OHSU Healthcare

School of Medicine
Department of Pediatrics
Division of Pediatric Pulmonology &
Cystic Fibrosis

Mail code: CDRC-P
707 S.W. Gaines Street
Portland, OR 97239-3098
Tel. 503 494-8023
Fax 503 494-8898

Michael R. Powers, M.D.
*Professor and Division Head*
*CF Center & Pediatric Program Director*

Michael A. Wall, M.D.
*Professor Emeritus*

Holger W. Link, M.D.
*Clinical Associate Professor*
*Director, Sleep Education*

Kelvin D. MacDonald, M.D., R.R.T.
*Assistant Professor*
*Associate Director,*
*Cystic Fibrosis Center*

Danny Hsia, M.D.
*Assistant Professor*
*Medical Director,*
*Doernbecher Aerodigestive Center*

Alexandra Cornell, M.D.
*Assistant Professor*
*Associate Director,*
*Pediatric Cystic Fibrosis Center*

Ben McCullar, R.N.
*Cystic Fibrosis Clinical Coordinator*

Jessica Marks, R.N.
*Pulmonary Clinical Coordinator*

July 20, 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,

This letter details reasons I believe that Ivacaftor (Kalydeco) should be approved for CF patients with G551D or a similar gating mutations, for patients ages 2-5, in addition to the current approval for CF patients age 6 and older. Kalydeco has been approved by the FDA for ages 2-5 for patients with G551D and other gating mutations. However, this groundbreaking medication directed specifically at the underlying cause of his cystic fibrosis was not approved at the May meeting of the P and T Committee. I would like to provide supportive information detailing how, in my mind, it is not medically reasonable to deny this efficacious medication for a life-limiting disease until there is a decline in health and loss of lung function.

Kalydeco was first approved in 2012 by the FDA for CF patients 12 and older with G511D mutations and was hailed as the drug of the year by science magazine. This year President Obama used it as an example of personalized medicine for life limiting diseases in his State of the Union address. In 2013, the use of Kalydeco was expanded to include 6-11 year olds based on an efficacy and safety study (Am J Respir Crit Care Med Col 187, pp1219-1225, 2013). Due to the fact we now know that lung disease starts at birth, is observed on chest CT as early as one year of life, and over 80% of 5 year olds demonstrate significant bronchiectasis (Sly et al., et al. Am J Respir Crit Care Med 2009;180:146; Hall, et al. PLoS One. 2011;6:e23932), the drug was studied in 2-5 year olds in 2014. The results of the Kalydeco study in 2-5 year olds was presented in abstract form at the North American Conference of the Cystic Fibrosis Foundation in 2014 and this past June at the European Cystic Fibrosis Meeting. This study demonstrated safety, pharmacokinetics, and pharmacodynamics of Kalydeco in 2-5 year olds with gating mutations, including G551D. These data supported the approval of Kalydeco in this patient population earlier this year by the FDA.

I have prescribed Kalydeco for a 3 year old patient at our center without issues or complications; she has been on the medication for approximately 2 months. We anticipate this will lead to a dramatic change in her airway lining fluid composition and help prevent significant lung disease in the future. I have prescribed this game-changing medication for a 5 year old, which has been denied by Yamhill County CCO. I have sent a letter of appeal to the CCO. Two follow-up publications have demonstrated that Kalydeco is a disease-modifying drug over the long term, leading to a longer and healthier life. The first publication is from

the GOAL study, supported by the CF foundation and not Vertex, demonstrated a 50% reduction in hospitalizations and a reduction in the number of patients colonized with Pseudomonas aeruginosa from 50% to 35% (Am J Respir Crit Care Med, Vol 190, pp 175-184, Jul 15, 2014). A 2nd publication (e-pub: Sawicki G et al, AJRCCM in press) showed that there is a sustained benefit from Kalydeco by reducing a decline in lung function over a three-year period as compared to control. The disease-modifying drug therefore is life-sustaining since lung function is a surrogate for mortality in CF patients.

I implore the OHA P & T Committee to approve Kalydeco for children with Cystic Fibrosis that have the appropriate gating mutation. Kalydeco is efficacious, results in disease prevention, and is demonstrated to be a life-sustaining medication, directed at the underlying cause of CF, a defective chloride channel protein.

Sincerely,

Michael R. Powers
Professor of Pediatrics
Division Head, Pediatric Pulmonology
CF Center and Pediatric Program Director
CF Therapeutics Development Center Director
Department of Pediatrics
Doernbecher Children's Hospital
Oregon Health & Science University
powersm@ohsu.edu
Office: 503-494-8023
Fax: 503-494-8898

OHSU Healthcare

School of Medicine
Department of Pediatrics
Division of Pediatric Pulmonology & Cystic Fibrosis

Mail code: CDRC-P
707 S.W. Gaines Street
Portland, OR 97239-3098
Tel. 503 494-8023
Fax 503 494-8898

Michael R. Powers, M.D.
*Professor and Division Head*
*CF Center & Pediatric Program Director*

Michael A. Wall, M.D.
*Professor Emeritus*

Holger W. Link, M.D.
*Clinical Associate Professor*
*Director, Sleep Education*

Kelvin D. MacDonald, M.D., R.R.T.
*Assistant Professor*
*Associate Director,*
*Cystic Fibrosis Center*

Danny Hsia, M.D.
*Assistant Professor*
*Medical Director,*
*Doernbecher Aerodigestive Center*

