Research for Living ~ Partners for Life

Roger A. Citron, RPh
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OHA Division of Medical Assistance Programs
500 Summer Street NE, E35
Salem, OR 97301-1079

November 3, 2016

Dear Mr. Citron,

I am writing to follow up on my October 5, 2016 letter expressing concerns regarding OHA's proposed criteria regarding access to Orkambi for both the pediatric and adult populations. I understand that there has been an updated proposed criterion that includes the removal of the upper FEV_1 limits for pediatric patients ages 6 to 11. CFRI is in full support of this proposed change.

My experience with living the challenging roller coaster ride of cystic fibrosis is extensive. Not only am I the executive director of Cystic Fibrosis Research, Inc. (CFRI), a 41-year-old cystic fibrosis (CF) nonprofit patient advocacy agency based in Palo Alto, CA, but with constituents across the world, including Oregon, but I have a 32-year-old daughter with CF who nearly died in the summer of 2015 due to end-stage CF and thankfully received a life-saving double lung transplant without a day to spare. I am grateful to be able to engage with you to express CFRI's concerns regarding OHA's revised proposed criteria that seems to restrict access to Vertex Pharmaceutical's Orkambi for those cystic fibrosis patients ages 12+ with the targeted mutations that have an FEV_1 less than 40% and above 90%.

It is still CFRI's position that the policy be constructed so that it is in the best interest of these patients with CF (with the targeted mutations for Orkambi) and that follows the FDA approved criteria to allow access even if these individuals fall outside the 40-90% FEV_1 range. It is important to note that the Phase 3 trials for Orkambi included CF patients that did fall outside this range, and it is of utmost importance to state again that the FDA approved the usage of the drugs without a pulmonary function range restriction. It is encouraging that three other states, Florida, Wisconsin and Tennessee (as of Nov. 1, 2016), removed the FEV_1 restrictions and are following the federally approved guidelines for using Orkambi.

Regarding the original proposed Renewal Criteria, specifically #2 and #4: these criteria for authorizing prescriptions should be determined by the prescribing physician's judgment based upon the individual patient's need. The Renewal Criteria is overly subjective and should be eliminated. Putting up barriers can result in a patient's health dramatically decreasing. Orkambi is the only drug that treats the basic underlying defects in the mutations for which they were developed. Trials and patient use have shown that using Orkambi can reduce pulmonary exacerbations, improve and stabilize lung function, decrease hospitalizations, increase body mass index, and provide a life of better health for those with the targeted mutations.

CFRI does not want any of the CF community in Oregon to be faced with having a life-saving drug in reach, but unable to access it because their state has imposed non-federally approved restrictions to its usage. Please, for the health and longevity of those with the targeted mutations by Kalydeco and Orkambi, approve a policy that excludes the pulmonary function restrictions as well as the #2 and #4 Renewal Criteria. The FDA did just that and for valid reasons based on the clinical research conducted. Both Kalydeco and Orkambi are life-changing drugs for those targeted CF populations and without question should be made accessible as mandated by the FDA.

Respectfully,

Sue

Sue Landgraf, Executive Director
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November 9, 2016

Meghan Herink, PharmD
Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35
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Dear Dr. Herink and Members of the Pharmacy and Therapeutics Committee,

On behalf of patients and families with cystic fibrosis (CF), we write to recommend Oregon Medicaid add lumacaftor/ivacaftor to the preferred drug list (PDL) for all cystic fibrosis patients age 6 years and older who have two copies of the *F508del* mutation in the CF gene per the Food and Drug Administration's (FDA) approved label. The FDA's label expansion to children age 6 years and older presents an opportunity to preserve health and lung function in these individuals and slow the progression of the disease. We are also writing with regard to the application of current reauthorization criteria to this expanded population.

About Cystic Fibrosis
Cystic fibrosis is caused by a genetic mutation resulting 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 that lead 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 120 care centers, including 2 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 extremely limited.

