

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**050814Orig1s000**

**OTHER REVIEW(S)**



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: February 5, 2010

To: Wiley Chambers, MD, Acting Director  
**Division of Anti-Infective and Ophthalmology Products**

Through: Mary Willy, PhD, Deputy Director  
**Division of Risk Management (DRISK)**

LaShawn Griffiths, MSHS-PH, BSN, RN  
Senior Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management**

From: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Patient Package Insert and Instructions for Use)

Drug Name(s): CAYSTON (aztreonam for inhalation solution)

Application Type/Number: NDA 50-814

Applicant/sponsor: Gilead Sciences, Inc.

OSE RCM #: 2009-1761

## **1 INTRODUCTION**

This review is written in response to a request by the Division of Anti-Infective and Ophthalmology Products (DAIOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for CAYSTON (aztreonam for inhalation solution). Please let us know if DAIOP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

## **2 MATERIAL REVIEWED**

- Draft CAYSTON (aztreonam for inhalation solution) Prescribing Information (PI) submitted on August 21, 2009 revised by DAIOP throughout the current review cycle and provided to DRISK on January 25, 2010.
- Draft CAYSTON (aztreonam for inhalation solution) Patient Package Insert (PPI) submitted on August 21, 2009, provided by DAIOP to DRISK on January 25, 2010 without revision.
- Draft CAYSTON (aztreonam for inhalation solution) Patient Instructions for Use (IFU) submitted on August 21, 2009 and provided by DAIOP to DRISK on January 25, 2010 without revision.

## **3 RESULTS OF REVIEW**

In our review of the PPI and IFU, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI and IFU are appended to this memo. Any additional revisions to the PI should be reflected in the PPI and IFU.

Please let us know if you have any questions.

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50814	ORIG-1	GILEAD SCIENCES INC	CAYSTON(AZTREONAM FOR INHALATION SOL)

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/s/

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SHARON R MILLS  
02/05/2010

MARY E WILLY  
02/05/2010

## SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 50-814
APPLICANT	Gilead Sciences, Inc.
DRUG NAME	CAYSTON (aztreonam for inhalation solution)
SUBMISSION DATE	August 21, 2009 (resubmission)
SEALD REVIEW DATE	December 29, 2009
SEALD REVIEWER(S)	Jeanne M. Delasko, RN, MS

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50814	ORIG-1	GILEAD SCIENCES INC	CAYSTON(AZTREONAM FOR INHALATION SOL)

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/s/

JEANNE M DELASKO  
07/09/2010

LAURIE B BURKE  
07/12/2010



**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**

Date: December 7, 2009

To: Wiley Chambers, M.D., Acting Director  
Division of Anti-Infective and Ophthalmology Products

Through: Todd Bridges, RPh, Team Leader  
Denise Toyer, Pharm.D., Deputy Director  
Carol Holquist, R.Ph., Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Cayston (Aztreonam) for Inhalation Solution  
75 mg/vial

Application Type/Number: NDA 050814

Applicant: Gilead Sciences, Inc.

OSE RCM #: 2009-1749

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## **1 INTRODUCTION**

This review is written in response to a request from the Division of Anti-Infective and Ophthalmology Products for assessment of revised labels and labeling for Cayston (Aztreonam) for Inhalation Solution.

## **2 REGULATORY HISTORY**

DMEPA reviewed the labels and labeling for Cayston May 29, 2008 (OSE# 2008-306).

## **3 METHODS AND MATERIALS**

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis<sup>1</sup> (FMEA) to evaluate the labels and labeling submitted as part of the November 10, 2009, submission (Appendix A thru E; no image of insert labeling). The Applicant submitted the vial label with two options to be considered.

## **4 CONCLUSIONS AND RECOMMENDATIONS**

Our evaluation noted areas where information on the label and labeling can be improved upon to minimize the potential for medication errors. Section 4.1 (*Comments to the Applicant*) contains our recommendations for the diluent label, vial label, carton labeling and tray labeling. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Brantley Dorch, OSE Regulatory Project manager, at 301-796-0150.

### **4.1 COMMENTS TO THE DIVISION**

We recommend the Division consult Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee, regarding the correct dosage form designation for this product.

### **4.2 COMMENTS TO THE APPLICANT**

We acknowledge the changes you have made to the labels and labeling based on our previous recommendations for improvement. However, we have the following additional recommendation to minimize vulnerability to medication errors.

#### **A. *Diluent Label***

1. Revise the second line to read: DILUENT for Cayston.
2. Revise the presentation of Gilead Sciences so that it is not in all capital letters. The current presentation makes it appear as the most prominent information on the label.

#### **B. *Container Label***

We prefer option 1, which includes the route of administration and single-use vial on the principle display panel.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

**C. Carton Labeling (14 day and 28 day)**

Increase the size of the product strength as in its current presentation it appears small.

