

November 18, 2008

Andrew von Eschenbach, M.D.  
Commissioner  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Dear Dr. von Eschenbach:

The Cystic Fibrosis Foundation is deeply concerned about the Food and Drug Administration (FDA)'s decision to require further clinical trials for Gilead Sciences' Aztreonam Lysine for Inhalation (AZLI). **We respectfully urge senior leadership at the FDA to promptly reconsider the drug application from Gilead Sciences.** The CF Foundation believes that the published clinical trial results support the efficacy of AZLI in the CF population. Combined with evidence of the drug's safety and the patients' significant unmet medical needs, we believe this creates a compelling case for AZLI's approval using existing data.

Cystic fibrosis (CF) is a life-threatening, orphan disease that affects 30,000 people in the U.S and warrants unique attention from the FDA. The disease primarily affects children and adolescents; the median age of the CF population in the U.S. is only 16 years, and the median age of death in 2007 was 26 years.<sup>i</sup> There is an immediate unmet medical need for more than one inhaled antibiotic to treat the most deadly complication of the disease – serious lung infections.

Currently, only one antibiotic for inhalation, TOBI<sup>®</sup>, is FDA-approved and available to CF patients. Although TOBI<sup>®</sup> has been a significant therapy for CF, it can only be used for a 28-day course. Patients must wait another 28-day cycle before taking another course of this aerosol antibiotic. During the 28-day interval without TOBI<sup>®</sup>, there is no FDA approved inhaled antibiotic to meet the patients' medical needs. Further, one third of all CF patients do not use TOBI<sup>®</sup>, including those who do not tolerate the medicine. For these patients, there is no FDA-approved inhaled antibiotic to meet their medical needs. Given these limitations for treatment with TOBI<sup>®</sup>, it is clear that FDA approval of additional inhaled antibiotics would fulfill an unmet medical need. More information on the community's unmet medical needs is found in the CF Foundation's white paper (enclosed).

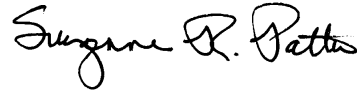
While we are pleased that Gilead Sciences is continuing its expanded access program, the program has only enrolled 300 patients. This only meets the needs of one percent of the CF patient population. The program is not large enough to help the nearly 23 percent of CF patients with severe lung function (with FEV1 < 40%).<sup>ii</sup> Severely compromised lung function is a highly significant prognostic indicator of mortality.

On behalf of patients with CF in the U.S., we appreciate FDA's prompt reconsideration of AZLI. The CF Foundation stands ready to work with you to address any questions you may have about CF and the unmet medical needs.

Sincerely,



Robert J. Beall, Ph.D.  
President and CEO



Suzanne R. Pattee, J.D.  
Vice President, Regulatory and Patient Affairs

CC: Janet Woodcock, M.D.  
Robert Temple, M.D.  
Douglas Throckmorton, M.D.

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<sup>i</sup> Cystic Fibrosis Foundation Patient Registry. 2007 Annual data report to the Center Directors. Bethesda, Maryland. © 2008.

<sup>ii</sup> Cystic Fibrosis Foundation Patient Registry. 2007 Annual data report to the Center Directors. Bethesda, Maryland. © 2008.

## **Cystic Fibrosis Foundation Requests FDA Reconsideration of Aztreonam Lysine for Inhalation Application to Fill Unmet Medical Needs for People with Cystic Fibrosis**

Cystic fibrosis (CF) is a progressive, life-threatening, genetic disease affecting about 30,000 Americans. The major cause of morbidity and eventual death among individuals with CF is from pulmonary disease. Chronic infections with resistant bacteria lead to progressive deterioration of the lungs, resulting in decreased lung function and death. Despite aggressive use of antibiotics by oral and intravenous administration, the benefits of inhaled antibiotics are an essential component to this regimen.

