July 10, 2018

Oregon Pharmacy and Therapeutics Committee
Drug Research and Management Division of Medical Assistance Programs
500 Summer Street NE, E35
Salem, Oregon 97301-1079

RE: Oral Cystic Fibrosis Modulators Class Update

Dear Oregon Pharmacy and Therapeutic Committee members:

Frank DeFord, the Hall of Fame sports writer, once described Cystic Fibrosis as "this desperate hopelessness". Much has changed since the death of the Deford's daughter in 1980. In 2018, those of us who are deeply affected by Cystic Fibrosis have hope, but our feelings of desperation are as keen as ever.

My wife and I have a six year old granddaughter with Cystic Fibrosis. In her young life she has endured three hospitalizations, numerous lung infections and significantly declining lung function. Our family is desperate to find a cure for this cruel disease. We will eagerly give of our time and treasure to fight this disease on behalf of our granddaughter and all the children who are suffering from Cystic Fibrosis. We cannot, however, be successful on our own. We need help; we need your help.

I am writing to you in support of Orkambi patients, both pediatric and adult. With the arrival of Symdeko, we are urgently in hope that our granddaughter will have access to these effective medications with current Oregon restrictions lifted. Please make it so our CF doctors can decide what our children need without the burden of so many hoops to jump through. We ask that current Oregon (40-90 FEV) restrictions be lifted and that these medicines are covered to the FDA label. It is our understanding that states like Wisconsin and Florida have removed similar restrictions and it is our firmest conviction that Oregon must do the same. Please help!

Sincerely,

Forrest Bell

Forrest Bell

July 10, 2018

Meghan Herink, PharmD
Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35
Salem, OR 97301-1079

Dear Dr. Herink and Members of the Pharmacy and Therapeutics Committee:

On behalf of people in Oregon living with cystic fibrosis (CF), we write to urge the Oregon Health Plan to include tezacaftor/ivacaftor (Symdeko™) on the preferred drug list (PDL) for all cystic fibrosis patients age 12 years and older who have two copies of the *F508del* mutation or at least one mutation in *CFTR* gene that is responsive to tezacaftor/ivacaftor per the Food and Drug Administration's (FDA) approved label.[1] We also ask that you revise the proposed initial authorization and renewal criteria for ivacaftor (Kalydeco®), lumacaftor/ivacaftor (Orkambi®), and tezacaftor/ivacaftor.

About the Cystic Fibrosis & the CF Foundation
Cystic fibrosis is caused by genetic mutations that result in the malfunction of a protein known as the cystic fibrosis transmembrane conductance regulator (CFTR). Decreased CFTR function causes irreversible damage and the associated symptoms of cystic fibrosis and leads to early death, usually by respiratory failure. As the world's leader in the search for a cure for CF and an organization dedicated to ensuring access to high quality, specialized CF care, the Cystic Fibrosis Foundation accredits 123 care centers, including 4 in Oregon, and 55 affiliate programs nationally that provide multidisciplinary, patient-centered care in accordance with systematically reviewed, data-driven clinical practice guidelines. Treatment options for this rare, life-threatening disease are limited.

About Tezacaftor/Ivacaftor
Tezacaftor/ivacaftor is an FDA-approved therapy that improves the function of the CFTR protein for individuals with specific mutations in the *CFTR* gene. People with cystic fibrosis have a fundamental medical need for increased CFTR protein function. This therapy presents an opportunity to preserve health and lung function in eligible individuals with CF by slowing the progression of the disease and preventing costly hospitalizations, declining health status, deteriorating quality of life, and premature death.

For those with two copies of the *F508del* mutation, evidence shows improvement in lung function (FEV_1), body mass index (BMI), and patient-reported respiratory outcomes (CFQ-R) as well as a reduction in pulmonary exacerbations.[2] This therapy presents a therapeutic alternative for those patients with two copies of the *F508del* mutation who are not able to take lumacaftor/ivacaftor (Orkambi®) due to adverse side effects such as chest-tightness or drug-drug interactions.[2] In particular, tezacaftor/ivacaftor decreases the likelihood of adverse events and the need for strict monitoring while on therapy for those with FEV_1 <40% who are more likely to experience adverse side effects on lumacaftor/ivacaftor.[2]

For those with eligible residual function mutations, evidence shows significant improvements in FEV_1 and CFQ-R as well as improvements in BMI and a reduction in pulmonary exacerbations.[3] This therapy provides a therapeutic alternative for some individuals with residual function mutations currently eligible for ivacaftor (Kalydeco®).[3]

We understand the following initial authorization and renewal criteria are required and urge you to integrate the following recommendations:

13. Is a baseline FEV1 is provided and is between ≥ 40% and ≤ 90% of predicted normal for age, sex and height for those ≥ 12 years of age and at least 40% for children 6-11 years?

Clinical trials inclusion parameters such as FEV_1 should not preclude access to lumacaftor/ivacaftor for patients that fall within the FDA approved label. Restricting access for patients with lung functions less than 40% is not grounded in evidence. This drug has been deemed safe and effective for all individuals with CF age 6 and over who are homozygous for the *F508del* mutation. There is no basis to conclude that patients who meet FDA label requirements but were excluded from the original studies would not benefit from lumacaftor/ivacaftor. Clinical trial results indicate that patients with lung function below 40% demonstrated greater improvements in FEV_1 than the over 40% group.[4] It is critical for providers to closely monitor improvement and potential adverse effects for this subset of patients on lumacaftor/ivacaftor, but this should not preclude patients from accessing this therapy.

For individuals age 12 and older with FEV_1 values above 90%, lumacaftor/ivacaftor represents the opportunity to preserve healthy lung function. As written, the current criteria require individuals to suffer a decline in lung function before starting or restarting this modulating therapy. Additionally, we are concerned about the potential misalignment between the criteria for individuals aged 6-11 years and those over age 12. For example, children receiving lumacaftor/ivacaftor who turn 12 years old should be able to continue therapy even if their lung function is greater than 90%. It is not medically reasonable or responsible to withhold an effective treatment until the patient suffers an irreversible decline in health and loss of lung function.

18. Is the patient on ALL the following drugs, or has had an adequate trial of each drug, unless contraindicated or not appropriate based on age < 6 years and normal lung function:

- ***Dornase alfa, AND***
- ***Hypertonic saline, AND***
- ***Inhaled or oral antibiotics (if appropriate)***

Making access to a modulating therapy contingent upon the trial and use of maintenance medications is not grounded in evidence. Symptomatic therapies such as inhaled antibiotics and mucolytics are intended to combat bacterial infections and aid in clearing mucus, respectively, but they do not increase CFTR protein function and do not address the underlying cause of CF. Timely access to modulating therapies for individuals with the appropriate *CFTR* mutations should not be dependent upon the patient's use of symptom-directed therapies.

