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CYSTIC FIBROSIS CANADA'S CF PHYSICIAN PANEL ON LUMACAFTOR/IVACAFTOR: RECOMMENDATIONS FOR CRITERIA FOR CLINICAL USE

I - INTRODUCTION

a) Cystic Fibrosis

Cystic fibrosis (CF) is the most common fatal genetic disease affecting Canadian children and young adults. There is no cure.

Cystic fibrosis causes various effects on the body, but mainly affects the digestive system and lungs. The degree of cystic fibrosis involvement differs from person to person. However, the persistent and ongoing infection in the lungs, with destruction of lungs and loss of lung function, causes chronic disability and eventually death in the majority of people who have cystic fibrosis.

Typical manifestations caused by cystic fibrosis are: difficulty in digesting fats and proteins leading to malnutrition, vitamin deficiencies due to loss of pancreatic enzymes, and progressive lung damage. Poor nutritional status is one of the factors leading to accelerated loss of lung function.

It is estimated that one in every 3,600 children born in Canada has cystic fibrosis.

In Canada, there are 42 CF clinics at which a small group of CF adult and pediatric specialist physicians follow almost all of the approximately 4,100 people in Canada who have CF.

b) Lumacaftor/ivacaftor

In January 2016, Health Canada approved lumacaftor/ivacaftor (ORKAMBI™). The drug is currently being evaluated by the CADTH Common Drug Review and INESSS.

Lumacaftor/ivacaftor is a new drug that, like Kalydeco before it, treats the underlying defect in CF. It is currently indicated for patients 12 years of age and older who have two copies of the F508del mutation.

Lumacaftor/ivacaftor can: i) improve lung function, ii) reduce the rate of pulmonary exacerbations, which can lead to hospitalizations and accelerated lung disease, and iii) improve nutritional status.

c) Cystic Fibrosis Canada's CF Physician Panel on lumacaftor/ivacaftor

CF Canada is a national charitable not-for-profit corporation established in 1960, and is one of the world's top three charitable organizations committed to finding a cure for cystic fibrosis. Less than 2% of CF Canada's funding comes from pharmaceutical companies.

Canada is fortunate to have 42 specialized CF clinics led by world-renowned CF specialists who provide some of the best CF care in the world. To develop criteria for the clinical use of lumacaftor/ivacaftor, CF Canada relied on that expertise. A CF Physician Panel on lumacaftor/ivacaftor was established by CF Canada. The names of the members and their declarations of conflict of interest are listed on page 6 of this document.

The panel drafted recommendations for the use of lumacaftor/ivacaftor in Canada which were then carefully reviewed by CF physicians across the country. A set of final recommendations were then developed; the final recommendations are being reviewed the CF Clinic Directors. CF Canada is in the process of gathering a list of endorsers. A list of the endorsements received to date is provided at the end of this document. The recommendations are guided by the principles of:

- High quality healthcare: people in Canada should have access to high-quality healthcare that provides evidence-based, timely, effective care and treatment
- Accessibility: people in Canada should have equitable access to necessary and appropriate medical care and treatment
- Sustainability: physicians have an integral role to play in protecting the strength, integrity and sustainability of Canada's healthcare system and our public drug plans.

d) Summary of clinical trials of lumacaftor/ivacaftor

Two large phase 3, randomized, double-blind, placebo-controlled studies, TRAFFIC (n = 559) and TRANSPORT (n = 563), were conducted to evaluate the efficacy and safety of twice daily doses of lumacaftor/ivacaftor in stable patients with CF managed according to current therapeutic standards who have two copies of the F508del-CFTR mutation and were age 12 years and older. These studies were both 24 weeks in duration and had the same study design. The two active therapy arms were lumacaftor 600 mg daily + ivacaftor 250 mg BID and lumacaftor 400 mg BID + ivacaftor 250 mg BID.

Outcome measures included change of absolute and relative $FEV_{1,}$ a measure of lung function, frequency of pulmonary exacerbations, change in weight and BMI (and BMI Z score) and change in quality of life, as measured by CFQ-R.

