am not exhausted after doing activities with them. My husband and I can attend social events together on occasion and again I am not exhausted and ready to leave shortly after arriving. I can do my groceries and not feel like I have run a marathon. These may seem like small things but they have made a world of difference in my day to day living; I truly feel like I was just existing before starting Orkambi, but since starting Orkambi I have a daily life again.*
- *I feel like I can do more exercise to a higher level and easily keep up with others my age. My husband, who is quite athletic, and I have been able to do some tough hikes together and enjoy travelling together. My sinus issues are virtually gone and I finally feel like I am a healthy weight and do not look emaciated for the first time in my life. Not having to do IV antibiotics for so long has allowed me to continue working and volunteering, instead of being sick. Mentally, it feels like we have stopped the progression of CF in its tracks. My husband I are planning our family (through surrogacy) and I look forward to a long career as an engineer. I was originally seeing the transplant clinic, as my CF clinic was worried it could be next for me and we have stopped any push forward on this for the time being.*
- *I think that it already has changed her long-term health trajectory. We are thrilled that her lung function has been maintained in the past 3+ years and that evidently any potential lung degradation is now being avoided. This is a HUGE win, for the long term health and well-being of our daughter and for others with CF.*
- *Our son started at a young age, so he's NOT battling with any decreased lung capacity due to chronic infections that scar the lungs. We are hoping that he will continue to have access to this life-changing medication so he can look forward to growing up without the fear of the progression of this awful childhood illness. He can stop watching friends die at a young age, be afraid of the future but rather look forward and challenge each day with confidence…in short to have a future..*
- *More energy, at least a slightly increased and stable lung function, feels like there is very little mucus inside, and less time doing physio because there is less mucus. Kept me out of hospital for over a year, was going every 4 months. Got over my exacerbation much faster. Gained almost 20 pounds.*
- *Absolutely no negative effects. Everything is positive! My weight is stable I have been on it for a little over a year now and I have avoided Hospitalizations/IV antibiotic therapy. My lung function is back at 90% and I feel good enough to go to the gym during the week.*
- *The positive impact has been amazing!! I'm 36 years old. I feel better than I ever have in my life. I actually decided to go to post-secondary school to get an education because I now know I'll live long enough and be healthy enough to have a career for the rest of my adult life. My quality of life has increased immensely and my lung function has increased as well. I couldn't be happier!*
- *Orkambi changed my life. It gave me more energy than I had in years, reduced my lung infections by over 60%, made me gain 15 pounds of weight easily for a healthy BMI. In my first 6 months on Orkambi, I reduced my hospital time from 45*

days to 10. In my first full year on Orkambi, I was not hospitalized once. I started working part-time and re-engaged in my studies. I was able to have social connection, meaningful leisure, and joy in my days for the first time in 3 years. It stopped my wishes to seek medically-assisted suicide. I went from coughing 3-4 hours a day, to maximum of ten minutes daily. I cleared multiple resistant lung infections and now culture only one as a baseline. I can walk a block, have a conversation, or laugh without losing my breath. My friends hardly recognize the happier, healthier, person I have become. I have new self-esteem and hopes of becoming financially self-reliant. Orkambi has given me a life beyond mere existence, but a life worth living.

- *In March 2015 we were offered the opportunity to participate in a CF study. There was only one spot offered, so we chose our most "sickly" child, our son, to participate. This was not easy, especially when we had to explain to our daughter why we didn't choose her. We didn't know what to expect and anything better than his deteriorating health condition was a welcome change. I was astounded to find that 7 hours after his first Orkambi dose our son, that only coughed when he was sick, had a productive cough, he was clearing out the mucous in the lungs that the antibiotics couldn't remove! The drug has changed my son's life. He is no longer deteriorating, he is thriving! The chronic, four year rattle in his lower right lobe disappeared immediately and no doctor has heard it since. He no longer rolls on the floor in abdominal agony, the pain is gone. His PFTs have increased. He has put on more weight. He sleeps better and wakes up energized, not sluggish like before. People are even noticing more colour in his face, he looks like a healthy 9 year old boy, not like the sickly, pale looking boy that existed pre-Orkambi. This is our first winter on Orkambi and to date he has not had a single sinus infection and has not needed antibiotics. My daughter is not on Orkambi. She is still rolling on the ground while my son now looks on. They both need access to this drug in Canada. I am a first-hand witness of the immense benefits of Orkambi and I know it will save my children's lives. This is a first generation drug that delays the progression of CF much more effectively than what all the physio and antibiotics can do alone.*