4. Does the patient have documented response to therapy as defined as below:
For patients age ≥ 6 years:

- ***a. An improvement or lack of decline in lung function as measured by the FEV1 when the patient is clinically stable; OR***
- ***b. A reduction in the incidence of pulmonary exacerbations; OR***
- ***c. A significant improvement in BMI by 10% from baseline***

We are encouraged by the recognition in this renewal criteria that several clinical responses can indicate a response to therapy. However, we advise that factors such as declines in FEV_1, pulmonary exacerbations, and BMI are often impacted by many factors outside of the patient's control. If a patient does not show significant improvement in the measures, evidence indicates health status would have been far worse without modulator treatment given the progressive decline in lung function that characterizes this disease.[5]

Pulmonary exacerbations are intrinsically sporadic and unpredictable in an individual and risk of pulmonary exacerbation is not uniformly distributed among CF patients.[6] It is not valid to take an arbitrary time interval and apply this to an individual patient as a one-time criterion for demonstrating benefit.

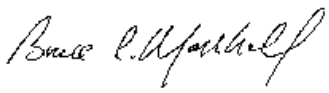
Additionally, for a patient with cystic fibrosis – a disease that causes malnutrition and difficulty gaining or maintaining weight –a 10% short-term improvement in BMI is highly unlikely to occur. Thus, we recommend this criterion be changed to require maintenance or improvement in nutritional status from baseline. This change would create an achievable renewal criterion indicating a positive response to therapy.

Policy Recommendations

The CF Foundation recommends the Oregon Health Plan make tezacaftor/ivacaftor available to all eligible CF patients per the FDA label when the patient's treating physician determines it is medically necessary and appropriate to begin therapy. We also ask that you revise the proposed initial authorization and renewal criteria for ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor per the evidence-based recommendations above.

We stand ready to answer any questions about CFTR modulators or other CF treatments. We would be happy to connect you with local CF experts to further discuss this important issue. Please contact Jackie Erdo, MPH, Manager of Policy and Advocacy, at jerdo@cff.org or 301-841-2628.

Sincerely,



Bruce C. Marshall, MD
Senior Vice President of Clinical Affairs

Lisa Feng, DrPH
Senior Director of Policy and Advocacy

[1]Eligible mutations include: E56K, R117C, A455E, S945L, R1070W, P67L, E193K, F508del (two copies), S977F, F1074L, R74W, L206W, D579G, F1052V, D1152H, D110E, R347H, 711+3A→G, K1060T, D1270N, D110H, R352Q, E831X, A1067T, 2789+5G→A, 3272-26A→G, 3849+10kbC→T

[2] Taylor-Cousar, Jennifer L., et al. "Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del." *New England Journal of Medicine* 377.21 (2017): 2013-2023.

[3]Rowe, Steven M., et al. "Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis." *New England Journal of Medicine* 377.21 (2017): 2024-2035.

[4]Wainwright, Claire E., et al. "Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR." *New England Journal of Medicine* 373.3 (2015): 220-231.

[5]Sawicki, Gregory S., et. al. "Sustained Benefit from Ivacaftor Demonstrated by Combining Clinical Trial and CF Patient Registry Data." American Journal of Respiratory and Critical Care Medicine. N.p., 01 July 2015.

[6]VanDevanter, et al. J Cyst Fibros 2015 Mar 5. pii: S1569-1993(15)00047-8.).

cfri Cystic Fibrosis Research Inc.
Research for Living ~ Partners for Life

July 18, 2018

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Oregon Health Authority
500 Summer Street NE, E35
Salem, OR 97301-1079

Dear Members of the Oregon Drug Use Review Pharmacy & Therapeutics Committee,

On behalf of Cystic Fibrosis Research, Inc. (CFRI), I write to express our profound concern with the final documents related to the "Class Update with New Drug Evaluation: Oral Cystic Fibrosis Modulators," which assess clinical effectiveness and recommend approval criteria for cystic fibrosis transmembrane conductance regulator (CFTR) modulators. My perspective on this topic is both professional and personal: as the Executive Director of CFRI, one of the largest national nonprofit community-based cystic fibrosis organizations, through which I have heard from both patients and medical providers about the benefits of these therapies; and as the mother of a young woman with cystic fibrosis (CF) who is benefitting from CFTR-modulating therapy. On behalf of Oregonians living with cystic fibrosis whose access to these life-saving drugs would be limited based on the contents of the review documents and proposed approval criteria, I urge you to reconsider the authorization recommendations and to expand access based on Food & Drug Administration (FDA) labeling.

CFRI's mission is to fund research, provide education and personal support, and spread awareness of cystic fibrosis to those living with and affected by this genetic disease. Cystic fibrosis remains a progressive and fatal diagnosis. Last year, half the individuals with CF who died were under 30 years old. For those with CF, every day is filled with hours of respiratory therapy and multiple medications. Despite adherence to a complex medical regimen, individuals with CF face multiple hospitalizations and rounds of IV antibiotics, catastrophic hemoptysis and/or pneumothorax – all of which are painful, isolating, frightening, and expensive. CFTR-modulating therapies have the ability to prevent these complications. To limit access to these medications is to disregard the progressive nature of the disease. Until the development of CFTR-modulators, lung function only worsened each year. To stop lung function decline is a victory – to have an improvement is extraordinary and life changing.

The following are key concerns:

- It is unclear in the Appendix 3: Prior Authorization Criteria, #4, whether the absence of an exacerbation in the past 12 months would make a person with CF being prescribed a CFTR modulator ineligible. If this is the case, we are concerned that patients are forced to wait to experience lung infections – which often lead to permanent lung function loss – prior to receiving access. Preventing loss of lung function is key to patient survival.
- The FDA does not place an FEV1 restriction for patients aged 12 and older to use Orkambi. Why is it recommended that patients' eligibility is limited to those with FEV1 above 40% and below 90% of predicted (Recommended Approval Criteria #13)? This is contrary to logic: the goal is to maintain lung function and avoid complications. Why wait until people have irreversible lung damage before approving use? A person with lung function below 40% may experience a stabilization or increase in FEV that keeps that individual off a transplant list. A person with lung function above 90% will be more likely to maintain this level, and avoid costly and painful exacerbations, hospitalizations and other CF-related complications.
- Similarly, the FDA does not limit the use of Orkambi for 6-11 year olds whose lung function is below 40% of predicted. Why does this report recommend this (Recommended Approval

Criteria #13)? The use of a CFTR modulator, when prescribed by a physician, could mean the difference between catastrophic respiratory failure and the need for lung transplantation.