The formulation approved and available for clinical use consists of lumacaftor 400 mg BID and ivacaftor 250 mg BID. Results of the trial are reported for this dose. Compared with placebo, treatment with lumacaftor/ivacaftor in both studies was associated with a statistically significant improvement in absolute percent predicted FEV_1 (absolute increase of 2.8% (pooled result of 2 studies)) and relative improvement of FEV_1 (4.8% (pooled result of 2 trials)). About one third of patients on active therapy (36.8-41.2 %) had at least a 5% relative improvement in FEV_1 and one quarter of the patients (22.6-29.9%) on active therapy had an absolute improvement in FEV_1 of at least 5%. Subgroup analysis showed that FEV_1 response was seen across all subgroups of gender, age, baseline FEV_1, and *Pseudomonas* status.

The patients on lumacaftor/ivacaftor in both TRAFFIC and TRANSPORT had a statistically significant reduction in pulmonary exacerbations (all protocol-defined exacerbations and exacerbations requiring IV antibiotics and hospitalizations) with a reduction in total exacerbations by 39%. The reduction in pulmonary exacerbations was seen even in patients who did not have an improvement in FEV_1. Exacerbations requiring hospitalizations are a significant contributor to the overall healthcare costs in CF.

The outcomes of nutritional status varied between the TRAFFIC and TRANSPORT studies. The TRANSPORT trial showed that patients on lumacaftor/ivacaftor had statistically significant improvements in BMI, weight and BMI Z scores whereas there was no improvement seen in the TRAFFIC study. Poor nutritional status accelerates loss of lung function.

There was minor change in quality of life as measured by CFQ-R and the degree of change did not reach the minimal clinically relevant difference and was not statistically significant.

The results of these clinical trials are promising. Based on the results, it is predicted that CFTR modulator therapy in patients with CF, homozygous for the F508del-CFTR mutation, may alter the course of cystic fibrosis by preventing or slowing the pulmonary damage and prolonging life. Of course, this hypothesis cannot be tested in short-term trials of therapy. The improvements in FEV_1 seen in this trial, although statistically significant, were clinically modest and the mean degree of change was within the variability of the test. In the long term, reduction in the rate of decline in FEV_1 is more clinically important than short term improvement in FEV_1 but this measure cannot be captured in the duration of most clinical trials. Reduction in exacerbations (as measured by reduction in exacerbation rate or in prolongation of the time between exacerbations) has clinical significance, as pulmonary exacerbations have been shown to be associated with increased mortality and a greater decline in lung function. There was a clinically and statistically significant reduction in all exacerbations, including those exacerbations associated with need for IV antibiotic therapy and hospitalizations, in the lumacaftor/ivacaftor-treated patients. This reduction was seen independent of improvements in FEV_1.

II - 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 FEV_1 in litres and % predicted
v) Calculation of the change in FEV_1 (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.

III- 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.

Included as an Appendix to this document is a template for the clinical tests that are recommended for CF patients during their first two years of undergoing treatment with lumacaftor/ivacaftor.

IV- 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 FEV_1 % predicted:
   a) Relative change > 5% predicted
   b) Absolute change > 5% predicted
   c) Maintenance of lung function (% predicted FEV_1) 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.)

V - CONCLUSION

The CF Clinic Directors who have endorsed this criteria are confident that the clinical guidelines recommended here are responsible and reasonable, based on the available data and our collective expertise in CF. Still, it is important to stress that given individual variations in CF and responses to treatments, the clinical judgment of the CF physician for her/his individual patients is essential in the use of lumacaftor/ivacaftor.

All clinical guidelines require ongoing assessment and revision. In the case of a new drug such as lumacaftor/ivacaftor, assessment and revision based on new data and real world experience of the drug are essential. Assuming, the CADTH Drug Review and negotiations at the pan-Canadian Pharmaceutical Alliance are completed in an efficient manner and lumacaftor/ivacaftor becomes more widely available in Canada, the CF Physician Panel will reconvene in approximately 18 months to review the guidelines outlined here.

Canada's CF physicians can and should be entrusted to ensure appropriate access to lumacaftor/ivacaftor for people in Canada with CF.

VI – MEMBERS OF THE CF PHYSICIAN PANEL ON lumacaftor/ivacaftor AND CONFLICTS OF INTEREST

Harvey R Rabin MD, FRCPC
Professor, Departments of Medicine and Microbiology, Immunology and Infectious Diseases, University of Calgary
Former Adult CF Clinic Director
Dr. Harvey Rabin was a local site investigator for Vertex clinical trials.

Dr. Felix Ratjen MD PhD FRCP(C) FERS
Head, Division of Respiratory Medicine
Sellers Chair of Cystic Fibrosis
Professor, University of Toronto
Hospital for Sick Children
Dr. Ratjen has received research grants from Vertex, acted as a consultant for Vertex, been on Vertex Advisory Boards and been paid to give talks by Vertex.