Alexandra Cornell, M.D.
*Assistant Professor*
*Associate Director,*
*Pediatric Cystic Fibrosis Center*

Ben McCullar, R.N.
*Cystic Fibrosis Clinical Coordinator*

Jessica Marks, R.N.
*Pulmonary Clinical Coordinator*

HIV ALLIANCE

1966 Garden Avenue
Eugene OR 97403
541-342-5088 office
541-342-1150 fax

1034 Oak Street
Roseburg OR 97470
541-440-2761 office
541-440-9665 fax



www.hivalliance.org
twitter @HIVAlliance
facebook.com/HIVAlliance

United Way
United Way of Lane County

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

RE: P&T HIV Drug Class Review

Mr. Citron and Members of the P&T Committee:

I am writing on behalf of HIV Alliance and the people living with HIV/AIDS that we serve. HIV Alliance serves people living with HIV/AIDS in 11 counties in Oregon and in that region we are the only community based organization providing people with HIV testing, prevention education and supportive services. We are proud to be a partner in care with the Oregon Health Authority and CAREAssist.

We want to share with the Pharmacy and Therapeutics Committee the importance of access to HIV medications for those we serve. It is our understanding that the committee will review HIV drugs in all classes in an upcoming meeting. We strongly support access to early initiation of antiretroviral therapy (ART) for patients and the availability of all of the 2015 DHHS preferred regimens. For all people living with HIV, including those on Oregon Health Plan, access to medications is critical. Many patients face multiple diagnoses and limiting access to HIV medication can impact treatment for other conditions due to interactions. We are proud to serve in a state where access to HIV medication is comprehensive and we have seen the impact in lives saved and new infections prevented.

There are recent changes in guidelines regarding CD4 count and beginning ART. The current clinical guidelines from the National Institutes for Health[i] (NIH) recommend initiating antiretroviral therapy (ART) are:

- Patients with CD4 <350 cells/mm3
- Patients with CD4 counts between 350 – 500 cells/mm3
- All HIV infected individuals to prevent transmission

The publication of data from the Strategic Timing of Anti-Retroviral Treatment (START) study, presented at the 2015 International AIDS Society in Vancouver, BC offer compelling evidence to begin therapy immediately after diagnosis:

> *The "benefits of starting antiretroviral treatment immediately at CD4+ cell counts above 500 cells/mm3 outweigh the risks.*
>
> *Specifically, the DSMB found that over an average follow-up of three years, the risk of AIDS, other serious illnesses or death was reduced by 53 percent among those in the early treatment group compared to those in the deferred treatment group. In its review, the DSMB found 41 instances of AIDS, serious non-AIDS illness or death among those enrolled in the study's early treatment group compared to 86 such events in the deferred treatment group. These results indicate that starting anti-HIV treatment soon after diagnosis of HIV infection protects people's health."*[ii]

We understand that there has been a concern of black-market and counterfeit medications as referred to in the HIV Drug Review document drafted by Dr. Gibler. We share your concern for the safety and quality of all prescription medications, especially HIV therapies. We also agree that medications should be used only by the patients who they were prescribed for, in accordance with Federal and Oregon law. However, we have not seen any evidence that there is such a black market, nor have we heard similar concerns from any pharmacy or medical provider serving our clients.

With respect to the recommendations listed in the meeting materials and the results of the START Trial data, it is our opinion that the recommendations should include linking patients to care immediately after diagnosis and the early initiation of ART therapy which would include all of the 2015 DHHS preferred regimens. Access to medication partnered with adherence strategies has been proven to effectively reduce community viral load, improve health and reduce transmission of HIV.

Thank you for the opportunity to provide comments on this issue. Please contact me if we can be of assistance in this process.

Sincerely,

Renee Yandel

Executive Director

---

[i] *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* Initiating Antiretroviral Therapy in Treatment-Naive Patients (Last updated May 1, 2014; last reviewed May 1, 2014), Page 2 National Institutes of Health, Accessed July 2015
https://aidsinfo.nih.gov/contentfiles/lvguidelines/AA_Recommendations.pdf

[ii] QUESTIONS AND ANSWERS The START HIV Treatment Study
July 20, 2015 , National Institutes of Health, National Institutes of Allergy & Infectious Disease
http://www.niaid.nih.gov/news/QA/Pages/STARTqa.aspx, Accessed July 2015

July 24, 2015

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

[Submitted electronically to roger.a.citron@state.or.us on July 24, 2015]

Dear Mr. Citron,

On behalf of people with cystic fibrosis (CF) and their families, we write to express our extreme concern surrounding the recently published criteria for the coverage of ivacaftor (Kalydeco®). We appreciate and agree with your efforts to ensure that administration of ivacaftor is governed by scientific evidence. Based on review of the available evidence, the CF Foundation recommends that the Oregon Health Authority 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 including G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D; and for adult patients with the R117H mutation where the existing data show clear benefit. For pediatric patients with the R117H mutation, we recommend a manual review to determine whether the severity of disease manifestations support potential benefit. We believe these therapies should be started as soon as possible to prevent lung disease and that these criteria be consistently updated as new evidence emerges.