- Orkambi is approved by the FDA for those 12 years and younger. Requiring a referral to the Medical Director for review and approval for Orkambi's use by patients younger than 12 years old this (Recommended Approval Criteria #13) potentially increases barriers to access, and the risk that access will be denied.

Please allow me to share my daughter's experiences with CF and CFTR modulators. Diagnosed in 1995 due to extreme failure to thrive and pneumonia, Tess takes nearly 50 pills per day, injects insulin to manage her CF-related diabetes, and spends a minimum of three hours per day doing respiratory therapy. Through the years, Tess endured multiple long hospitalizations for damaging lung infections, five sinus surgeries, and countless PICC-line placements for multi-week home IV antibiotic treatments. Despite rigid adherence to her medical regimen, her health was declining.

Two years ago, Tess (who is homozygous for the F508del mutation) began taking Orkambi (lumacaftor/ivacaftor). Since then, she has maintained her lung function, had no exacerbations, has needed no IV antibiotics, and has not been hospitalized. Tess has now successfully switched to Symdeko. Each person is unique, and access to whichever CFTR-modulator is the best fit should not be limited.

During my decades of involvement with the cystic fibrosis community I have heard horrific tales of suffering and loss: people forced to leave beloved careers due to declining health; young adults unable to live on their own due to complex medical regimens; families repeatedly separated for weeks at a time due to hospitalizations; and of course, the excruciating pain of losing a child, sibling or spouse. In recent months, four CFRI friends have lost their children – aged 10, 18, 26, and 40. CF is an extremely capricious disease - an individual's health can rapidly spiral out of control. Cystic fibrosis must be treated aggressively and early. It is imperative that FEV-1 and age requirements – that are inconsistent with FDA recommendations - not be a barrier to access to these life-saving therapies.

Our community needs options. It is imperative that individuals have access to new CFTR-modulating therapies and are not forced to wait until their lung function has declined before being able to use them. We fear that the approval criteria you are considering do not accurately convey the importance of preventing lung function decline. For many without CFTR modulators, this decline is inevitable.

The arrival of the first CFTR-modulating therapies has brought realistic hope that the downward course of the disease can be halted. It is a tragedy that for many – either due to their specific CFTR mutation or lung disease that is too advanced – these therapies are not an option. It would be an equal tragedy and travesty if the Oregon Health Authority, by virtue of the Oregon Drug Use Review / Pharmacy & Therapeutics Committee, denied access to individuals who would benefit from these medications.

Cystic fibrosis is a rare disease. It is challenging to entice investment in new therapies. In addition to impacting the lives of CF patients in Oregon, limiting access to therapies based on criteria that do not follow FDA labeling creates the potential to suppress research and discourage investment in new drug discovery and development.

Please develop and implement approval criteria for CFTR modulating therapies that will expand access. The current recommendations under review place the lives of Oregonians with cystic fibrosis at risk.

Sincerely,

Siri Vaeth, MSW
CFRI Executive Director

Marilyn Sue Hartzell

15399 SW Burgundy Street, Portland OR 97224-1184 | 503-516-4297 | stanhart@comcast.net

July 18, 2018

Members of the Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Oregon Health Authority
500 Summer Street NE, E35
Salem OR 97301-1079

Dear Members of the Oregon Drug Use Review / Pharmacy & Therapeutics Committee:

Access to the most current and potentially lung capacity-saving medications for people living with Cystic Fibrosis (CF) in Oregon is an issue of concern to me as an Oregonian who cares about Oregonians living with CF. The final documents related to the "Class Update with New Drug Evaluation: Oral Cystic Fibrosis Modulators," are deeply troubling as *they present an unnecessary barrier to access to the most current therapies* that may prevent or reduce loss of lung function for Oregon citizens living with CF. Preservation of lung function is essential in the daily battle people living with CF must wage.

Also, the recommendations stand as a barrier between physician and patient - an unnecessary intrusion into the most important relationship for a person with living with CF by delimiting a physician's ability to treat their patient with the most current and potentially life-saving medications or therapies available. One's physician should be able to access, on behalf of their patients, all available treatments and therapies that may benefit their patients. I am writing to urge you to reconsider your recommendations and to expand access for Oregonians living with CF to be based on the Food & Drug Administration labeling.

Request to Oregon Pharmacy & Therapeutics Committee: While I don't usually speak to specific CF medicines, I understand the purpose of this meeting is to consider specific coverage, so in the spirit of what I have said above:

- Cover SYMDEKO to FDA label. Technically the way the criteria flows, there is no FEV1 restriction listed for Symdeko, although I believe this is a mistake and will be corrected to mirror the rules for Orkambi.
- Oppose FEV1 restriction for 12+ Orkambi >40% and <90%.
- Oppose Orkambi FEV1 restriction for ages 6-11years >40% and continue with no upper "cap."

I write from two perspectives. First, and foremost, I write as the mother of an adult son living with CF. I have walked the walk of advocating for our son in *accessing timely and appropriate medical care* during the difficult days of "managed care" which positioned primary care providers as 'gatekeepers' – thereby, as in our case, limiting families with children with chronic conditions and special health care needs access to critical specialty care. It was the specialty care our son needed, but was being

denied by his gatekeeper that, ultimately, when received, led to his diagnosis of cystic fibrosis. Our diagnosis should have occurred within his first 3 months, but the healthcare system was not working for us at that time. Every day matters in the lives of children born with CF and a delayed diagnosis means delayed treatment. *What does it mean to a parent, today, to receive an early diagnosis of CF for one's child only, then, to be denied access to potentially life-saving drugs that can prevent or slow the loss of critical lung function?*

I also write from the perspective of having worked with and, ultimately, directing a program focused on assuring accessible systems of care for children and youth with special health care needs (CYSHCN). Throughout my tenure in this field, it was the issue of *access to timely, coordinated and appropriate care,* including necessary therapies and treatments, which presented as the most challenging issue for families of CYSHCN.

Our Story. When our son was diagnosed with CF at 16 months in 1989 we were told we were facing a dire diagnosis, but at a "never better time in medical history." Progress was gaining momentum and the future looked better than ever for effective treatments to support our child. Our son was an 'early adopter' of some of the newest protocols as medical science began to make great strides in the care and treatment of cystic fibrosis. We believe each advancement has aided him in preserving his lung function - including the administration of ibuprofen to reduce systemic inflammation and, later, Pulmozyme just as soon as it became available. These advancements in treatments gave us hope and courage.