Dr. Elizabeth Tullis MD, FRCPC
Director, Adult Cystic Fibrosis Clinic
Head, Division of Respirology
St Michael's Hospital
Professor of Medicine
Cystic Fibrosis Canada Chair in Adult Cystic Fibrosis
University of Toronto
Dr. Tullis has received research grants from Vertex, acted as a consultant for Vertex, been on Vertex Advisory Boards and been paid to give talks by Vertex.

VII – ENDORSEMENTS TO DATE

Dr. Darryl Adamko
Director, Pediatric Cystic Fibrosis Clinic
Royal University Hospital, Saskatoon

Dr. Christian Allard
Co-Director, Combined Adult & Pediatric Cystic Fibrosis Clinic
Hôpital de Chicoutimi, Chicoutimi

Dr. Wendy Alexander
Director, Combined Adult & Pediatric Cystic Fibrosis Clinic
Saint John Regional Hospital, Saint John

Dr. Lara Bilodeau
Director, Adult Cystic Fibrosis Clinic
Hôpital Laval, Laval

Dr. Candice Bjornson
Director, Pediatric Cystic Fibrosis Clinic
Alberta Children's Hospital, Calgary

Dr. André Cantin
Director, Adult Cystic Fibrosis Clinic
Centre Hospitalier Université de Sherbrooke, Sherbrooke

Dr. Mark Chilvers
Director, Pediatric Cystic Fibrosis Clinic
University of Calgary Medical Clinic of the Foothills Medical Centre, Calgary
Dr. Chilvers is a principal investigator on several Vertex studies, has received educational grants from Vertex and attended Vertex Advisory Boards.

Dr. Raquel Consunji-Araneta
Director, Pediatric Cystic Fibrosis Clinic
Winnipeg Children's Hospital, Winnipeg

Dr. Andreas Freitag
Director, Adult Cystic Fibrosis Clinic
Chedoke-McMaster Hospital, Hamilton
Dr. Freitag is a member of Vertex's National Medical Board.

Dr. Dan Hughes
Director, Pediatric Cystic Fibrosis Clinic

IWK Health Centre, Halifax

Dr. Vijay Kumar
Director, Combined Adult & Pediatric Cystic Fibrosis Clinic
Health Sciences North, Ramsey Lake Health Centre, Sudbury

Dr. Larry Lands
Director, Pediatric Cystic Fibrosis Clinic
Montreal Children's Hospital, Montréal

Dr. Annick Lavoie
Director, Adult Cystic Fibrosis Clinic
Hôtel-Dieu de Montréal, Montréal
Dr. Lavoie was paid by Vertex to give one talk in 2015.

Dr. Winnie Leung
Director, Adult Cystic Fibrosis Clinic
University of Alberta Hospitals, Edmonton
Dr. Leung has been a local site co-investigator for Vertex clinical trials.

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Dr. Ian Waters
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Dr. Pearce Wilcox
Director, Adult Cystic Fibrosis Clinic
St. Paul's Hospital, Vancouver
Dr. Wilcox has participated in Vertex research studies as a principal investigator and a co-principal investigator, attended Vertex Advisory Boards and received honorarium from Vertex for continuing medical education.

Appendix: Assessments of 508del/508del CF Patients Undergoing Treatment with Orkambi

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	-7 d to Day 0	+30±10 d	+90±10 d	+6 mo ±15d	+12 mo ±15d	+24mo ±15d
Clinical tests						
Clinical assessment and review of genotype, initial sweat test, medications, past medical history	**X**					
Height and weight	**X**	**X**	**X**	**X**	**X**	**X**
Blood pressure	**X**	**X**	**X**	**X**	**X**	**X**
Acute Medical History	**X**	**X**	**X**	**X**	**X**	**X**
Blood for CBC and liver enzymes	**X**	**X**	**X**	**X**	**X**	**X**
Spirometry	**X**	**X**	**X**	**X**	**X**	**X**
Lung volumes	**X**	**X**			**X**	**X**
Sweat Chloride Test	**X**	**X**		**X**		
Eye exam for cataracts	**X**				**X**	**X**
Sputum microbiology	**X**	**X**	**X**	**X**	**X**	**X**
CFQr (optional)	***X***		***X***	***X***	***X***	***X***