To date, only two FDA-approved therapies are available which were specifically developed to treat CF pulmonary symptoms, including lung infections: Pulmozyme<sup>®</sup> (a treatment that thins mucus in the lungs) and TOBI<sup>®</sup> (inhaled tobramycin). There is an immediate, unmet medical need for more treatments for CF lung infections that can continue to improve the health and longevity of people with CF. The CF Foundation urges senior leadership at the FDA to promptly reconsider the drug application from Gilead Sciences for Aztreonam Lysine for Inhalation (AZLI).

### **Unmet Medical Need for FDA Approved Inhaled Antibiotics**

Patients with CF need access to new antibiotics approved for use by inhalation. Chronic infection with the bacteria, *Pseudomonas aeruginosa*, in persons with CF is associated with a higher risk for accelerated disease progression and early death. These outcomes are believed to be mediated by a prolonged innate host immune response that irreversibly damages lung tissue. A vast majority (>80%) of deaths in people with CF is due to loss of pulmonary function.<sup>i</sup>

Only one inhaled antibiotic—TOBI<sup>®</sup>—is approved by FDA. The CF community has seen significant improvements in health over the past decade following the FDA approval of TOBI<sup>®</sup>. Yet, TOBI<sup>®</sup> alone is not sufficient to meet the medical needs of all CF patients for several reasons.

First, TOBI<sup>®</sup> can only be used for a 28-day course with a break of 28 days before it can be used again. Because there is only one FDA approved inhaled antibiotic, there is an immediate, unmet medical need for a second product to fill the gaps in the CF therapeutic regimen. There also is no FDA approved inhaled antibiotic available to meet patients' medical needs during the 28-day break from TOBI<sup>®</sup>. Therefore, even patients benefitting from TOBI<sup>®</sup> have an unmet medical need every other month. One potential alternative is the off-label use of other antibiotics by inhalation with potentially grave consequences,<sup>ii</sup> which is not acceptable.

Second, not every patient with CF has an infection caused by bacteria that are sensitive to TOBI<sup>®</sup>. For them, there is no approved inhaled antibiotic to meet their medical need. Only 2/3 of CF patients are taking TOBI<sup>®</sup>,<sup>iii</sup> as many others do not tolerate the drug.

Based upon study results released to date, the CF community is confident that AZLI exerts a significant suppressive effect on *P. aeruginosa* infections. We believe that AZLI will provide these patients with a treatment to chronically suppress their persistent *P. aeruginosa* infections. Approval of AZLI would fill this serious need that is not met by the only currently approved inhaled antibiotic.

FDA approval of more than one class of antibiotics for inhalation will help to address the general concern about acquired resistance to antibiotics overall. Delivery of antibiotics by inhalation was designed to reduce chances of systemic resistance, thereby enabling people with CF to take aerosol antibiotics daily to treat chronic lung infections. If each CF patient has a finite period of time during which an inhaled antibiotic treatment regimen will sustain lung function and prolong survival, then each additional class of antibiotic available for inhalation will provide an incremental but important gain in lung function, with survival increasing correspondingly. While other classes of antibiotics are available for extemporaneous off-label formulation as inhaled treatments, there is a strong need for approval of a second commercially manufactured product with a full safety and efficacy portfolio for reference.

Also, new antibiotics are needed for a currently deadly and untreatable bacteria, *Burkholderia cepacia* complex, which can cause rapid death in people with CF.<sup>iv</sup> Acquisition of *B. cepacia* decreases survival after lung transplantation,<sup>v</sup> and is a contraindication for this life-saving procedure. While it remains at a relatively low level in the CF community (three percent in the past 10 years), there is a great need for treatments for *B. cepacia* infections as none currently exist. Post approval trials to show efficacy against *B. cepacia* can be implemented and would be welcomed by the CF community.

#### **Additional Benefits with Relief of Treatment Burden**

People with CF currently spend 2-4 hours per day on delivery of aerosol medications and airway clearance. This is in addition to other burdensome aspects of CF care, such as airway clearance and maintenance of a high calorie diet. While it is not central to its benefit as a new drug, the new delivery system with AZLI is faster than other common delivery systems for inhaled medications. This new system will improve compliance and allow more time for airway clearance and other treatments that comprise the standard daily regimen of CF care necessary to sustain health. In particular, adolescents and young adults could benefit from this new delivery device and faster delivery to help them stay healthy now while other therapies are being developed.