There is no alternative or substitute for ivacaftor. All other treatments address the symptoms of CF, not the underlying cause of the disease. For the small portion of the CF population for whom ivacaftor is indicated, it represents a "game-changing" therapy which preserves lung function, improves BMI, and is predicted to significantly extend the length of life. Further, long-term studies have shown reductions in pulmonary exacerbations and hospitalizations for patients treated with ivacaftor (Ramsey, et al. N Engl J Med 2011;365:1663-1672). Waiting for other treatments to fail serves only to delay the use of ivacaftor and to delay its benefit in protecting lung function.

*About Cystic Fibrosis*

As you know, CF 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 CF 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. Because the absence of CFTR function leads to an early death, it is medically necessary for people with CF to receive a medication that will improve the function of their CFTR protein to reduce the

pulmonary and digestive symptoms of CF and to reduce or halt the irreversible loss of lung capacity.

*Proposed Coverage Criteria & Summary of Efficacy*
Ivacaftor is the first therapy for CF that addresses the basic inherited defect that causes the disease. All other treatments address the symptoms and clinical implications of CF and have contributed to improvements in the length and quality of life for those with this disease. But all of those treatments ultimately "fail" and individuals taking those treatments experience an irreversible progression in their disease and premature death.

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. 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). 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 and premature death. It is not medically reasonable or responsible to withhold an effective treatment until the patient suffers a permanent and irreversible decline in health and loss of lung function.

We understand the following coverage criteria are required for the use of ivacaftor and strongly urge you to consider the following recommendations:

***Authorization criteria (valid for 30 days); 6 month Reauthorization Period***

There is no clinically effective method to demonstrate statistically significant lung function decline within 30 days due to the nature of CF and inherent variability of lung function testing. $FEV_1$, as measured by spirometry, is such that accurate regression to determine a rate of $FEV_1$ change over time requires use of measures collected over more than a year (Konstan, et al. J Cyst Fibros 2010:9;332-338). Therefore, we suggest increasing the initial authorization period to at least a minimum of 90 days to see a significant benefit with a subsequent annual reauthorization process.

***Does the patient have a documented G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene detected by an FDA-cleared CF mutation test?***

Please clarify for clinicians what constitutes an FDA-cleared CF mutation test. Also, it is important to note that because R117H patients have residual function they are different from patients with gating mutation. There is evidence of meaningful clinical benefit for a subset of adults with the R117H mutation, as well as a subset of children with the R117H mutation who have evidence of established disease; these individuals should have access to ivacaftor.

***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 (<6y/o) and normal lung function: Dornase alfa AND Hypertonic saline, AND Inhaled or oral antibiotics (if appropriate)?***

Access to modulating therapies like ivacaftor for individuals with the appropriate CFTR mutations should not be dependent upon the patient's use of symptomatic therapies. The mechanism of action for these types of therapies are fundamentally different as ivacaftor targets the underlying defect of cystic fibrosis. Moreover, it's critical to consider that inhaled therapies in general may not be well-tolerated by all patients and thus may not be incorporated into every patient's treatment regimen.

Analysis of the long-term efficacy of ivacaftor has shown that this modulator therapy has a marked impact on the disease trajectory (Sawicki, et al. Am J of Respir Crit Care Med). In order to assess the long-term benefits of ivacaftor, researchers compared data from patients who received ivacaftor in the phase 3 clinical trials and an open-label extension for up to 144 weeks with data from a carefully matched, pre-specified "control" group with a similarly severe genotype (F508 del homozygotes) from the CF Foundation patient registry data. Previous work has shown that this control group is expected to have a similar rate of decline as a group of untreated G551D patients (McKone, et al. *Lancet.* 2003;361:1671-6). Over the three-year period of the study, the rate of lung function decline in ivacaftor-treated patients was slower by nearly half. Moreover, researchers found that treatment with ivacaftor improved BMI and WFA scores over the three-year period. It is therefore critical that patients begin treatment with ivacaftor as soon as possible, as damage (lung, pancreatic insufficiency) is permanent and irreversible once it has occurred.

***Does the patient have documented response to therapy as defined as: Sweat chloride test below 60 mmol/L or decreased by 30% if the baseline was less than 60 mmol/L OR Lack of decline in $FEV_1$?***

We agree that the magnitude of sweat chloride change does not correlate with or predict the extent of ivacaftor's response on lung function. However, a sweat chloride response *does* indicate that the drug is having a physiologic effect on CFTR, the pharmacologic target of ivacaftor, in a given patient. Thus, we agree that change in sweat chloride could be included as evidence of ivacaftor response, but note that there is no scientific/medical basis for establishing an arbitrary threshold of reduction below 60 mmol/L or a 30% decline as indicative of 'response'.

Additionally, it is simply not feasible nor scientifically sound to show a lack of decline in $FEV_1$ in 30 days – exacerbations are sporadic, and there is variability in $FEV_1$, particularly for young patients. The inherent variability of $FEV_1$ as measured by spirometry is such that accurate regression to determine a rate of $FEV_1$ change over time requires use of measures collected over more than a year (Konstan, et al J Cyst Fibros 2010:9;332-338). There is also the question of what constitutes the patient's baseline and whether a patient would be excluded from access to the drug for life based on one $FEV_1$ test.