About lumacaftor/ivacaftor
Lumacaftor/ivacaftor is the only FDA-approved medication that improves the function of *CFTR* for individuals with the *F508del* mutation. Restricted access to this lifesaving therapy could result in severe and avoidable health consequences for CF patients. People with cystic fibrosis have a fundamental medical need for increased *CFTR* protein function.

The fixed dose combination therapy of lumacaftor and ivacaftor has been shown to improve airway surface liquid properties, reduce airway obstruction, and improve deficiencies in non-respiratory organ systems. Evidence shows significant improvements in lung function (FEV_1) as well as trends indicating a reduced rate of pulmonary exacerbations, increased body mass index (BMI), and improvement in patient-reported respiratory outcomes (CFQ-R). Furthermore, a post-approval study of cystic fibrosis patients treated with lumacaftor/ivacaftor showed a reduced rate of decline in lung function compared to controls.[1]

Initiation of lumacaftor/ivacaftor at an early age provides the greatest potential for an enduring health benefit and extended quality of life. Evidence of the beginnings of CF-related damage to the lungs has been observed in CF children studied within the first year of their lives, including air trapping, bronchial wall thickening, obstruction, and bronchiectasis.[2-5] By preserving lung function in children with FDA-indicated CFTR mutations, this modulating therapy can mitigate disease progression and may keep young people from experiencing costly hospitalizations, declining health status, deteriorating quality of life and premature death.

We understand the following initial authorization 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 this lifesaving therapy for patients that fall within the Food and Drug Administration's (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.

People with cystic fibrosis experience an average decline in lung function of 1-3% per year (CF Patient Registry, 2013). Even with exemplary treatment compliance on symptomatic therapies, lung infections are common and many patients experience chronic exacerbations requiring hospital visits, additional therapies, and treatment with antibiotics. For all patients with cystic fibrosis, but especially those with diminished FEV_1 values, seemingly modest increases in lung function can yield great benefits in health and quality of life. Thus, patients with FEV_1 values below 40% would experience the most significant clinical benefit. Phase 3 trial results indicated that patients with lung function below 40% actually demonstrated greater improvements in FEV_1 than the over 40% group.[6]

Additionally, ongoing studies have thus far not indicated safety concerns related to lung function, which is consistent with the FDA's decision to approve lumacaftor/ivacaftor without lung function limitations. It is critical for providers to closely monitor improvement and potential adverse effects for this subset of patients, but patients certainly should not be denied this lifesaving drug.

For individuals age 12 and older with FEV1 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.

14. 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 therefore do not address the underlying cause of cystic fibrosis. Moreover, it's critical to consider that inhaled therapies may not be well-tolerated by all patients and thus may not be incorporated into every patient's treatment regimen. Timely access to modulating therapies for individuals with the appropriate CFTR mutations should not be dependent upon the patient's use of symptomatic therapies.

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

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

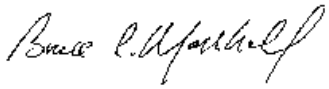
We are encouraged by the recognition in this renewal criteria that a number of clinical responses (maintenance of lung function, reductions in pulmonary exacerbations, or improvements in BMI) can indicate a response to therapy for different patients. However, we advise against the use of stringent measures due to the reality that they 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 given the progressive decline in lung function that characterizes this disease.[7]

Pulmonary exacerbations are intrinsically sporadic and unpredictable in an individual. Risk of pulmonary exacerbation is not uniformly distributed among CF patients.[8] Between 2009 and 2013, less than 25% of CF patients followed in the CF Foundation Patient Registry averaged more than 1 pulmonary exacerbation per year, and >50% had at least one calendar year in which no exacerbations occurred.[9] It is simply not scientifically 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.

We appreciate the committee's swift review of the expanded label and we stand ready to answer additional questions about these modulating therapies or cystic fibrosis treatment. Please contact Lisa Feng, MPH, Senior Director for Access Policy and Innovation, at lfeng@cff.org or 240-200-3792. We would be happy to connect you with local CF experts to further discuss this important issue.

Sincerely,



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

Lisa Feng, MPH
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