We formed a vigorous partnership with the pediatric CF care team to assure we implemented best practice in all treatments that were deemed as definitively or potentially helpful in the protection and preservation of lung function. We are grateful that our son, today, has a relatively healthy lung function. We believe this results from a great amount of hard work, the excellence of his medical team, and the access to new therapies and treatments made available as they were developed and released along the way.

In Summary. Living with CF is a "team sport" played best with an effective and tight team of family, friends and, most essentially, one's medical providers specializing in CF who have access to the full array of therapies and treatments that may be needed by their patients. This scenario presents the best chance of successfully supporting each child, youth, and adult living with CF and the preservation of their lung function as we wait for the cure.

Please reconsider your recommendations in light of the handicap they present to the success of that team in their race against time to preserve critical lung function.

Respectfully,

Marilyn Sue Hartzell

Marilyn Sue Hartzell

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

Roger A. Citron, RPh
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079

Dear Mr Citron,

I'm writing today to share with you important additional information for consideration for your Class Update with New Drug Evaluation: Oral Cystic Fibrosis (CF) Modulators. The information below is intended to help the committee consider the clinical treatment objectives of treating patients with CF, better understand the challenges of measuring outcomes in patients with CF where the goal in treating CF is to maintain lung function from birth, and highlight additional clinical evidence presented in the publication Cystic Fibrosis Foundation Pulmonary Guidelines: Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis.[1]

Proven strategies aimed at improving outcomes and survival in CF include early diagnosis, optimizing nutrition, use of airway clearance, and decreasing the frequency of pulmonary exacerbations.[2-9] As CF is progressive, patients present with varying severity of lung disease.[10,11] Early treatment initiation is critical for optimal effect.[6,12] Reducing the frequency of pulmonary exacerbations and optimizing nutrition helps maintain FEV_1 and decrease the rate of lung function decline.[13,14] Any intervention that can achieve these goals is critical to patient wellbeing.

Stability in lung function and respiratory status are primary objectives in CF care.[14] The average rate of lung function decline achieved with current standard symptomatic CF care (mucolytics, chest physiotherapy, antibiotics and maximizing nutrition) is approximately 2.5% per year, resulting in a median age of death of 29.6 years.[6,9,15] Thus, a major treatment goal of CF is to stabilize FEV_1 or slow the rate of FEV_1 decline.[15] Additionally, any decrease in the rate of pulmonary exacerbations helps preserve FEV_1 and thus, a therapy that reduces exacerbations is expected to improve the lives and outcomes for patients with CF.[12]

In March 2018, Ren *et al.* published Cystic Fibrosis Foundation Pulmonary Guidelines: Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis.[1] Using a systematic approach, the authors provide recommendations for the use of KALYDECO® (ivacaftor) and ORKAMBI® (lumacaftor/ivacaftor) in patients with CF. SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) was not an FDA approved product when these guidelines were published.

KALYDECO® is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of CF in patients 2 years and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or *in vitro* assay data.[16]

KALYDECO was approved by the FDA in May 2017 for use with CF patients 2 years and older who have one of 23 mutations considered to be responsive to ivacaftor potentiation.[17] This precision medicine decision was based on analysis of *in vitro* data and supported by more than five years of real-world clinical data that demonstrate KALYDECO's safety and efficacy profile in patients with other *CFTR* gene mutations. Five additional ivacaftor responsive splicing defect mutations were approved for use with KALYDECO by the FDA in August 2017.[18] The efficacy and safety of KALYDECO in patients with residual function mutations (5 splicing, 12 missense mutations) was evaluated as part of the Phase 3 EXPAND study in which the KALYDECO monotherapy arm met its primary efficacy endpoint with a safety profile consistent with other clinical studies.[16,19,20] In an *ad hoc* analysis of individual mutations, results for change in percent predicted FEV1 ($ppFEV_1$), to the average of the week 4 and week 8, varied by genotype with a 95% confidence interval of 3.7 to 5.8.[19]

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

ORKAMBI® is a combination of lumacaftor and ivacaftor, indicated for the treatment of CF in patients age 6 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.[21]

SYMDEKO® is a combination of tezacaftor and ivacaftor, indicated for the treatment of patients with CF aged 12 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the *CFTR* gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.[22]

Our responses below are specific to observations noted in the Oregon Health Authority (OHA) proposed prior authorization approval criteria and renewal criteria.
Prior Authorization **Approval Criterion 9** provides guidance for patients determined to carry an *R117H* mutation. Wagener *et al.* (2017) analyzed data of CF patients in the US Cystic Fibrosis Foundation Patient registry and reported CF patients with *R117H* mutations as having pulmonary disease consistent with a delayed onset, but ultimately a similar progression of lung disease compared with homozygous *F508del* patients.[23] *R117H* is an indicated mutation for KALYDECO® and the recently published "Cystic Fibrosis Foundation Pulmonary Guidelines: Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis" suggest the use of ivacaftor for patients with this mutation, dependent on a patient's severity of lung disease measured by FEV_1 and age.[1,16]

Patients with *R117H* can have a progressive, life-limiting disease. The median age of survival for patients with residual function mutations, including *R117H*, is approximately 50 years of age,[24] well below the general population.[25] Although many patients with *R117H* develop symptoms at a later stage, the CF disease process is insidious and can actively progress even in the absence of changes in pulmonary function that involves not just abnormal lung function but also exacerbations. Treatment of CF is complex and nuanced; this is particularly true for patients who carry the *R117H* mutation. Some patients with the *R117H* mutation may not show any complications of disease, while others suffer greatly, regardless of age.

Ivacaftor is a therapeutic option for CF patients, 2 years and older, with an *R117H* mutation. We urge the committee to make ivacaftor available, as approved by the FDA, for CF patients over 2 years of age with the *R117H* mutation when their CF practitioners decide that they may benefit from it.

Prior Authorization **Approval Criterion 13**, as written, states that baseline FEV_1 needs to be ≥40% and ≤90 percent predicted (pp). The FDA approved indication for ORKAMBI does not restrict use based on patient lung function, as is the case for other CF therapies considered standard of care such as tobramycin or dornase alfa.[26,27] Also, Elborn *et al.* (2016) analyzed the outcomes of a subgroup of patients enrolled in Trials 1 and 2 homozygous for the *F508del CFTR* mutation and treated with lumacaftor/ivacaftor for 24 weeks. Eighty-one patients had baseline $ppFEV_1$ less than 40. Improvements in the absolute change from baseline at week 24 (least-squares mean treatment difference *vs* placebo) of 3.3 percent (P=0.036) predicted FEV_1 points were observed in patients with baseline $ppFEV_1$ levels lower than 40% who received the FDA approved dose. These analyses suggest that lumacaftor/ivacaftor combination therapy benefits patients with CF homozygous for *F508del* CFTR who have varying degrees of lung function impairment.[28]

Therefore any indicated patient (based on age, CF diagnosis, and genotype) should be provided access regardless of baseline $ppFEV_1$.