***Does the patient have documented response to therapy as defined below?***
***For patients ≥ 6 y/o:***

- ***A sustained absolute improvement in FEV1 of ≥5%, OR***

- ***A reduction in the incidence of pulmonary exacerbations by 50%***

***For patients 2-5 y/o (cannot complete lung function tests)***

- ***Significant improvement in BMI, OR***
- ***Improvement in exacerbation frequency or severity***

***If no improvement in either of the above, repeat sweat chloride test:***

- ***Sweat chloride test below 60 mmol/L or decreased by 30% IF the baseline was less than 60 mmol/L***

We advise against the use of these stringent measures due to the reality that these are often impacted by many factors outside of the patient's control. For example, should the patient contract severe influenza or another illness, this could significantly impact lung function, weight, and pulmonary exacerbations regardless of consistent use of ivacaftor. Furthermore, 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 (Sawicki, et al. Am J of Respir Crit Care Med).

All people with CF suffer a decline in lung function even with the best standard of care. The average annual $FEV_1$ decline is approximately 2% over the course of the patient's lifetime. Ivacaftor slows the rate of decline, but age and other factors will cause an inevitable drop in $FEV_1$ over time. Therefore, maintaining lung function and preventing lung damage is as important as improving lung function. Modulators like ivacaftor can prevent permanent, irreversible damage among people with CF, but cannot correct damage that has already occurred. Prevention is critical. Modulating therapies should be delivered to eligible patients at the earliest opportunity to halt further decline and to preserve current health.

Pulmonary exacerbations are intrinsically sporadic and unpredictable in an individual. Risk of pulmonary exacerbation is not uniformly distributed among CF patients (VanDevanter, et al. J Cyst Fibros 2015 Mar 5. pii: S1569-1993(15)00047-8.). Between 2009 and 2013, less than 25% of CF patients followed in the CF Foundation Patient Registry (CFFPR) averaged more than 1 pulmonary exacerbation per year, and >50% had at least one calendar year in which no exacerbations occurred (CFFPR data on file). It is simply not scientifically valid to take an arbitrary time interval such as 6 months and apply this to an individual patient as a one-time criterion for demonstrating benefit. Such a strategy is not justified by scientific evidence, epidemiological studies, or the natural course of disease.

The requirements to demonstrate a reduction in exacerbations of 50% or greater to retain access to treatment is scientifically unsound. These patients have a potential to respond dramatically to ivacaftor that is independent of their exacerbation risk. In addition, for children at higher risk for exacerbation, there is no recognized method to measure the 'severity' of a pulmonary exacerbation. For this reason, there is no justification for use of change in exacerbation *severity* as an indication of treatment response.

It is important to note that for an individual patient the requirement for a "significant" improvement in BMI is inappropriate; rather, the criterion should be altered to require an improvement in BMI from baseline.

Again, we note that the 60 mmol/L and 30% thresholds for a reduction in sweat chloride levels are not appropriate and should be revised.

***Has the patient been compliant with therapy, as determined by refill claims history?***

People who are struggling with complicated regimens should not be excluded from receiving life-saving treatments, and care providers are best-positioned to understand the nuances associated with adherence in CF and work with patients to improve adherence. Imperfect adherence should not preclude a patient's ability to gain access to this lifesaving therapy indefinitely.

Further, compliance with symptomatic therapies is not necessarily indicative or predictive of adherence to modulator therapy.

***If within first year of treatment, are liver function tests (AST/ALT) within normal limits in the past 3 months? If after 1 year of treatment, are liver function tests (AST/ALT) within normal limits in past 1 year?***

The CF Foundation agrees that liver enzyme tests should be administered to establish a baseline and at certain intervals during administration of ivacaftor. This recommendation is also consistent with FDA labeling. However, LFTs are intrinsically variable and elevations are seen as part of disease pathogenesis. Thus this decision should rest upon long-term evaluation of LFT's by the treating physician and clinical assessment as to the risk of liver damage versus benefit of treatment. If LFT criteria are to be used, they should take into account their fluctuating nature and be based on multiple or serial tests.

The CF Foundation recommends that the Oregon Health Authority 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 including G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D; and for adult patients with the R117H mutation where the data shows benefit. For pediatric patients with the R117H mutation, we recommend a manual review to determine disease manifestation and potential benefit.

We stand ready to answer additional questions about ivacaftor. Please contact Lisa Feng, Senior Director of Coverage and Reimbursement Policy, 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,

Preston W. Campbell, III, M.D.
Executive Vice President for Medical Affairs

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

July 20, 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,

Thank you for the opportunity to communicate with you regarding the use of ivacaftor (Kalydeco) for cystic fibrosis (CF) patients who carry the R117H mutation. As you are aware, Kalydeco has been approved for CF patients with G551D and other gating mutations as well as for the R117H mutation. The medication is considered a ground-breaking advance in CF care based on the initial studies with the G551D mutation published in the New England Journal of Medicine in 2011 (New England Journal of Medicine, Vol 365, pp 1663-72, November 3, 2011). This mutation results in a gating defect the chloride channel which results in the underlying problem with cystic fibrosis. Because the R117H mutation has a gating defect (in addition to a conductance issue), it followed that Kalydeco could be a useful medication for this patient population.

