



May 18, 2015

Roger A. Citron, RPh
OSU-College of Pharmacy
Drug Use Research & Management
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35
Salem, OR 97301-1079

Dear Mr. Citron,

On behalf of people with cystic fibrosis (CF) and their families, we write to recommend that the Oregon Health Authority provide coverage on the preferred drug list (PDL) for ivacaftor (Kalydeco®) for all patients with the gene mutations that have been approved by the FDA, including children age 2-5 years per the FDA's recently approved label expansion. As a recognized expert in CF, the Cystic Fibrosis Foundation accredits 115 care centers and 60 affiliate programs nationally that provide treatment and care in accordance with evidence-based, systematically reviewed clinical practice guidelines. Ivacaftor is like no other drug available to people with cystic fibrosis as it is the only therapy that targets the underlying cause of the disease.

As you know, cystic fibrosis is caused by a genetic mutation resulting in the malfunction of a protein known as the cystic fibrosis transmembrane conductance regulator (CFTR). The malfunction of CFTR causes the symptoms of cystic fibrosis and leads to a progressive decline in lung function of 1-3% per year and ultimately premature death, most commonly as a result of respiratory failure. Treatment options for this rare, life-threatening disease are extremely limited, and restricted access to FDA-approved treatments could result in a severe decline in health and quality of life.

Initiation of ivacaftor treatment at an early age provides the greatest potential for an enduring health benefit and extended quality of life because evidence of the beginnings of CF-related damage to the lungs have been observed in CF children studied within the first year of their lives, including air trapping, bronchial wall thickening, obstruction, and bronchiectasis (Kraemer, et al. *Pediatr Res.* 1998;44:920; Kraemer, et al. *Respiration* 2000;67:477; Sly et al., et al. *Am J Respir Crit Care Med* 2009;180:146; Hall, et al. *PLoS One.* 2011;6:e23932). The ivacaftor label expansion to children age 2-5 years old presents an opportunity to preserve health and lung function in these individuals and significantly slow the progression of the disease. While there are currently other respiratory therapies that are beneficial to patients with respiratory symptoms, they do not and cannot meet the patient's fundamental medical need prevention of damage by correction or potentiation of mutant CFTR protein. By preserving lung function in children with FDA-indicated CFTR mutations, ivacaftor can mitigate disease progression and may keep young people from experiencing costly hospitalizations, declining health status, and deteriorating quality of life. It is not medically reasonable or responsible to

withhold an effective treatment until the patient suffers a decline in health and loss of lung function.

The CF Foundation recommends that Oregon Medicaid make ivacaftor available to all patients who are two years of age and older who have one of the mutations in the CFTR gene indicated on the FDA label (i.e. G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D and R117H) when the patient's treating physician determines it is medically necessary and appropriate to begin the therapy.

Please contact Jackie Erdo, Policy Manager, at jerdo@cff.org or 301-841-2628 should you have questions, concerns, or require further information.

Sincerely,



Bruce C. Marshall, M.D.
Senior Vice President of Clinical Affairs



Mary Dwight
Senior Vice President for Policy &
CF Community Affairs

Low chest-imaging scores	3 45,133,161	3 45,100,162
Bronchiectasis	5 59,62,83,133,134	5 62,83,100,134,162
Airway wall thickening/ smaller luminal area	5 62,84,90,97,133	5 62,84,90,97,162
High airway resistance/ mucus plugging/obstruction	3 62,76,99	7 10,62,76,100,107,154,162
Air-trapping/hyperinflation	8 59,64,76,77,83,90,106,133	7 76,77,83,90,100,106,144
Lung dysfunction^b	12 4,12,14,64,72,82,85,90,106,118,121,137	15 4,10,12,14,70,82,85,88,90,95,106,114,118,137,153

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May 20, 2015

Roger A. Citron

OSU-College of Pharmacy

Re: ODURP&T May 28, 2015 Meeting / Kalydeco

Dear Mr. Citron,

I am writing to you today as the executive director of Cystic Fibrosis Research, Inc. (CFRI) a nonprofit based in Palo Alto, California, but with global reach, and as a mother of a precious 30-year-old daughter with cystic fibrosis.

As I say, many times a day, "I hate cystic fibrosis." I hate that it begins to take the breath away from our children the day they are born, and ravages their bodies until they can fight no more. I hate that they suffer excruciating pain from endless lung exacerbations and gastrointestinal problems. I hate that there is no cure, and that the fate of so many with CF is to die from drowning in their sputum, or blood from hemorrhaging lungs... or from liver failure... or from lungs that simply cannot take another breath. I hate that my daughter's lungs have been destroyed by CF and that she was listed on May 12 for a double lung transplant in order to survive, after having a liver transplant at age 12. I hate cystic fibrosis.

