



Research for Living ~ Partners for Life

May 20, 2020

Drug Utilization Review /
Pharmacy and Therapeutics Committee
Oregon Health Authority

Dear Members of the DUR / Pharmacy and Therapeutics Committee,

On behalf of Cystic Fibrosis Research, Inc., and the thousands of individuals with cystic fibrosis that we serve, I write to express our sincere hope that patients with cystic fibrosis whose mutations make them eligible for the CFTR modulator Trikafta will have access to this transformative therapy. Specifically, we hope that the authorization criteria for Trikafta use follows the clear direction provided by FDA-approved labeling.

Cystic Fibrosis Research, Inc. (CFRI) is one of the largest nonprofit cystic fibrosis organizations in the country, whose mission is to fund research, provide education and personal support, and spread awareness of cystic fibrosis to those living with and affected by the disease. Our Board of Directors and staff include renowned CF clinicians and researchers, parents of children with CF, spouses of those with CF, and adults with CF. I myself have a young adult daughter with cystic fibrosis. We know this disease intimately and work directly with members of the CF community from across the United States, including in Oregon. As such, we receive broad input on the devastating impact of CF, as well as the unprecedented positive impact that CFTR modulators – specifically Trikafta – have had on the lives of many with this debilitating disease.

Cystic fibrosis remains a fatal disease. Last year, half the individuals with CF who died were under 30 years old. Those who battle CF face hours of respiratory therapy, countless pills, and often multiple injections, IVs, and hospitalizations. Every hospitalization is painful, isolating, frightening, and expensive. For those with advanced lung disease, the fear of a catastrophic hemoptysis or pneumothorax is ever present. Transplant offers hope for an extended life, but is fraught with its own tremendous risks, and is not a cure.

Trikafta has given many individuals with CF hope that they will have a better quality of life, and a longer life span. I have heard countless stories of improved lung function, reduced dependence on insulin, reduced hospital stays, fewer exacerbations, and improved nutrient absorption and positive weight gain. These positive physical impacts translate to improved mental health. The importance of Trikafta in enhancing lung function and physical health is especially critical in light of the COVID-19 pandemic.

CFRI and the Oregon CF community we serve thank you in advance for following FDA-approved labeling criteria when determining your authorization criteria for Trikafta. Life with CF is a daily battle to slow the progression of the disease. Prior to the arrival of CFTR-modulating therapies, a decline in lung function was inevitable, regardless of one's adherence to the time-consuming daily CF medical regimen. CFTR-modulating therapies – most notably Trikafta – have brought realistic hope that the disease's downward course can be halted, and health improved. Thank you for helping those who desperately need this therapy to have access.

Sincerely,

Siri Vaeth, MSW
Executive Director
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May 27, 2020

Oregon Pharmacy and Therapeutics Committee
OSU-College of Pharmacy

Dear Members of the Oregon Pharmacy and Therapeutics Committee,

On behalf of people with cystic fibrosis (CF) and their families, we write to comment on the proposed coverage criteria for elexacaftor/tezacaftor/ivacaftor (Trikafta™) and the changes to criteria for ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor, as outlined in the “Oral Cystic Fibrosis Modulators” final document posted May 6, 2020.

Thank you for taking our previous comments on the draft document (submitted February 25, 2020) into consideration and for revising the following criteria:

Elexacaftor/tezacaftor/ivacaftor

- Updating the initial approval period duration from 3 months to 6 months
- Updating the reauthorization period duration from 3 months to 12 months

As we have expressed, modulators are transformative therapies for those who are eligible to take them as they target the underlying protein defect in cystic fibrosis. We urge Oregon Health Authority to make these therapies— ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor —available to patients who meet eligibility requirements as defined by their respective Food and Drug Administration (FDA) label.

About Cystic Fibrosis

CF is caused by a genetic mutation resulting in the absence or defect of a protein known as the cystic fibrosis transmembrane conductance regulator (CFTR). The absence or reduced function of the CFTR protein causes progressive damage to vital organs, including the lungs. Respiratory failure is the most common cause of premature death in CF.

Proposed Coverage Criteria & Summary of Efficacy

While symptom-directed treatments improve health outcomes and are a critical component of care, they cannot stop the clinical manifestations of CF and ultimately “fail” the patient. Ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor are CFTR modulators that address the underlying defect that causes cystic fibrosis. CFTR modulators are critical to prolonging life and reducing irreversible lung and other organ damage.

We understand the following criteria are required for coverage of ivacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor and urge you to revise in accordance with the following recommendations:

For lumacaftor/ivacaftor

Is the patient younger than 12 years of age?

If yes: Refer case to OHP Medical Director for manual review and assessment of clinical severity of disease

Per the FDA label, lumacaftor/ivacaftor is an available modulator therapy for patients aged 2 years or older and are homozygous for the *F508del* mutation. Requiring eligible patients younger than 12 to be referred to the OHP Medical Director could add undue burden to their authorization process and unnecessarily delay access to this crucial therapy. We recommend the removal of this criterion.