The R117 group, however, poses a greater challenge to study than the G551D group, primarily because the number of patients affected. In the landmark NEJM paper with the G551D group, there were 161 total patients enrolled in the clinical trial. In the recent KONDUCT study with R117H patients, there were fewer than half (69) the patients enrolled (Lancet Respir Med, 3(7) pp 524-33; June 10, 2015). Second, the R117H group is a heterogeneous group of patients based on the number of poly-thymidine (poly-T) residues that are present in intron 8 of the CFTR gene. We know that the fewer the number of poly-T residues (e.g. 5T as opposed to 7T or 9T), the greater the chance for advanced CF lung disease (Am J Respir Crit Care Med; Vol 162, pp 1919-24, November 2000). Thus, within an already small population of R117H patients, there are subsets of patients that behave differently. Though on average, the R117H population has milder disease than the typical CF patient with 2 severe mutations, the 5T patient population has the capacity to have "traditional" CF lung disease.

We acknowledge that the outcome of the KONDUCT study was a negative study with respect to change in FEV1 % predicted when all patients are taken into account together. However, a deeper dive into the data indicates there are subpopulations of patients for which the patient has a clinical response. In reviewing the data, 2 patient populations emerge as benefactors from Kalydeco: patient > 18 years old and those with the 5T mutation.

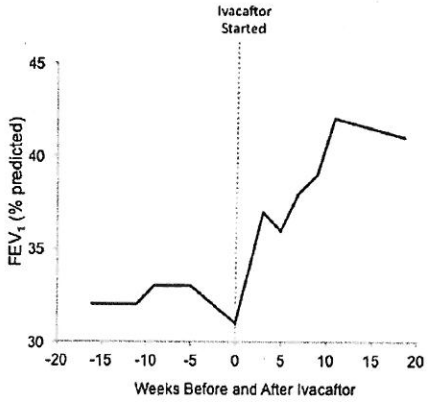
| | | Absolute Change through Week 24[a] - All Randomized Patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | % Predicted $FEV_1$ (Percentage Points) | | | CFQ-R Respiratory Domain Score (Points) | | | Sweat Chloride (mmol/L) | | |
| Subgroup Parameter | Study Drug | n | Mean | Treatment Difference (95% CI) | n | Mean | Treatment Difference (95% CI) | n | Mean | Treatment Difference (95% CI) |
| *Subgroup by Poly-T Status*[b] | | | | | | | | | | |
| 5T | placebo<br>ivacaftor | 24<br>14 | 0.7<br>6.0 | 5.3<br>(1.3, 9.3) | 24<br>14 | −0.6<br>14.7 | 15.3<br>(7.7, 23.0) | 24<br>13 | −4.6<br>−28.7 | −24.2<br>(−30.2, −18.2) |
| 7T | placebo<br>ivacaftor | 5<br>11 | −0.9<br>−0.7 | 0.2<br>(−8.1, 8.5) | 5<br>11 | −6.0<br>−0.7 | 5.2<br>(−13.0, 23.4) | 5<br>10 | 3.9<br>−20.2 | −24.1<br>(−33.9, −14.3) |

| | | Absolute Change through Week 24[a] - All Randomized Patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | % Predicted $FEV_1$ (Percentage Points) | | | CFQ-R Respiratory Domain Score (Points) | | | Sweat Chloride (mmol/L) | | |
| Subgroup Parameter | Study Drug | n | Mean | Treatment Difference (95% CI) | n | Mean | Treatment Difference (95% CI) | n | Mean | Treatment Difference (95% CI) |
| **Age** | | | | | | | | | | |
| >18 | placebo | 26 | −0.5 | 5.0 | 26 | −0.5 | 12.6 | 26 | −4.0 | −21.9 |
| | ivacaftor | 24 | 4.5 | (1.1, 8.8) | 24 | 12.2 | (5.0, 20.3) | 23 | −25.9 | (−26.5, −17.3) |

Lung function clearly improved in these subgroups. Symptoms were also significantly improved using the validated CFQ-R questionnaire for which a change of 4 is considered clinically significant. The changes seen in the 5T and adult groups were 15.3 and 12.6, respectively, which are actually a *greater* effect than that observed for Kalydeco and the G551D mutation. The sweat chloride values also changed significantly, though we acknowledge the change in sweat chloride does not always correlate with change in lung function. It does, however, buttress the argument that Kalydeco has on impact on chloride transport for R117H patients, which is the underlying defect in CF.

Based on these results, I believe Kalydeco should be approved for CF patients with R117H who carry the 5T mutation and for patients > 18 years old. I believe there is both biologic plausibility and clinical evidence of meaningful efficacy. I feel the negative study was a failure of patient enrollment (small numbers) and heterogeneity of the study population rather than a failure of the medication.

Finally, I would like to reference a case report of an R117H adult patient with the 5T variant who was put on Kalydeco (Journal of Cystic Fibrosis Vol 14, pp e4-e5, February 16, 2015). In the 2 years prior to being placed on Kalydeco in February 2014, he had > 6 exacerbations per year resulting in the use of IV and oral antibiotics. He was assessed and deemed appropriate to be placed on the lung transplant wait list. His lung function was considered severe, with an FEV1 predicted of 31%. After 5 months on Kalydeco, his weight increased by 4.3 kg and lung function increased up to 42% (see image below). He was taken off the transplant list because of the clinical effect seen with Kalydeco.




We believe this information supports the use of Kalydeco in specific CF patients with the R117H mutation. The CF center agrees with judicious use of state resources and is on board with partnering with state agencies to place these resources for patients who will be helped the most.