CADTH's data from the 2016 CDR review of Orkambi states that one in four patients sees a clinically significant five per cent improvement in FEV1, the most commonly used clinical measure of a CF patient's health, and one in eight patients are "super-responders," seeing a dramatic 10 per cent or more increase.

However some patients endure uncomfortable side effects and not all patients show improvement on Orkambi. The most serious side effect appears to be a 'tightness' in the chest when starting Orkambi, but in general the symptoms fade within weeks or months. We have also heard from or about patients for whom the side effects were not worth the gain, and who have chosen to stop. It is this variability that prompted the CF clinic Directors to recommend a managed care program for Orkambi in 2016 (see below).

7. Companion Diagnostic Test

Since the discovery of the gene responsible for cystic fibrosis in 1989 and the development of new technologies, it has become possible, in most families, to detect the mutations in the gene through laboratory tests, using blood samples or cheek swabs. Samples are sent to specialized molecular diagnostic laboratories for analysis. Over 2,000 mutations in the gene responsible for cystic fibrosis have been identified. Most medical diagnostic laboratories screen for approximately 40 of the most common mutations in Canada. Laboratory tests detect the mutations in approximately 98% of the Canadian CF population. If medically indicated, a complete mutation sequencing can be arranged to provide a more detailed analysis. Both the costs and the availability of genetic testing may vary across Canada. Orkambi is genetically tailored to treat the basic defect in CF for those with the homozygous F508del mutation to the CFTR gene. According to the patient registry genetic mutations have been identified in about 90% of patients meaning that the vast majority of individuals for whom Orkambi is indicated are known.

While it is not currently possible to determine who will benefit from Orkambi in advance of administering the drug, the 2016 managed care program described below aims to ensure that only patients seeing actual benefit stay on the drug. What is more, Cystic Fibrosis Canada has partnered with SickKids Hospital and Genome Canada on a precision medicine project –

CFIT – to develop such predictive tools that will help clinicians determine the right medicine for the right patient. The team will examine how genetic factors, which can be assessed from a non-invasive blood test, can help predict individual treatment responses. They will also examine if drug testing on patient-derived tissue samples can be used to inform the potential clinical response to drugs by each patient. The team will work with industry partners, patient organizations and the Ontario Ministry of Health and Long-Term Care to integrate these strategies into patient care once they have been shown to be effective. In the meantime, CF clinicians in Canada have developed start and stop criteria for Orkambi, as well as recommendations for monitoring patients on Orkambi.

START CRITERIA: Lumacaftor/ivacaftor can be considered for patients 12 years and older with two copies of the F508del mutation, regardless of lung function who are following the prescribed standard of care. The drug should only be prescribed by a CF physician at one of Canada's specialized CF clinics.

Before starting therapy, the patient should have their baseline condition carefully documented including:

i) Baseline ophthalmologic/optometric exam to screen for cataracts

ii) Baseline testing of liver function tests (AST, ALT, alkaline phosphatase, bilirubin, GGT)

iii) Baseline measurements of height, weight and BMI

iv) Baseline measurement of FEV1 in litres and % predicted

v) Calculation of the change in FEV1 (relative change) in year prior to starting therapy

vi) Number of exacerbations requiring oral, inhaled and/or IV antibiotics in previous 12-24 months

vii) Number of hospitalizations in previous 12 months

viii) Baseline measurement of sweat chloride

The purpose of gathering this data is to allow for accurate monitoring and measuring of response to the drug.