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)?**

The standard of care for CF can vary significantly depending on the patient. An appropriate treatment regimen for each patient should be determined by the prescribing physician. Further, access to modulators, an entirely unique class of drugs, should not be contingent on the use of specific standard of care therapies. We recommend changing the wording of this criterion to instead say “ANY, IF APPROPRIATE, of the following drugs” of this criterion.

We understand the following criteria to be required for the renewal of modulators, and propose the following changes:

Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?

We caution against adherence requirements. CF care regimens are complex and require significant time each day to administer treatment. People who are struggling with complicated regimens should not be excluded from receiving life-saving modulator treatments. Should adherence be a challenge, care providers are best-positioned to understand the nuances of individual treatment regimens and work with patients to improve adherence. For example, there are instances when modulator therapies may be intentionally interrupted, such as during treatment with certain antibiotics and other medications with drug-drug interactions. Imperfect adherence to modulators should not preclude a patient’s ability to gain access to this lifesaving therapy.

Does the patient have documented response to therapy as defined as below:

For patients age ≥6 years:

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

For patients age 2-5 years (cannot complete lung function tests)

- **Significant improvement in BMI by 10% from baseline; OR**

- **Improvement in exacerbation frequency or severity; OR**
- **Sweat chloride test has decreased from baseline by 20 mmol/L from baseline?**

We appreciate Oregon Health Authority's acknowledgement that individuals can exhibit clinical benefit through a variety of indicators; however, we would like to highlight that maintenance of all of these endpoints (e.g. maintaining body mass index, pulmonary exacerbations, etc.) is also clinically meaningful in patients living with cystic fibrosis. We recommend that this criterion be altered to require either improvement or maintenance in at least one of the listed clinical endpoints.

For the specific BMI improvement criteria, we recommend the removal of the 10% threshold. Given that patients exhibit clinical benefit from modulators in varying ways, removing this arbitrary threshold better reflects the diversity in individual response to modulators. We recognize that comparing a patient's BMI to baseline data is one of the many ways to evaluate responsiveness to these therapies, however there is no basis to conclude that an improvement in BMI less than 10% is not a meaningful response.

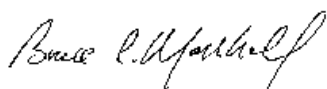
The magnitude of sweat chloride change does not correlate with or predict the extent of a modulator's impact on lung function. However, we agree that a sweat chloride response *does* indicate that the drug is having a physiologic effect on CFTR, the pharmacologic target of CFTR modulators, in a given patient. Thus, the change in sweat chloride could be included as evidence of ivacaftor response but there is no scientific or medical basis for establishing an arbitrary threshold of at least a 20 mmol/L reduction from baseline as indicative of response. We recommend removing the 20 mmol/L threshold from this criterion.

Policy Recommendation

The CF Foundation recommends that the Oregon Health Authority make modulators available to all patients who meet the indicated age and mutation requirements per the FDA label.

We stand ready to answer additional questions about ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor.

Sincerely,



Bruce C. Marshall, MD
Executive Vice President
Chief Medical Officer



Mary B. Dwight
Senior Vice President
Chief Policy and Advocacy Officer

Cc: Roger A. Citron, RPh, OSU-College of Pharmacy, Drug Use Research & Management, Health Policy & Analytics, Office of Delivery System Innovation

From: Gopal Allada

Sent: Monday, June 1, 2020 12:48:18 PM (UTC-08:00) Pacific Time (US & Canada)

To: Pharmacy Drug Information

Subject: Written Testimony

Oregon Pharmacy & Therapeutics Committee

Thank you for the opportunity to provide written testimony regarding the drug class update on oral Cystic Fibrosis modulators, specifically on the new medication elxacaftor/tezacaftor/ivacaftor (aka Trikafta). As you are aware, Trikafta was approved by the FDA for patients 12 and older with cystic fibrosis and at least one copy of the DeltaF508 mutation. For those of the appropriate age, this accounts for roughly 90% of cystic fibrosis patients. In the OHSU adult CF clinic, we follow approximately 200 patients so this medication will have a significant impact for our patients.

Your committee has already reviewed the 2 major trials recently published in NEJM and Lancet Respiratory Medicine that are relevant for Trikafta. These articles provide insight into the short term effects of Trikafta which include unprecedented improvements in lung function and symptoms.

I would add some thoughts now that I have been able to prescribe and see many patients in follow up.

First, this medication is the real deal. I have been caring for CF patients since the 1990's and have served as the Adult CF director at OHSU since 2005 and I can say unequivocally that this is by far the most impactful medication I have ever seen. It has not been an unusual scene in our CF clinics to see a patient nearly (or actually) in tears after they perform their first pulmonary function test after having started Trikafta. As I write this today (6/1/20), we have only 1 CF patient in the hospital and she is post lung transplant! That is to say, whereas our CF inpatient census is normally between 5-10 patients, we currently have none. I have no doubt that the biggest impact on this is Trikafta.