Approximately 10% of CF patients, *F508del*/*F508del*, six years and older, have $ppFEV_1$ of <40%.[29] Denying these patients access to ORKAMBI® significantly limits the therapeutic options available to these patients in critical medical need.

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

Patients with a ppFEV$_1$ ≥90% being denied access to ORKAMBI will disproportionately impact children, as approximately two-thirds of the 6 to 11-year-old population and approximately 30% of patients 12 years of age and older have mutations expected to be responsive to ORKAMBI or SYMDEKO®.[30] Denying indicated children and adults the opportunity to access ORKAMBI or SYMDEKO could mean the unnecessary, permanent loss of lung function.

Regarding Prior Authorization Approval **Criterion 17,** as noted above, the FDA has approved SYMDEKO for the treatment of patients with CF aged 12 years and older who are either homozygous for the *F508del* mutation or who have at least one mutation in the *CFTR* gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.[22]

Based on the FDA approved indication for SYMDEKO, there is not a requirement for the *F508del* mutation for those patients who have at least one mutation in the *CFTR* gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence. The listing of eligible mutations can be found in section 12.1 of the SYMDEKO US Prescribing Information and as noted in Table 4, also provided below.

Vertex strongly recommends that FDA eligibility be adhered to and that the proposed requirement for the patient to be heterozygous, requiring the *F508del* mutation, be removed.

Table 4: List of *CFTR* Gene Mutations that Produce CFTR Protein and are Responsive to SYMDEKO[22]

E56K	*R117C*	*A455E*	*S945L*	*R1070W*	*3272-26A→G*
P67L	*E193K*	*F508del**	*S977F*	*F1074L*	*3849+10kbC→T*
R74W	*L206W*	*D579G*	*F1052V*	*D1152H*	
D110E	*R347H*	*711+3A→G*	*K1060T*	*D1270N*	
D110H	*R352Q*	*E831X*	*A1067T*	*2789+5G→A*	
*A patient must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented in Table 4 to be indicated.					

Prior Authorization **Renewal Criterion 2** relates to first renewal of ivacaftor, requiring that patients have a documented sweat chloride decrease of 20 mmol/L from baseline after 30 days of treatment. Vertex strongly recommends these renewal criteria be deleted. While reductions in sweat chloride values generally occur after the initiation of ivacaftor, no correlations can be drawn on an individual patient level between sweat chloride response and clinical benefit achieved from treatment.

Sweat chloride concentration is a biomarker of CFTR modulation with decreases from baseline in clinical trials consistent with the mechanism of action of CFTR modulation. There is however no established change in sweat chloride that signifies a clinically meaningful response.[16] The magnitude of change in sweat chloride concentration that was observed with ivacaftor trials is variable, even when robust lung function and CFQ-R respiratory domain changes were observed at a study population level in these studies.[16,20,31] The requirement for a 20 mmol/L decrease from baseline in sweat chloride concentration to permit renewal, is not based on any scientific data and is unfair to patients as the available evidence supports the variability in sweat chloride concentration response to CFTR modulators in individual patients.

Evaluating sweat chloride concentrations of patients is a routine test in establishing the diagnosis of CF.[32] However, repeating this test post-diagnosis is not part of routine clinical care. Sweat chloride measurements are costly and time consuming tests and while they are not invasive, do result in an inconvenience to the patient and CF center staff. Routine use of repeat sweat chloride measurements are not considered standard practice when considering

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

CFTR modulators as a surrogate marker for clinical response. Also, the 2018 CFTR modulator guidelines recognize that sweat chloride changes may not be informative for monitoring and evaluation[1].

Renewal Authorization **Criterion 4** proposes KALYDECO®, ORKAMBI®, SYMDEKO® and documented response to therapy subsequent to initial renewal as defined by improvement or lack of decline in lung function when the patient is clinically stable, a reduction in the incidence of pulmonary exacerbations, or an improvement in BMI by 10% from baseline, in patients age ≥6 years. In patients 2-5 years of age a 10% increase in BMI from baseline, an improvement in exacerbation frequency or severity, or a sweat chloride decrease from baseline by 20 mmol/L is proposed. Vertex strongly recommends these renewal criteria be deleted in their entirety for the following reasons:

ppFEV$_1$

Acute improvement in lung function as measured by ppFEV$_1$ is an important surrogate for CFTR modulation activity, but provides an incomplete evaluation of therapeutic effects in an individual. As described above, in the overall CF population, the average reduction in FEV$_1$ is estimated to be 1-3 percentage points per year; thus preservation of lung function by slowing the rate of lung function decline over time is one of the main goals of CF treatment.[6,7,14]

Data from propensity score matched cohort analyses have been presented that suggest both ivacaftor, in CF patients 6 years and older with *G551D CFTR* mutations, and lumacaftor/ivacaftor, in CF patients 12 years and older, and homozygous *F508del*, slow the estimated annual rate of lung function decline by 47% and 42%, respectively.[15,33] Therefore, having an "improvement or lack of decline in lung function" as criteria is inappropriate since it does not reflect the benefit that patients may see through a reduction in their rate of FEV$_1$ decline over time.

There is also a known relationship between ppFEV$_1$ and pulmonary exacerbations in the natural history of CF and this can be used to determine an underlying exacerbation risk in patient's 12 years and older, with computer models. A post-hoc analysis showed that patients treated with lumacaftor/ivacaftor had a reduction in rate of pulmonary exacerbations versus placebo regardless of the initial improvement they have in ppFEV$_1$.[34]

Pulmonary Exacerbations

We agree with OHA's assessment that a reduction in pulmonary exacerbation frequency is a clinically meaningful outcome and since pulmonary exacerbation frequency is linked to lung function decline it is an important goal in the care of patients with CF. We also agree with the criteria for 2-5 year olds, which states "improvement in exacerbation frequency or severity," and would encourage that same language be adopted for the ≥ 6-year-old criteria if the criteria are retained.

If not deleted, we suggest OHA consider increasing the length of time to determine the reduction in exacerbation frequency and severity when looking at individuals as opposed to populations. There is variability on an individual basis that can be based on age, prior exacerbation history, and treatment, which makes assessing these criteria for all patients a challenge.[9,35] Frequency of pulmonary exacerbation are typically measured on an annual basis. The rate of pulmonary exacerbations for the overall CF population is 0.7 events per patient per year, so a long time horizon is required to observe pulmonary exacerbation frequency, particularly for patients who are earlier in their disease course.[9]

Body Mass Index

The OHA criteria as currently written for reauthorization requires significant improvement in BMI by 10% from baseline as an acceptable measure of treatment effectiveness. This type of an improvement in BMI for a patient with CF is not realistic and not based on any available scientific data or clinical treatment guidelines.