Thank you,

Gopal Allada MD
Associate Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Department of Internal Medicine
Oregon Health and Science University
Director, Adult Cystic Fibrosis program
Director, Pulmonary Clinic
Portland, OR 97239
alladag@ohsu.edu
Pulmonary Office: 503-494-2284
Pulmonary Fax: 503-494-6670

p 503 775 3497
10117 SE Sunnyside Rd.
Suite F-408
Clackamas, OR 97015

one in four
chronic health

a voice for patients
1in4.org

July 30,2015

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

RE: P&T HIV Drug Class Review

Mr. Citron and Members of the P&T Committee:

We are jointly writing to the Committee on behalf of Oregonians living with HIV/AIDS. The organizations listed below are committed to protecting access to life sustaining therapies for people living with HIV/AIDS.

We would lie to share some concerns about the upcoming June 30th P&T HIV Drug Class Review. We are curious why you have made the decision to review this class now, when no new therapies have been approved. Are there considerations to implement changes or restriction to medication access?

The meeting materials present a concise explanation of HIV pathogenesis and treatment, however there is a discrepancy between the initiation of antiretroviral therapy (ART) and CD4 count. You cite JAMA and International Antiviral Society[i]

The current clinical guidelines from the National Institutes for Health[ii] (NIH) recommend initiating antiretroviral therapy (ART) are:

- Patients with CD4 <350 cells/mm3
- Patients with CD4 counts between 350 – 500 cells/mm3
- All HIV infected individuals to prevent transmission

p 503 775 3497
10117 SE Sunnyside Rd.
Suite F-408
Clackamas, OR 97015

one in four
chronic health

a voice for patients
1in4.org

The publication of data from the Strategic Timing of AntiRetroviral Treatment (START) study, presented at the 2015 International AIDS Society in Vancouver, BC offer compelling evidence to begin therapy immediately after diagnosis:

> *The "benefits of starting antiretroviral treatment immediately at CD4+ cell counts above 500 cells/mm3 outweigh the risks.*

> *Specifically, the DSMB found that over an average follow-up of three years, the risk of AIDS, other serious illnesses or death was reduced by 53 percent among those in the early treatment group compared to those in the deferred treatment group. In its review, the DSMB found 41 instances of AIDS, serious non-AIDS illness or death among those enrolled in the study's early treatment group compared to 86 such events in the deferred treatment group. These results indicate that starting anti-HIV treatment soon after diagnosis of HIV infection protects people's health."*[iii]

We are also concerned about the misleading language on page six of the meeting materials:

> *Other, non-clinical challenges also exist. Recently the Community Access National Network (CANN), a group that supports access to HIV care, and the Partnership for Safe Medicines, a non-profit organization targeting counterfeit medication, published a document alerting clinicians and patients to evidence that HIV medications are being resold illegally. In some cases, counterfeit medications were sold to patients or pharmacies; in other cases, fraudulently acquired medications were repackaged and sold to pharmacies.*

It is our experience, and the experience of the HIV providers we represent, that the claim of counterfeit medications and illegal resale of HIV medications is not validated by our providers or pharmacists we work with. Further, the source (cited for this data) does not cite the claims they have made in their publication, *Black Market HIV/AIDS Drug*[iv]*s*. The lack of any evidence to support their claim raises serious doubt to the validity of their information.

We share your concern for the safety and quality of all prescription medications, especially HIV therapies. We also agree that medications be used only by the patients who they were prescribed for, in accordance with Federal and Oregon law.

p 503 775 3497

10117 SE Sunnyside Rd.
Suite F-408
Clackamas, OR 97015

one in four
chronic health

a voice for patients
1-in-4.org

With respect to the recommendations listed in the meeting materials and the results of the START Trial data, it is our opinion that the recommendations should include linking patients to care immediately after diagnosis and the initiation of ART therapy. This should be followed by improved adherence strategies and monitoring of community viral load burden and the use of ART treatment as prevention.

Thank you for the opportunity to provide comments on this issue. Should you have any questions, please contact BJ Cavnor at 206/601-8453 or via email; BJ@1-in-4.org .

Sincerely,

BJ Cavnor
Executive Director,
One in Four Chronic Health
Portland, OR

William McColl
Director of Health Policy,
AIDS United
Washington, DC

David Evans
Project Inform
Director of Research Advocacy,
San Francisco, CA

Shelly J. Bailey
Central Drugs Pharmacy
Portland, OR

References

[i] Günthard H, Aberg J, Eron J, et al. *Antiretroviral treatment of adult HIV-1 infection: 2014 recommendations of the International Antiviral Society* - USA Panel. *JAMA*. 2014;312:410-425. doi:10.1001/jama.2014.8722.

[ii] *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and* https://aidsinfo.nih.gov/contentfiles/lvguidelines/AA_Recommendations.pdf

[iii] *QUESTIONS AND ANSWERS The START HIV Treatment Study* July 20, 2015 , National Institutes of Health, National Institutes of Allergy & Infectious Disease http://www.niaid.nih.gov/news/QA/Pages/STARTqa.aspx, Accessed July 2015

[iv] *Black Market HIV/AIDS Drugs in the News*, 2006 - 2013 http://www.tiicann.org, Accessed July 2015

HIV ALLIANCE

1966 Garden Avenue
Eugene OR 97403
541-342-5088 office
541-342-1150 fax

1034 Oak Street
Roseburg OR 97470
541-440-2761 office
541-440-9665 fax



www.hivalliance.org
twitter @HIVAlliance
facebook.com/HIVAlliance

United Way of Lane County

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

RE: P&T HIV Drug Class Review

Mr. Citron and Members of the P&T Committee:

I am writing on behalf of HIV Alliance and the people living with HIV/AIDS that we serve. HIV Alliance serves people living with HIV/AIDS in 11 counties in Oregon and in that region we are the only community based organization providing people with HIV testing, prevention education and supportive services. We are proud to be a partner in care with the Oregon Health Authority and CAREAssist.