#### **Concerns about Impact on Therapeutic Development**

With more than 30 products in development for CF, the community is already having difficulty meeting enrollment needs for clinical trials. Patients participating in further AZLI studies would be excluded from participating in studies of other CF drugs in development. This would substantially reduce the availability of study subjects for other drugs and delay the progress of their development. The continuation of Gilead's expanded access program, while essential for

the small percent of the population who are eligible and have access through one of the 41 national sites,<sup>vi</sup> is not sufficient to meet the medical needs of the broader community and also would make patients ineligible to participate in other clinical trials. Approval of AZLI would enable many more patients to benefit from this therapy and would not exacerbate enrollment issues for all trials.

### **Community Responds with Disappointment**

Prior to the FDA's recent decision, people in the CF community were very excited about the prospect of adding AZLI to their daily treatment regimen. Promising trial results and direct reports from patients who participated in clinical trials for this drug gave hope to the community that the drug would effectively treat their underlying bacterial lung infections and relieve some of the suffering caused by the disease.

Since the FDA's decision to require an additional clinical trial was made public in September, members of the CF community have expressed great disappointment. We have heard from many individuals with CF who were upset to learn that access to the drug would be significantly delayed by the FDA's requirement. Individuals have expressed concern that the FDA may not truly understand the reality of how children and adults with CF struggle just to breathe every day. Patients who spend hours each day on their medical regimen cannot imagine how this unmet medical need for new CF therapies to treat lung infections can go unrecognized, particularly for those with bacteria resistant to TOBI<sup>®</sup> or for those who do not tolerate TOBI<sup>®</sup>.

With the CF population primarily composed of adolescents and young adults, new treatment options that will keep them healthy and facilitate ease of delivery are particularly important. This age group begins to suffer more severe effects of this progressive disease. In addition, these increased health burdens come just when young people's access to health insurance declines as they become independent and need their own insurance. As the disease primarily affects young people, adolescents and young adults with CF are the most vulnerable sector of the CF population – and the age group most likely to benefit from approval of AZLI.

### **Summary**

People with CF are desperate for new treatment options. The CF Foundation is working diligently to bring new therapies to the CF community. We recognize that each new therapy adds to the incremental gains in life expectancy that will buy us the time needed to meet our ultimate goal: finding the cure for CF. We believe that the addition of AZLI to current treatment options would be a tremendous benefit. We stand ready to work with FDA now to enable more people with CF to benefit from this new treatment.

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<sup>i</sup> Cystic Fibrosis Foundation Patient Registry. 2007 Annual data report to the Center Directors. Bethesda, Maryland. © 2008.

<sup>ii</sup> In 2007, a CF patient died after using a compounded colistin product. See "Information for Healthcare Professionals; Colistimethate (marketed as Coly-Mycin M and generic products)." <http://www.fda.gov/CDER/DRUG/InfoSheets/HCP/colistimethateHCP.htm> Colistin was used by 15 percent of the CF patient community, according to the 2007 patient registry.

<sup>iii</sup> Cystic Fibrosis Foundation Patient Registry. 2007 Annual data report to the Center Directors. Bethesda, Maryland. © 2008.

<sup>iv</sup> Personal correspondence with Dr. John LiPuma, at the CF Foundation's National *B. cepacia* Repository Lab, University of Michigan.

<sup>v</sup> Alexander BD, Petzold EW, Reller LB, Palmer SM, Davis RD, Woods CW, Lipuma JJ. Survival after lung transplantation of cystic fibrosis patients infected with *Burkholderia cepacia* complex. *Am J Transplant*. 2008 May;8(5):1025-30.

<sup>vi</sup> <http://www.clinicaltrials.gov/ct2/show/NCT00499720?term=aztreonam+lysine+cystic+fibrosis&rank=2>.