Data has been presented that shows both ivacaftor and lumacaftor/ivacaftor result in a statistically significant improvement in BMI in certain age groups when compared to placebo.[31,34] In the lumacaftor/ivacaftor pivotal trials in patients 12 years and older, the baseline BMI was 21.5 kg/m^2. Considering the mean height of the study

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

population of 166.6 and 165.9 cm in the 2 Phase 3 pivotal studies , a 10% improvement would represent an increase of nearly 6 kg over the course of 24 weeks.[36,37] In the pooled analysis of lumacaftor/ivacaftor clinical trials in patients 12 years and older, we saw a treatment difference of a 0.24 kg/m^2 improvement in BMI when compared to placebo over 24 weeks ($p<0.001$).[34] Data has been presented that show BMI continued to increase with up to 96 weeks of lumacaftor/ivacaftor treatment (in an open-label extension study within-group change from pre-treatment baseline of 0.69 kg/m^2 [$p<0.0001$]).[15]

It is important to understand that although the overall population treated with lumacaftor/ivacaftor in some studies showed improvement in BMI, not every patient with CF is underweight or in need of BMI improvement. There is no accepted level of BMI improvement within the CF community that designates an appropriate level of improvement. A lack of improved BMI by 10% does not equate with a lack of clinical response.

Sweat Chloride

As outlined above, while reductions in sweat chloride values generally occur after the initiation of ivacaftor, no correlations can be drawn on an individual patient level between sweat chloride response and clinical benefit achieved from treatment. As stated in the KALYDECO, ORKAMBI and SYMDECO prescribing information, there is no direct correlation between decrease in sweat chloride levels and improvement in lung function (FEV_1).[16,21,22]

Additional Information and data clarification

Long term ivacaftor data was presented at the recent 41st European Cystic Fibrosis Conference, held in Belgrade, Serbia, June 6-9, 2018. Analyses of 2016 data from the fifth and final year of the completed, 5 year post approval observational safety study of KALYDECO is the largest analysis of KALYDECO patients to date. In the U.S., data from 1858 patients treated with KALYDECO show they had significantly lower risks of death, transplantation, hospitalizations, and pulmonary exacerbations compared to matched untreated patients over the course of the fifth year of the study. In the U.K., data from 462 patients show similar trends.[38]

Additional, longer-term analyses of patients who received KALYDECO for up to 5 years (635 patients in the U.S.) or up to 4 years (247 patients in the U.K.) show that patients on KALYDECO had consistently better preserved lung function, improved nutritional measures and reduced frequency of pulmonary exacerbations and hospitalizations. While general limitations of observational research apply, these findings were generally consistent with previous interim analyzes. No new safety concerns were identified.[39]
See [Volkova ECFS Posters] for additional information, including limitations associated with this analysis, such as population matching criteria, the observational nature of the study, and sample size and event rates.[38,39]

O'Callaghan *et al.* (2017) used a modeling approach to project survival among a cohort of patients who, at any point in time, initiated lumacaftor/ivacaftor, including those who discontinued, and a cohort of patients who remain on lumacaftor/ivacaftor for their lifetime.[40] The resultant median projected survival was predicted to be 6.1 years longer in the lumacaftor/ivacaftor plus Standard of Care (SC) cohort than in the SC cohort when discontinued patients are included. Incremental median predicted survival based on initiation of lumacaftor/ivacaftor at 6, 12, 18, and 25 years of age was 17.7, 12.6, 8.0, and 3.8 years, respectively in this cohort. Assuming all patients remained on lumacaftor/ivacaftor treatment for a lifetime, incremental median predicted survival was 7.8 years longer in the lumacaftor/ivacaftor+SC cohort; Initiating lumacaftor/ivacaftor at 6, 12, 18, and 25 years of age resulted in incremental median predicted survival of 23.4, 18.2, 11.0, and 4.8 years, respectively. Treatment with lumacaftor/ivacaftor is projected to improve survival for patients with CF with earlier initiation and higher persistence predicts greater benefits including greater proportion of time with higher lung function and a lower risk of lung transplantation. The limitations of this approach include assumptions in model inputs, inputs from multiple data sources and extrapolation of data; see O'Callaghan *et al*. (2017) for additional information, including limitations associated with this model.[40]

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

In conclusion, I would ask that the above information would be taken into consideration during your review of CF modulators. CF modulators work on the underlying defect in patients with CF and not one, specific, endpoint can be used to measure clinically meaningful responses in an individual patient. The totality of an individual's clinical response needs to be taken into account to include: preserving lung function, reducing pulmonary exacerbations, improving nutritional status and overall respiratory symptoms.

Thank you for your careful consideration of this very important issue.

Respectfully,

Deborah Long, MD FCCP
VP, US Medical Affairs
Vertex Pharmaceuticals

Enclosures: US Prescribing Information for KALYDECO®, ORKAMBI® and SYMDEKO®

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

KALYDECO®is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 2 years and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

IMPORTANT SAFETY INFORMATION for **KALYDECO**

Transaminase (ALT or AST) Elevations

- Elevated transaminases have been reported in patients with CF receiving KALYDECO. Transaminase elevations were more common in patients with a history of transaminase elevations or in patients who had abnormal transaminases at baseline.
- It is recommended that ALT and AST be assessed prior to initiating KALYDECO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring of liver function tests should be considered.

- Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal. Following resolution of transaminase elevations, consider the benefits and risks of resuming KALYDECO dosing.

Concomitant Use with CYP3A Inducers

- Use of KALYDECO with strong CYP3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor, which may reduce the therapeutic effectiveness of KALYDECO. Co-administration of KALYDECO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort is not recommended.

Cataracts

- Cases of non-congenital lens opacities/cataracts have been reported in pediatric patients treated with KALYDECO. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating KALYDECO treatment.

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

Pediatric Use

- The safety and efficacy of KALYDECO® in patients with CF younger than 2 years of age have not been studied. The use of KALYDECO in children under the age of 2 years is not recommended.

Serious Adverse Reactions

- Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in patients treated with KALYDECO included abdominal pain, increased hepatic enzymes, and hypoglycemia.

Adverse Reactions

- The most common adverse reactions in patients with a *G551D* mutation in the *CFTR* gene (Trials 1 and 2) with an incidence of ≥8% and at a higher incidence for patients treated with KALYDECO (N=109) than for placebo (N=104) were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea, and dizziness.