It is because of the love for my daughter that I have dedicated my life to fighting CF. I am proud to be the executive director of CFRI. Our mission is to fund CF research, provide education and personal support and to spread awareness of cystic fibrosis. For 40 years, we have played an integral role in the search for new medical treatments and for a cure. We have funded innovative research that has unlocked many of the mysteries of CF, and provided the building blocks for some of today's most exciting treatments.

It is because of our commitment to CF research and to working toward a cure, and because I am a mother of a daughter with CF, that I write to appeal for your support in favor of the Oregon Health Authority providing coverage for Kalydeco for adults with the R117H mutation and children (ages 2 – 5) with any of the following mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or R117H. This therapy could be life changing for these individuals, and I strongly urge the Committee to approve coverage of the drug by OHA. Approve coverage of Kalydeco for these populations, and you will provide increased odds for a life with less pulmonary damage.

Cystic fibrosis is a progressive disease. This means that those with CF must spend hours each day **just to slow the disease's inevitable damage to their lungs.** This drug not only will help them to **maintain their lung function** until better drug options arrive, it will even help to **improve lung functions.** Clinical trials also showed that this population of patients using Kalydeco had reduced exacerbations, improved weight, and overall better quality of life.

I fear that if this application is declined, those in the targeted population will experience declines in lung function, and their opportunity to take advantage of future therapies may be impacted. I strongly encourage you to

approve Kalydeco for coverage by the OHA for adults with R117H and children (ages 2-5) with any of the following mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or R117H.

It is because of CFRI's commitment to CF research and to working toward a cure, and because I am a mother of a daughter with CF, that I am advocating in favor of the OHA to provide coverage of Kalydeco for the CF population noted above. The ability to have OHA-covered access to Kalydeco is a right to life issue.

Does the Declaration of Independence not state that we have the 'right to life, liberty and the pursuit of happiness?' By approving OHA coverage of Kalydeco for those with the R117H mutation in adults and the G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or R117H in children (ages 2 – 5), you are upholding these rights. By providing OHA coverage, you are increasing the ability to use Kalydeco for children with these mutations **before** CF lung disease progresses and providing them with the right to live - **Kalydeco is the only FDA approved drug available that treats the underlying defect in CF** - and it can in those with the R117H, G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R genetic mutations. Allow OHA-covered access to Kalydeco and you are upholding the 'liberty' to use a drug that can have a positive outcome in those with CF; and you will allow those with these mutations the ability to pursue happiness.

Kalydeco is here. Many in Oregon are waiting to use it. I honestly believe that if my daughter had R117H, G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R, and had access as a child she would not be where she is today. Don't let those who have R117H and the other mutations noted above that can benefit from Kalydeco now and in the future get to the point where their only hope, like my daughter's, is to receive a successful lung transplant in order to live... and to breathe easy. I urge you to allow OHA coverage of Kalydeco for adults with the R117H mutation and children (ages 2 – 5) with any of the following mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or R117H.

On behalf of the CF community in Oregon, I thank you for the opportunity to present CFRI's views and my views as a mother of a 30-year-old daughter with CF who is in end stage CF lung disease and fighting for her life.

Sincerely,



Sue Landgraf
Executive Director
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Roger A. Citron, RPh
OSU-College of Pharmacy
Drug Use Research & Management
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35
Salem, OR 97301-1079

Dear Mr. Citron,

I'm writing today to share with you some additional information regarding your review of ivacaftor (KALYDECO®) for cystic fibrosis. In the recent review by Dr. M. Herink the recommendation reads:

“Limited, inconsistent, and unpublished evidence at this time prohibits adequate and fair evaluation of the efficacy of ivacaftor for the new FDA-approved indications. It is prudent to further await published data supporting statistically significant improvements in FEV₁, or other clinically relevant outcomes, in patients with the *R117H* mutation in the *CFTR* gene and in pediatric patients aged 2 to 5 years before approving use in these populations¹”

The information below is intended to help the committee understand the challenges in conducting clinical trials in an orphan disease like cystic fibrosis and provide more clarity around the outcomes that the FDA considered when they approved both the *R117H* and pediatric 2 – 5 year old label expansions.

Currently, ivacaftor is indicated for the treatment of cystic fibrosis in patients age 2 years and older who have one of the following mutations in the *CFTR* gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *R117H*.

Ivacaftor for CF Children aged 2- 5

The OSU review stated: “There is insufficient to low quality evidence, based on one small pharmacokinetic study in pediatric CF patients' aged 2 to 5 years...¹” It is important to understand that the ***FDA does not require efficacy studies in pediatric populations when efficacy has already been demonstrated in older patients.***

According to ICH Guidance E11: Clinical Investigation of Medicinal Products in the Pediatric Population, “When a medicinal product is to be used in younger pediatric patients for the same indication(s) as those studied in older pediatric patients, the disease process is similar, and the outcome of therapy is likely to be comparable, extrapolation of efficacy from older to younger pediatric patients may be possible. In such cases, pharmacokinetic studies in the relevant age groups of pediatric patients likely to receive the medicinal product, together with safety studies, may be sufficient to provide adequate information for pediatric use.²”

CF is the same disease in children as it is in adults, and progression of disease begins from birth, with evidence of chronic infection and structural abnormalities in the lung common by 3 years of age^{3,4}. The FDA approved ivacaftor for use in children aged 2-5 years on the basis of a favorable safety profile and extrapolated efficacy (with support

from pharmacokinetic analysis) from older CF patients (ages 6+) with these same mutations where ivacaftor use has been FDA approved as safe and effective.