We want to share with the Pharmacy and Therapeutics Committee the importance of access to HIV medications for those we serve. It is our understanding that the committee will review HIV drugs in all classes in an upcoming meeting. We strongly support access to early initiation of antiretroviral therapy (ART) for patients and the availability of all of the 2015 DHHS preferred regimens. For all people living with HIV, including those on Oregon Health Plan, access to medications is critical. Many patients face multiple diagnoses and limiting access to HIV medication can impact treatment for other conditions due to interactions. We are proud to serve in a state where access to HIV medication is comprehensive and we have seen the impact in lives saved and new infections prevented.

There are recent changes in guidelines regarding CD4 count and beginning ART. The current clinical guidelines from the National Institutes for Health[i] (NIH) recommend initiating antiretroviral therapy (ART) are:

- Patients with CD4 <350 cells/mm3
- Patients with CD4 counts between 350 – 500 cells/mm3
- All HIV infected individuals to prevent transmission

The publication of data from the Strategic Timing of Anti-Retroviral Treatment (START) study, presented at the 2015 International AIDS Society in Vancouver, BC offer compelling evidence to begin therapy immediately after diagnosis:

> *The "benefits of starting antiretroviral treatment immediately at CD4+ cell counts above 500 cells/mm3 outweigh the risks.*
>
> *Specifically, the DSMB found that over an average follow-up of three years, the risk of AIDS, other serious illnesses or death was reduced by 53 percent among those in the early treatment group compared to those in the deferred treatment group. In its review, the DSMB found 41 instances of AIDS, serious non-AIDS illness or death among those enrolled in the study's early treatment group compared to 86 such events in the deferred treatment group. These results indicate that starting anti-HIV treatment soon after diagnosis of HIV infection protects people's health."*[ii]

We understand that there has been a concern of black-market and counterfeit medications as referred to in the HIV Drug Review document drafted by Dr. Gibler. We share your concern for the safety and quality of all prescription medications, especially HIV therapies. We also agree that medications should be used only by the patients who they were prescribed for, in accordance with Federal and Oregon law. However, we have not seen any evidence that there is such a black market, nor have we heard similar concerns from any pharmacy or medical provider serving our clients.

With respect to the recommendations listed in the meeting materials and the results of the START Trial data, it is our opinion that the recommendations should include linking patients to care immediately after diagnosis and the early initiation of ART therapy which would include all of the 2015 DHHS preferred regimens. Access to medication partnered with adherence strategies has been proven to effectively reduce community viral load, improve health and reduce transmission of HIV.

Thank you for the opportunity to provide comments on this issue. Please contact me if we can be of assistance in this process.

Sincerely,

Renee Yandel

Executive Director

---

[I] *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* Initiating Antiretroviral Therapy in Treatment-Naive Patients (Last updated May 1, 2014; last reviewed May 1, 2014), Page 2 National Institutes of Health, Accessed July 2015
https://aidsinfo.nih.gov/contentfiles/lvguidelines/AA_Recommendations.pdf

[II] QUESTIONS AND ANSWERS©The START HIV Treatment Study
July 20, 2015 , National Institutes of Health, National Institutes of Allergy & Infectious Disease
http://www.niaid.nih.gov/news/QA/Pages/STARTqa.aspx, Accessed July 2015

NPAF National Patient Advocate Foundation

The Patient's Voice | since 1996

July 29, 2015

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

RE: P&T HIV Drug Class Review

Mr. Citron and Members of the P&T Committee:

The National Patient Advocate Foundation is a national non-profit organization providing the patient voice in improving access to, high-quality healthcare through regulatory and legislative reform at the state and federal levels. We work with individuals facing barriers to healthcare access for chronic and disabling disease, medical debt crisis and employment-related issues at no cost. We at NPAF expect to have helped our 1 millionth patient in 2016.

We are writing the Committee on behalf of Oregonians living with HIV/AIDS. We would lie to share some concerns about the upcoming June 30th P&T HIV Drug Class Review.

The meeting materials present a concise explanation of HIV pathogenesis and treatment, however there is a discrepancy between the initiation of antiretroviral therapy (ART) and CD4 count. The current clinical guidelines from the National Institutes for Health[i] (NIH) recommend initiating antiretroviral therapy (ART) are:

- Patients with CD4 <350 cells/mm3
- Patients with CD4 counts between 350 – 500 cells/mm3
- All HIV infected individuals to prevent transmission

The publication of data from the Strategic Timing of AntiRetroviral Treatment (START) study, presented at the 2015 International AIDS Society in Vancouver, BC offer compelling evidence to begin therapy immediately after diagnosis:

> *The "benefits of starting antiretroviral treatment immediately at CD4+ cell counts above 500 cells/mm3 outweigh the risks.*
>
> *Specifically, the DSMB found that over an average follow-up of three years, the risk of AIDS, other serious illnesses or death was reduced by 53 percent among*

NPAF National Patient Advocate Foundation

The Patient's Voice | since 1996

*those in the early treatment group compared to those in the deferred treatment group. In its review, the DSMB found 41 instances of AIDS, serious non-AIDS illness or death among those enrolled in the study's early treatment group compared to 86 such events in the deferred treatment group. These results indicate that starting anti-HIV treatment soon after diagnosis of HIV infection protects people's health."*[II]

We share your concern for the safety and quality of all prescription medications, especially HIV therapies. We also agree that medications be used only by the patients who they were prescribed for, in accordance with Federal and Oregon law.