RECOMMENDATIONS FOR MONITORING: Patients starting on lumacaftor/ivacaftor need to be carefully monitored, especially in the first year. It is recommended that patients be seen a minimum of four times within the first six months of starting lumacaftor/ivacaftor. Careful and frequent monitoring ensures physicians and patients are: i) carefully examining how the patient is responding to the drug, ii) able to address concerns, and iii) equipped to make informed decisions. As part of these recommendations, CF clinicians developed a template for the clinical tests that are recommended for CF patients during their first two years of undergoing treatment with lumacaftor/ivacaftor.

CONTINUATION CRITERIA/STOPPING CRITERIA To determine if lumacaftor/ivacaftor is suitable for a patient, it is recommended that patient response to lumacaftor/ivacaftor should be monitored for one year. Therapy should be discontinued earlier, if safety concerns exist. At the end of year one, improvement should be assessed, compared to the baseline measurements taken before starting treatment. At this time a recommendation to continue or stop lumacaftor/ivacaftor should be made. Ongoing monitoring is required. Response to therapy would be determined by any one of the following criteria, compared to the baseline measurements taken before starting treatment:

i) Evaluation of FEV1 % predicted:
   a) Relative change > 5% predicted
   b) Absolute change > 5% predicted
   c) Maintenance of lung function (% predicted FEV1) during treatment

ii) Reduction in pulmonary exacerbations

iii) Reduction in hospitalizations, or courses of IV antibiotics, related to pulmonary exacerbations

iv) Improvement in weight, or weight percentiles (if age < 18),_by > 5%

v) Improvement in BMI or BMI percentiles (if age < 18) by > 5%

The measurements outlined above should be considered in conjunction with clinical improvement of CF symptoms (including cough, sputum production, shortness of breath, exercise tolerance, energy level, and abdominal pain.)

Given the sheer volume of medications people with CF take to manage their health, they are quite used to being monitored on their response to medications. Orkambi is no different.

8. Anything Else?

Cystic Fibrosis Canada thanks the CADTH and CDEC for this opportunity to share our community's thoughts and experiences with Orkambi. We would be happy to provide further documentation should CDEC require any additional insights for your deliberations.

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[1] Stephenson, A. L., Sykes, J., Berthiaume, Y., Singer, L. G., Aaron, S. D., Whitmore, G. A., & Stanojevic, S. (2015). Clinical and demographic factors associated with post-lung transplantation survival in individuals with cystic fibrosis. *The Journal of Heart* and *Lung Transplantation: the Official Publication of the International Society for Heart Transplantation*, *34*(9), 1139–1145. http://doi.org/10.1016/j.healun.2015.05.003

[2] Source material: https://marikasmotorcyclediaries.wordpress.com/2014/02/19/typical-day-at-home/

Appendix 1: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   Cystic Fibrosis Canada developed this submission independently.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   Cystic Fibrosis Canada collected and analyzed the data in this report using internal resources, though some external sources were utilized. Any external sources used have been noted in this submission.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

   Cystic Fibrosis Canada receives non-restricted grants from industry. These funds account for approximately 2-6% of overall revenue year over year. We are committed to ensuring that CFC is free from undue Industry influence, and avoiding potential conflicts of interest.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astellas Pharma Canada, Inc.	X			
AstraZeneca Canada Inc.	X			
Bayer Canada Inc		X		
Corealis Pharma Inc	X			
Gilead Sciences Canada Inc	X			
Gilead Sciences Inc.				X
Horizon Pharmaceuticals			X	
Innovative Medicines Canada		X		
Lanurent pharmaceuticals	X			
McKesson Canada			X	
Merck Frosst Canada Inc.			X	
Mylan Pharmaceuticals			X	
Novartis		X		
Pfizer Canada Inc.				X
Pharmascience Canada	X			
Prometic Life Sciences Inc.			X	
Spyryx Biosciences Inc.				X
Vanguard Pharma	X			
Vertex Pharmaceuticals (Canada) Incorporated				X
Vertex Pharmaceuticals Incorporated				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Dr. John Wallenburg