One of the primary goals of any CF treatment is to maintain lung function⁵. CF patients can lose between 1-3% ppFEV₁ per year⁵. Denying indicated children the opportunity to access ivacaftor could mean the unnecessary permanent loss of lung function.

We urge the committee to allow ivacaftor to be available, as approved by the FDA, for CF patients aged 2-5 years old who have one of the 10 mutations in the *CFTR* gene already approved for use in patients aged 6 and above when their CF practitioners feel they will benefit from it (see indications below).

Ivacaftor for CF patients with the *R117H* mutation:

In October 2014, a 15-member FDA Advisory Committee reviewed clinical data and heard testimony regarding an additional ivacaftor indication for cystic fibrosis patients 6 and older who have an *R117H* mutation in their *CFTR* gene. There are approximately 500 people in the US who meet these criteria⁶.

The *R117H* mutation is a residual function mutation with gating and conductance defects, associated with variable clinical outcomes. *R117H* typically retains some ability to transport chloride⁷. *CFTR* activity is the greatest predictor of clinical manifestations of disease.

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 age⁸, well below the general population. Although many patients with *R117H* develop symptoms at a later stage than the classical CF patient, 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. No current treatments address the underlying cause of CF in this population.

As the OSU review accurately states, the primary endpoint for the overall population of the *R117H* trial (study 110) (treatment difference for absolute change in % predicted FEV₁ through week 24) was 2.1% and did not reach statistical significance. However, change in sweat chloride and improvement in cystic fibrosis respiratory symptoms (as assessed by the CFQ-R respiratory domain score) were statistically significant. Absolute change in BMI, and time to first pulmonary exacerbation were not statistically significant.

Statistically significant improvements in clinical efficacy, including FEV₁ and patient-reported respiratory symptoms were seen in several subgroup analyses and decreases in sweat chloride were also observed. Elevated concentrations of chloride in sweat are a known characteristic of CF patients and reduced sweat chloride concentrations indicate improved functioning of the *CFTR* protein. In this study, ivacaftor treatment resulted in substantial reductions in sweat chloride concentrations, regardless of age: -24 mmol/L (-35%) in the overall *R117H* population⁹.

The FDA advisory committee listened to testimony from CF practitioners and patients with the *R117H* mutation and discussed the details of the study at length. The panel

overwhelming supported approval of ivacaftor for *R117H* patients voting 13-2 in favor of the expanded indication.

There are several nuances to treating *R117H* CF patients that CF practitioners understand. Some *R117H* patients may not show any complications of disease, while others suffer greatly, regardless of age. Ivacaftor is a therapeutic option for *R117H* patients who are showing disease progression.

We urge the committee to allow ivacaftor to be available, as approved by the FDA, for CF patients over 2 years with the *R117H* mutation when their CF practitioners decide that they may benefit from it.

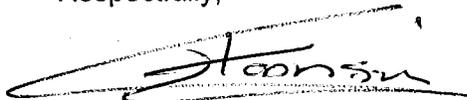
The safety profile for the patients with CF with an *R117H* mutation enrolled in the 24-week placebo-controlled trial, and the patients ages 2 to less than 6 years in the 24-week, open-label clinical trial were similar to that observed in the 48-week placebo-controlled trials for *G551D*. In phase 3 trials of CF patients with a *G551D* mutation, the most serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with ivacaftor were abdominal pain, increased liver enzymes, and hypoglycemia. The most common adverse events occurring in 8% or more in patients treated with ivacaftor and higher than in patients receiving placebo were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea and dizziness.

There are no known contraindications to ivacaftor. Elevated transaminases have been reported in CF patients receiving ivacaftor. Therefore, it is recommended that ALT and AST be assessed prior to initiating therapy, every 3 months during the first year of treatment, and annually thereafter. In the pediatric trial, 5 of 34 patients (14.7%) had transaminase elevations greater than 8 x ULN. Transaminase elevations were more common in patients with a history of transaminase elevations. In patients with a history of transaminase elevations, more frequent monitoring of liver function tests should be considered. Dosing should be interrupted in a patient whose ALT or AST is greater than 5 times the upper limit of normal and consideration given to the benefits and risks of resuming ivacaftor therapy. Ivacaftor should not be given with strong CYP3A inducers which substantially decrease the exposure of ivacaftor.

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

Thank you for considering this additional information.

Respectfully,



Craig Hopkinson
SVP, Global Medical Affairs
Vertex Pharmaceuticals

Enclosure: U.S. Kalydeco Package Insert

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