The stories we have heard from our patients have certainly impacted our CF team. But what is also very interesting to me (and our patients) is the potential long term impact of highly effective CFTR modulators. Obviously, this information for Trikafta cannot be determined for years. However, I would turn the committee to the closest comparator for Trikafta which is ivacaftor (Kalydeco) for patients with a class 3 gating CFTR mutation. Kalydeco was approved in 2012 for a small percentage of CF patients, but we have recently been privy to long term data from an ongoing longitudinal study which encompassed patients not only from the US but the UK as well. I will include the reference (J Cyst Fibrosis. 2020 Jan;19(1):68-79) and abstract below, but the short of it shows significant and sustained impact of highly effective CFTR modulators on lung function and nutrition/weight. I would add that by objective standards, Trikafta had *more* impact than Kalydeco when comparing the phase 3 studies which led to the approval of each. The final reference (Thorax 2018;73:731-740.) suggests that highly effective CFTR modulation is *disease-modifying* in this typically fatal genetic disease.

In conclusion, Trikafta is the most impactful medication for CF in history. The short term effects are unprecedented and outlined well in the 2 major studies published in NEJM and Lancet Respiratory Medicine in 2019. There is strong reason to believe that Trikafta will be proven to be disease-modifying and will have an impact on need for lung transplantation and mortality. In short, this is a medication we will want to get for patients quickly and have them stay on this

indefinitely. I look forward to working with the Oregon Pharmacy & Therapeutics Committee in making this medication as accessible as possible for our patients.

Thank you and as always, I am happy to talk with the committee any time.

Stay safe!

Gopal

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J Cyst Fibrosis. 2020 Jan;19(1):68-79. (attached)

Disease Progression in Patients With Cystic Fibrosis Treated With Ivacaftor: Data From National US and UK Registries

Abstract

Background: Ivacaftor is the first in a class of drugs, CFTR modulators, that target the underlying defect in cystic fibrosis (CF). This long-term observational safety study evaluated CF disease progression in patients treated with ivacaftor in a real-world setting for up to 5 years.

Methods: Data from existing US and UK CF patient registries were used to assess longitudinal patterns in lung function, nutritional status, pulmonary exacerbations and hospitalizations, CF-related diabetes (CFRD), and *Pseudomonas aeruginosa* in ivacaftor-treated vs untreated comparator cohorts matched by age, sex, and disease severity.

Results: US analyses included 635 ivacaftor-treated patients and 1874 comparators followed for 5 years from year 1 of market availability (2012-2016). Evaluation of outcome patterns from pretreatment baseline (2011) through year 5 (2016), showed that relative to comparators, ivacaftor-treated patients had better preserved lung function (mean change in percent predicted FEV₁, -0.7 percentage points with ivacaftor vs -8.3 percentage points in comparators) and improved nutritional status (mean body mass index change +2.4 kg/m² with ivacaftor vs +1.6 kg/m² in comparators). US patients treated with ivacaftor had significantly lower frequencies of exacerbations and hospitalizations in each of the 5 years of follow-up relative to pretreatment baseline and comparators. Favorable trends in CFRD and *P. aeruginosa* prevalence were also observed. Findings from the smaller UK registry were directionally similar to and consistent with US findings.

Conclusions: This observational study represents the largest longitudinal analysis of patients treated with ivacaftor in a real-world setting. The findings support disease modification by CFTR modulation with ivacaftor.

Thorax 2018;73:731–740. (attached)

Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor

Abstract

Background Ivacaftor is the first cystic fibrosis transmembrane conductance regulator (CFTR) modulator demonstrating clinical benefit in patients with cystic fibrosis (CF). As ivacaftor is intended for chronic, lifelong use, understanding long-term effects is important for patients and healthcare providers.

Objective This ongoing, observational, post approval safety study evaluates clinical outcomes and disease progression in ivacaftor-treated patients using data from the US and the UK CF registries following commercial availability.

Methods Annual analyses compare ivacaftor-treated and untreated matched comparator patients for: risks of death, transplantation, hospitalization, pulmonary exacerbation; prevalence of CF-related complications and microorganisms and lung function changes in a subset of patients who initiated ivacaftor in the first year of commercial availability. Results from the 2014 analyses (2 and 3 years following commercial availability in the UK and USA, respectively) are presented here.

Results Analyses included 1256 ivacaftor-treated and 6200 comparator patients from the USA and 411 ivacaftor-treated and 2069 comparator patients from the UK. No new safety concerns were identified based on the evaluation of clinical outcomes included in the analyses. As part of safety evaluations, ivacaftor-treated US patients were observed to have significantly lower risks of death (0.6% vs 1.6%, $p=0.0110$), transplantation (0.2% vs 1.1%, $p=0.0017$), hospitalization (27.5% vs 43.1%, $p<0.0001$) and pulmonary exacerbation (27.8% vs 43.3%, $p<0.0001$) relative to comparators; trends were similar in the UK. In both registries, ivacaftor-treated patients had a lower prevalence of CF-related complications and select microorganisms and had better preserved lung function.

Conclusions While general limitations of observational research apply, analyses revealed favorable results for clinically important outcomes among ivacaftor-treated patients, adding to the growing body of literature supporting disease modification by CFTR modulation with ivacaftor.