- The safety profiles for patients with additional approved mutations enrolled in Trials 4, 5, and 7, and for patients ages 2 to less than 6 years enrolled in Trial 6, were similar to that observed in Trials 1 and 2.

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

ORKAMBI is a combination of lumacaftor and ivacaftor indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *F508del* mutation on both alleles of the *CFTR* gene.

Limitations of Use

The efficacy and safety of ORKAMBI have not been established in patients with CF other than those homozygous for the *F508del* mutation.

IMPORTANT SAFETY INFORMATION for ORKAMBI

Use in Patients With Advanced Liver Disease
Worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease has been reported. Liver function decompensation, including liver failure leading to death, has been reported in CF patients with pre-existing cirrhosis with portal hypertension while receiving ORKAMBI. Use ORKAMBI with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If ORKAMBI is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced.

Liver-related Events
Serious adverse reactions related to elevated transaminases have been reported in patients with CF receiving ORKAMBI. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin.

It is recommended that ALT, AST, and bilirubin be assessed prior to initiating ORKAMBI, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Patients who develop increased ALT, AST, or bilirubin should be closely monitored until the abnormalities resolve.

Dosing should be interrupted in patients with ALT or AST greater than 5 x upper limit of normal (ULN) when not associated with elevated bilirubin. Dosing should also be interrupted in patients with ALT or AST elevations greater than 3 x ULN when associated with bilirubin elevations greater than 2 x ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming dosing.

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

Respiratory Events

Respiratory events (e.g., chest discomfort, dyspnea, and respiration abnormal) were observed more commonly in patients during initiation of ORKAMBI® compared to those who received placebo. These events have led to drug discontinuation and can be serious, particularly in patients with advanced lung disease (percent predicted FEV_1 (ppFEV1) <40). Clinical experience in patients with ppFEV1 <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy.

Effect on Blood Pressure

Increased blood pressure has been observed in some patients treated with ORKAMBI. Blood pressure should be monitored periodically in all patients being treated with ORKAMBI.

Drug Interactions

Substrates of CYP3A

Lumacaftor is a strong inducer of CYP3A. Administration of ORKAMBI may decrease systemic exposure of medicinal products that are substrates of CYP3A, which may decrease therapeutic effect. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended.

ORKAMBI may substantially decrease hormonal contraceptive exposure, reducing their effectiveness and increasing the incidence of menstruation-associated adverse reactions, e.g., amenorrhea, dysmenorrhea, menorrhagia, menstrual irregular. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with ORKAMBI.

Strong CYP3A Inducers

Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Use of ORKAMBI with strong CYP3A inducers, such as rifampin, significantly reduces ivacaftor exposure, which may reduce the therapeutic effectiveness of ORKAMBI. Therefore, co-administration with strong CYP3A inducers is not recommended.

Cataracts

Cases of non-congenital lens opacities have been reported in pediatric patients treated with ORKAMBI and ivacaftor, a component of ORKAMBI. Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with ORKAMBI.

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

Adverse Reactions

Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with ORKAMBI® included pneumonia, hemoptysis, cough, increased blood creatine phosphokinase, and transaminase elevations. These occurred in 1% or less of patients.

The most common adverse reactions in patients age 12 years and older in Phase 3 trials (Trials 1 and 2) occurring in ≥5% of patients treated with ORKAMBI (N=369) vs placebo (N=370) and at a rate higher than placebo were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, blood creatine phosphokinase increased, rash, flatulence, rhinorrhea, and influenza.

The safety profile in patients age 6 through 11 years from an open-label Phase 3 trial (Trial 3; N=58) and a placebo-controlled Phase 3 trial (Trial 4; patients treated with ORKAMBI, N=103 vs placebo, N=101) was similar to that observed in Trials 1 and 2. Additional common adverse reactions were reported in Trial 4, but were not reported in Trials 1 and 2. The adverse reactions in Trial 4 that occurred in ≥5% of patients treated with ORKAMBI with an incidence of ≥3% higher than placebo included: productive cough, nasal congestion, headache, abdominal pain upper, and sputum increased.

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

SYMDEKO is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

IMPORTANT SAFETY INFORMATION for SYMDEKO

Transaminase (ALT or AST) Elevations

- Elevated transaminases have been observed in patients with CF treated with SYMDEKO, as well as with ivacaftor monotherapy. Assessments of transaminases (ALT and AST) are recommended prior to initiating SYMDEKO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations more frequent monitoring of liver function tests should be considered.

- Dosing should be interrupted in the event of significant elevations and laboratory tests should be closely followed until abnormalities resolve. Following resolution of transaminase elevations, consider the benefits and risks of resuming SYMDEKO dosing.

Concomitant Use With CYP3A Inducers

- Exposure to ivacaftor is significantly decreased and exposure to tezacaftor may be reduced by concomitant use of CYP3A inducers, which may reduce the therapeutic effectiveness of SYMDEKO. Co-administration of SYMDEKO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort is not recommended.

Cataracts

- Cases of non-congenital lens opacities have been reported in pediatric patients treated with SYMDEKO, as well as with ivacaftor monotherapy. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with SYMDEKO

Pediatric Use

- The safety and efficacy of SYMDEKO in patients with CF younger than 12 years of age have not been studied

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

Serious Adverse Reactions

- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with SYMDEKO® compared to placebo included distal intestinal obstruction syndrome (3 [0.6%] SYMDEKO-treated patients vs. 0 for placebo).

Most Common Adverse Reactions

- The most common adverse reactions in Trials 1 and 3 occurring in ≥3% patients treated with SYMDEKO (N=334) and at a higher rate than for placebo (N=343) were headache, nausea, sinus congestion, and dizziness

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

References

1 Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines: Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis. *Ann Am Thorac Soc.* 2018;15(3):271–280.

2 Doull IJ, Ryley HC, Weller P, Goodchild MC. Cystic fibrosis-related deaths in infancy and the effect of newborn screening. *Pediatr Pulmonol*. 2001;31(5):363-366. doi:10.1002/ppul.1059.

3 Doull IJM. Recent advances: Recent advances in cystic fibrosis. *ArchDis Child*. 2001;85(1):62-66. doi:10.1136/adc.85.1.62.

4 Farrell PM, Kosorok MR, Laxova A, et al. Nutritional Benefits of Neonatal Screening for Cystic Fibrosis. *N Engl J Mede*. 1997;337(14):963-969. doi:10.1056/nejm199710023371403.

5 Koletzko S, Reinhardt D. Nutritional challenges of infants with cystic fibrosis. *Early Hum Dev*. 2001;65. doi:10.1016/s0378-3782(01)00206-7.

6 Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic Fibrosis Pulmonary Guidelines. *Amer J Respir Crit Care Med*. 2013;187(7):680-689. doi:10.1164/rccm.201207-1160oe.