Position: Chief Science Officer

Patient Group: Cystic Fibrosis Canada

Date: March 15, 2018

Patient Group | Cystic Fibrosis Treatment Society

1. About Your Patient Group

The Canadian Cystic Fibrosis Treatment Society is a not for profit organization that has the singular purpose of advocating for individual cystic fibrosis patients that require life sustaining medication or any medical therapy that their doctor has prescribed. We have no funding from Pharma at all or from individuals other than the founder of the group, Chris MacLeod. Frankly, it is operated on a shoestring. It was founded in 2012 following MacLeod's release from St. Michael's hospital after a lengthy stay for infection related to cystic fibrosis. Macleod was prescribed Kalydeco and it dramatically changed his life. He went from 4 litres of oxygen a minute and less than 30% lung function on admission to hospital to back to work full time at his office with no machine generated oxygen within 10 days of receiving the drug Kalydeco.

2. Information Gathering

All information has been gathered through on-line forums such as facebook or direct communication with cystic fibrosis patients and /or their parents. Any direct experience relates to the writer's experience with cystic fibrosis as a patient.

3. Disease Experience

One of the very real challenges that is not appreciated is weight loss and gain. Before Kalydeco I could determine the onset of an infection by my weight. If it fell below 150 lbs I knew an infection was coming on. This cannot be understated. Weight control is central to infection control. The next is infection control and the ability to fight infection. We have a slim envelope of antibiotics to fight infection. We need to limit our use of these drugs to prevent resistance. Drugs that help increase weight gain, reduce infection and most importantly stop the decline of the condition need to made available to patients.

4. Experiences with Currently Available Treatments

There are drugs available that treat the symptoms of cystic fibrosis such as antibiotics, enzymes and pulmozyme but none that treat the underlying condition for the D 508 gene type.

5. Improved Outcomes

The central goal needs to be first and foremost to stop the decline in lung function. If any increases can occur in lung function, that is a secondary benefit. I have very real concerns on the focus of increased pulmonary function scores. After years of damage to a lung, to ask that a drug help improve lung function would be nice but cannot be the benchmark. We need to stop the decline. These drugs ie. Kalydeco and Orkambi allow renewed momentum in the fight against this disease. Without it, a patient will surely die. I know, I was there.

6. Experience with Drug Under Review

The drug Orkambi relates to the specific gene type DF508. We have a series of select quotes from patients some who are currently on the drug and some who could be if it were made available. They follow further in this submission.

7. Anything Else?

We respectfully submit that this review panel focus on the possible benefits of patient access to this life-sustaining medication and if the benefit is recognized then allow the PCPHA to negotiate with the pharmaceutical company. We remain one of the only G-7 countries not to provide the drug Orkambi on a public formulary or be actively engaged in negotiations of the price.

We must sit at the table and negotiate a price. The following is a selection of quotes from across the country from patients or parents of patients:

"I have been doing everything possible to stay alive long enough to one day benefit from a medication that could hopefully save my life or dramatically change my life forever. Now that this miracle medication, Orkambi, has arrived it costs $245,000/year. Why is it that there is a price tag on if I live or die? Shouldn't we all have a right to live? Even at age 51, I still have a lot of living to do and I would like the opportunity to have that chance. My greatest wish is to survive long enough to see my nieces and nephews get married." L.L. from Gatineau, Quebec.

A mother from a Facebook page where I sought input.

"My son's lung function keeps dropping. He'll be 20 years in July. We live in Essex, Ont. Orkambi is the med we've been waiting for since the day he was born and diagnosed with CF. A doctor prescribed it but I am waiting to hear from an insurance company. Not so optimistic given the cost! Fear he'll be denied."

"Both of our sons, B age 4 and C age 1, have the double Delta F508 CF gene. They are loving and happy boys who deserve access to this drug that could drastically improve their lung function and quality of life. We hope that early intervention and access to new treatments will extend their life expectancy to ever higher levels. Affordable access to this new drug could make all the difference to our family." - Coaldale, Alberta.

"Having Orkambi funded will mean that my 4-year-old will lead a longer and healthier life. It means not watching my child suffer as his body deteriorates and fails him. It means greater quality of life and a longer life expectancy." - Calgary, Alberta.