With respect to the recommendations listed in the meeting materials and the results of the START Trial data, it is our opinion that the recommendations should include linking patients to care immediately after diagnosis and the initiation of ART therapy. This should be followed by improved adherence strategies and monitoring of community viral load burden and the use of ART treatment as prevention.

Thank you. We look forward to continued discussion on these important issues.

Sincerely,

Sheila Stickel, NPAF
Regional Field Director, Western States
National Patient Advocate Foundation
sheila.stickel@npaf.org

---

[I] *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* Initiating Antiretroviral Therapy in Treatment-Naive Patients (Last updated May 1, 2014; last reviewed May 1, https://aidsinfo.nih.gov/contentfiles/lvguidelines/AA_Recommendations.pdf

[II] QUESTIONS AND ANSWERS The START HIV Treatment Study
July 20, 2015 , National Institutes of Health, National Institutes of Allergy & Infectious Disease
http://www.niaid.nih.gov/news/QA/Pages/STARTqa.aspx, Accessed July 2015

Cascade AIDS Project CAP

July 24, 2015

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

RE: P&T HIV Drug Class Review

Mr. Citron and Members of the P&T Committee:

I am writing on behalf of Cascade AIDS Project (CAP) and the people living with HIV/AIDS who we serve. CAP is the largest community based organization providing people with HIV testing, prevention, education and supportive services in Oregon. We are proud to be a partner in care with the Oregon Health Authority and CAREAssist.

Recent changes have occurred in guidelines regarding CD4 count and beginning antiretroviral therapy (ART). The current clinical guidelines from the National Institutes for Health[i] (NIH) recommend initiating antiretroviral therapy (ART) are:

- Patients with CD4 <350 cells/mm3
- Patients with CD4 counts between 350 – 500 cells/mm3
- All HIV infected individuals to prevent transmission

The publication of data from the Strategic Timing of AntiRetroviral Treatment (START) study, presented at the 2015 International AIDS Society in Vancouver, BC, offer compelling evidence to begin therapy immediately after diagnosis:

> *The "benefits of starting antiretroviral treatment immediately at CD4+ cell counts above 500 cells/mm3 outweigh the risks.*
>
> *Specifically, the DSMB found that over an average follow-up of three years, the risk of AIDS, other serious illnesses or death was reduced by 53 percent among those in the early treatment group compared to those in the deferred treatment group. In its review, the DSMB found 41 instances of AIDS, serious non-AIDS illness or death among those enrolled in the study's early treatment group compared to 86 such events in the deferred treatment group. These results indicate that starting anti-HIV treatment soon after diagnosis of HIV infection protects people's health."*[ii]



208 Southwest Fifth Avenue, Suite 800 Portland, Oregon 97204

t › 503 223 5907
f › 503 223 6437
cascadeaids.org

The claim of black-market and counterfeit medications referred to in the meeting materials is one not supported by our experience, nor any of the HIV specialty providers and pharmacists we work with.

> *"Other, non-clinical challenges also exist. Recently the Community Access National Network (CANN), a group that supports access to HIV care, and the Partnership for Safe Medicines, a non-profit organization targeting counterfeit medication, published a document alerting clinicians and patients to evidence that HIV medications are being resold illegally. In some cases, counterfeit medications were sold to patients or pharmacies; in other cases, fraudulently acquired medications were repackaged and sold to pharmacies."*

Further, the source cited for this data does not cite the claims they have made in their publication, *Black Market HIV/AIDS Drug*[iii]*s*. The lack of any evidence to support their claim raises serious doubt to the validity of their information.

We share your concern for the safety and quality of all prescription medications, especially HIV therapies. We also agree that medications be used only by the patients who they were prescribed for, in accordance with Federal and Oregon law.

With respect to the recommendations listed in the meeting materials and the results of the START Trial data, it is our opinion that the recommendations should include linking patients to care immediately after diagnosis and the initiation of ART therapy. This should be followed by improved adherence strategies and monitoring of community viral load burden and the use of ART treatment as prevention.

Thank you for the opportunity to provide comments on this issue.

Sincerely,

Tyler TerMeer
Executive Director
Cascade AIDS Project

Sincerely,

Robert Lusk, MD
President, Board of Directors
Cascade AIDS Project

---

[i] *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* Initiating Antiretroviral Therapy in Treatment-Naive Patients (Last updated May 1, 2014; last reviewed May 1, 2014), Page 2 National Institutes of Health, Accessed July 2015
https://aidsinfo.nih.gov/contentfiles/lvguidelines/AA_Recommendations.pdf

[ii] QUESTIONS AND ANSWERS The START HIV Treatment Study
July 20, 2015 , National Institutes of Health, National Institutes of Allergy & Infectious Disease
http://www.niaid.nih.gov/news/QA/Pages/STARTqa.aspx, Accessed July 2015

[iii] Black Market HIV/AIDS Drugs in the News, 2006 - 2013
http://www.tlicann.org, Accessed July 2015