7 Orenstein DM, Winnie GB, Altman H. Cystic fibrosis: a 2002 update. *J Pediatr* 2002, 140:156–164.

8 Yankaskas JR, Marshall BC, Sufian B, Simon RH, Rodman D. Cystic Fibrosis Adult Care. *Chest*. 2004;125(1). doi:10.1378/chest.125.1_suppl.1s.

9 Cystic Fibrosis Foundation. 2016 Patient Registry Annual Data Report. Accessed June 11, 2018. https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2016-Patient-Registry-Annual-Data-Report.pdf

10 O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet*. 2009;373(9678):1891-1904. doi:10.1016/s0140-6736(09)60327-5.

11 Lahiri T, Hempstead SE, Brady C, et al. Clinical Practice Guidelines From the Cystic Fibrosis Foundation for Preschoolers With Cystic Fibrosis. *Pediatrics*. 2016;137(4). doi:10.1542/peds.2015-1784.

12 Justicia JL, Solé A, Quintana-Gallego E, et al. Management of pulmonary exacerbations in cystic fibrosis: still an unmet medical need in clinical practice. *Expert Rev Respir Med*. 2015;9(2):183-194. doi:10.1586/17476348.2015.1016504.

13 Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review. *J Am Diet Assoc*. 2008;108(5):832-839. doi:10.1016/j.jada.2008.02.020.

14 Liou, T., Elkin, E., Pasta, D., Jacobs, J., Konstan, M., Morgan, W., et al. (2010). Year-to-year Changes in Lung Function in Individuals with Cystic Fibrosis. *J Cystic Fibros, 9*; 250-256.

15 Konstan MW, Mckone EF, Moss RB, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *Lancet Respiry Med*. 2017;5(2):107-118. doi:10.1016/s2213-2600(16)30427-1.

16 KALYDECO® [US Prescribing Information]. Boston, MA: Vertex Pharmaceuticals Incorporated; August 2018.

17 Vertex Pharmaceuticals. (2017, 05 17). *Vertex Pharmaceuticals*. Retrieved June 12, 2018, from Vertex Pharmaceuticals Archived Press Release: https://investors.vrtx.com/static-files/96f88d51-3508-4e24-abf5-9a78a598c1c9

18 Vertex Pharmaceuticals. (2017, 08 01). *Vertex Pharmaceuticals*. Retrieved June 12, 2018, from Vertex Pharmaceuticals Archived Press Release: https://investors.vrtx.com/static-files/8a0f411a-8b16-47da-8f85-d0dafede3492

19 Rowe et al, (2017) Tezacaftor‑Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis *N Engl J Med* 2017;377:2024-35.

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA
02210-1862
Tel: 617-341-6100
www.vrtx.com

20 Rowe et al, (2017) Tezacaftor‑Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis *N Engl J Med* 2017;377:2024-35. Supplement.
21 ORKAMBI® [US Prescribing Information]. Boston, MA: Vertex Pharmaceuticals Incorporated; January 2018
22 SYMDEKO® [US Prescribing Information]. Boston, MA: Vertex Pharmaceuticals Incorporated; February 2018
23 Wagener JS, Millar SJ, Mayer-Hamblett N, et al. Lung function decline is delayed but not decreased in patients with cystic fibrosis and the R117H gene mutation. *Cystic Fibr*. 2017. doi:10.1016/j.jcf.2017.10.003.
24 Mckone EF, Goss CH, Aitken ML. CFTR Genotype as a Predictor of Prognosis in Cystic Fibrosis. *Chest*. 2006;130(5):1441-1447. doi:10.1378/chest.130.5.1441.
25 Kochanek et al. (2017) Mortality in the United States, 2016. NCHS Data Brief No 293. http://www.cdc.gov/nchs/products/databriefs/db293.htm accessed June 13, 2018.
26 TOBI [US Prescribing Information]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; October 2015.
27 PULMOZYME [US Prescribing Information]. San Francisco, CA; Genetech, Inc; December 2014.
28 Elborn J, Ramsey B, Boyle M, et al. 143 Lumacaftor/ivacaftor combination therapy in CF patients homozygous for F508del-CFTR with severe lung dysfunction. *Cystic Fibro*. 2015;14. doi:10.1016/s1569-1993(15)30320-9. Presented at the 38th Annual European Cystic Fibrosis Society Conference, June 10-13, 2015, Brussels, Belgium.
29 Vertex Pharmaceuticals Incorporated. Data on File
30 Vertex Pharmaceuticals Incorporated. Date on File
31 Ramsey BW, Davies J, Mcelvaney NG, et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551DMutation. *N Engl J Med*. 2011;365(18):1663-1672. doi:10.1056/nejmoa1105185.
32 Legrys VA, Yankaskas JR, Quittell LM, Marshall BC, Mogayzel PJ. Diagnostic Sweat Testing: The Cystic Fibrosis Foundation Guidelines. *JPediatr*. 2007;151(1):85-89. doi:10.1016/j.jpeds.2007.03.002.
33 Sawicki GS, Mckone EF, Pasta DJ, et al. Sustained Benefit from Ivacaftor Demonstrated by Combining Clinical Trial and Cystic Fibrosis Patient Registry Data. *Amer J Respir Criticl Care Med*. 2015;192(7):836-842. doi:10.1164/rccm.201503-0578oc.
34 Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *N Engl JMed*. 2015;373(3):220-231. doi:10.1056/nejmoa1409547.
35 Waters V, Stanojevic S, Atenafu EG, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. *Eur Respir Jl*. 2011;40(1):61-66. doi:10.1183/09031936.00159111.
36 Vertex Pharmaceuticals Incorporated. Data on File
37 Vertex Pharmaceuticals Incorporated. Data on File
38 Volkova et al (2018) Real-world Outcomes in Patients With Cystic Fibrosis Treated With Ivacaftor: 2016 US and UK CF Registry Analyses Poster presented at 41st European Cystic Fibrosis Conference; June 6-9, 2018; Belgrade, Serbia.
39 Volkova et al (2018) Disease Progression in Patients With Cystic Fibrosis Treated With Ivacaftor: Analyses of Real-world Data From the US and UK CF Registries Poster presented at 41st European Cystic Fibrosis Conference; June 6-9, 2018; Belgrade, Serbia.
40 O'Callaghan et al (2017) Modeling of the longterm health outcomes of patients with Cystic Fibrosis who are homozygous for the *F508del* Mutation Treated with Lumacaftor/ivacaftor. Poster presented at the 31st North American Cystic Fibrosis Conference, Indianapolis, Indiana, November2-4, 2017.