"Orkambi is the only chance I see in the near future that has the potential to help me live a somewhat normal life. I have hope that it will help my cystic fibrosis, my CF-related asthma, CF-related diabetes and CF-related arthritis. I pray it helps keep me out of the hospital so I could finally go to school and get a job, like a real person, all be it with a 15-year late start. This could help us all, and has the potential to save lives."-western Canada

AD: "I need Orkambi and I'm on it now because I was on the trial but obviously will need it funded (PM me or add me if you need more info!). I have gained over 20 lbs. and also have 20% lung function gained in both FEV1 and FEVC. Plus, barely hospitalized anymore. That's why I need it!"

LN: "My daughter, K, is 16 years old and was diagnosed with cystic fibrosis at the age of 10. After years of visiting doctors, specialists and emergency rooms, we finally received the shocking diagnosis at SickKids Hospital. K has the most common mutation, she has Delta 508. Her weight is normal, her lung function is above average but her main complaint is stomach issues. She does have a lot of discomforts, pain and upset. We work VERY hard to keep her weight and lung function up. She takes a multitude of expensive supplements! Allicin, probiotics, NAC, Omega, extra Vitamin C, extra D, etc. We keep on her as a family to ensure she completes her twice daily breathing treatments. She dances daily at school, and enjoys horseback riding. She takes the TOBI Podhaler for her PA infection and Pulmozyme to thin her mucus. She has inhalers on hand to use when required. For us, Orkambi could be the most important weapon in our fight against CF. We believe that this new drug will help us keep K as healthy as possible for many years to come. This drug has the potential to help us maintain or even improve where she is at now. It gives us so much hope for the future. Nobody should be denied life extending treatments or any drugs that improve the quality of life, no matter the cost."

"Today is a remarkable day. After more than 2 years of participation in Phase 3 trial activity, and for which the health outcomes have been very positive, our daughter received her first official 3-months' supply of the drug Orkambi. Never could we have imagined that this day would come, a day that causes me both great joy and pain. Joy, because we are perhaps one of the lucky families whose private insurance has agreed to pay the $21,000 monthly cost of this life-changing drug, Orkambi. Pain, because I know that it's likely that many young Canadians with cystic fibrosis who can benefit from this drug will be denied access, because they do not have private insurance.

After funding world-leading research in Canada for more than 50 years, we are at a critical juncture. As these and other new drugs finally begin to emerge from the laboratories, patients with cystic fibrosis and their families must rally together once again, to ensure that all persons with cystic fibrosis have access to these medications, not just the lucky few who have adequate private insurance.

For people living with cystic fibrosis, time is a gift. Finally, this is "OUR TIME." Let's move forward quickly to gain access to these medications, with the same resolve that got us to this point.-parent GTA

"Though I don't know much about Orkambi, I do know that this is the revolutionary drug that will be changing how all of "us" see this world and all the scientific advancements that have and are being made. It would mean the world to me to finally find a medication that could once and for all solve the problems (or at least drastically help them) that we've been trying to resolve for years and years with my lungs and digestive system through many IV and oral medications. To be able to live a normal life is the "American Dream" of every person with a chronic illness... But being able to breathe without a struggle is ours. Having this medication won't just have the possibility of a new or improved future for me, but will also change the lives of thousands of other Canadians with cystic fibrosis. I believe that this is the beginning of this so-called cure that we've all been hoping and impatiently waiting for all these years... I just hope there won't be a cost for something that could be life-saving to so many and could have saved the ones we've lost."-AM, (the individual is not an American and resides in Canada).

Erica from Alberta: "Imagine there was 4 less hours in a day, 4 less hours every day to live your life. For me, that is not imagining. That is my life. With Orkambi, that time spent doing treatments is given back to me and I can live the way I want, not the way cystic fibrosis forces me to."

Appendix 1: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
None – all funding from Chris MacLeod	Yes			

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Chris MacLeod

Position: Cystic Fibrosis Treatment Society Chair

Patient Group: Cystic Fibrosis Treatment Society

Date: 03.15.18