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immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50814	ORIG-1	GILEAD SCIENCES INC	CAYSTON(AZTREONAM FOR INHALATION SOL)

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/s/

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DEVEONNE G HAMILTON-STOKES  
12/07/2009

TODD D BRIDGES  
12/07/2009

KELLIE A TAYLOR  
12/07/2009  
signing on behalf of C Holquist

## **REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)**

### **Division of Anti-Infective and Ophthalmology Products**

**Application Number:** NDA 50-814

**Name of Drug:** aztreonam for inhalation solution

**Applicant:** Gilead Sciences Inc.

### **Material Reviewed:**

**Submission Date(s):** November 16, 2007

**Receipt Date(s):** November 16, 2007

**Submission Date of Structure Product Labeling (SPL):** November 16, 2007

**Type of Labeling Reviewed:** WORD/SPL

### **Background and Summary**

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

### **Review**

The following issues/deficiencies have been identified in your proposed labeling and would be forwarded to the Sponsor for addressing.

#### **Highlights**

- Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
  - After Initial US Approval, delete 2008 and replace with 1986. Initial U.S. Approval is the four-digit year in which the FDA initially approved a new molecular entity or new combination of active ingredients. [See 21 CFR 201.57(a)(3)]
  - Type size for all labeling information, headings, and subheadings must be a minimum

of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21

CFR 201.57(d)(6) and Implementation Guidance]

- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57 (d)(8)]
- Insert one line of white space between each major heading in Highlights.
- The following statement regarding antibiotic resistance should follow after the initial US approval date. [See 21 CFR 201.24]: “To reduce the development of drug-resistant bacteria and maintain the effectiveness of TRADENAME and other antibacterial drugs, TRADENAME should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria”.
- All text of new paragraphs should consistently be either left justified or indented throughout the labeling.
- After “See 17 for PATIENT COUNSELING INFORMATION”, delete “and FDA approved patient labeling”. [See 21 CFR 201.57(a)(14)]

#### **Full Prescribing Information: Contents**

- The Contents subsection headings must be indented. [See 21 CFR 201.57(b)]
- Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous as the title for a subsection heading.

#### **Full Prescribing Information**

- Other than the required bolding [See 21 CFR 201.57(d)(1), d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
- Regarding references, are these references necessary? Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
- Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

### **Recommendations**

The Sponsor would be asked to address the identified deficiencies/issues and re-submit labeling by April 16, 2008 This updated version of labeling will be used for further labeling discussions.

Kyong Hyon, RN, MA  
Regulatory Project Manager  
Division of Anti-Infective and Ophthalmology Products

Supervisory Comment/Concurrence:

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Frances V. LeSane  
Chief, Project Management Staff

Drafted: KH/January 22, 2008

Revised/Initialed: February 15, 2008

Finalized: February 15, 2008

Filename: CSO Labeling Review Template (updated August 21, 2008).doc

**CSO LABELING REVIEW OF PLR FORMAT**

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Kyong Hyon  
8/21/2008 02:37:17 PM  
CSO

Frances LeSane  
9/10/2008 04:50:15 PM  
CSO

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY**

DATE: June 18, 2008

TO: Kyong Hyon, Regulatory Project Manager  
Menfo Imoisili, Medical Officer

FROM: Jean Mulinde  
Good Clinical Practice Branch II  
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.  
Acting Branch Chief, Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 50-814

APPLICANT: Gilead Sciences, Inc.

DRUG: Cayston (aztreonam lysine for inhalation)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: 1. Improvement in respiratory symptoms and pulmonary function in cystic fibrosis patients with *Pseudomonas aeruginosa*.

CONSULTATION REQUEST DATE: February 19, 2008

DIVISION ACTION GOAL DATE: September 5, 2008

PDUFA DATE: September 16, 2008

## I. BACKGROUND:

Gilead Sciences, Inc. submitted this NDA for the use of aztreonam lysine for inhalation for the treatment of cystic fibrosis patients with pulmonary *Pseudomonas aeruginosa*. Aztreonam is a monobactam that is currently approved in an intravenous formulation for treatment of the following infections caused by susceptible gram-negative microorganisms: 1) urinary tract infections (complicated and uncomplicated), 2) lower respiratory tract infections (pneumonia and bronchitis), 3) septicemia, 4) skin and skin-structure infections (including those associated with postoperative wounds, ulcers and burns), 5) intra-abdominal infections, 6) gynecologic infections (including endometritis and pelvic cellulitis), and 7) adjunctive therapy to surgery (surgical prophylaxis). In the current NDA, Gilead Sciences, Inc. requests approval of aztreonam lysine for inhalation for the indication “to improve respiratory symptoms and pulmonary function in cystic fibrosis patients with *Pseudomonas aeruginosa*.”

The NDA contains the following two pivotal studies submitted in support of the requested indication:

A. Protocol CP-AI-005: A Phase 3, Double-Blind, Multicenter, Randomized, Placebo-Controlled Trial with Aztreonam Lysinate for Inhalation in Cystic Fibrosis Patients with Pulmonary *P. aeruginosa* Requiring Frequent Antibiotics (AIR-CF2)

This was a double-blind, multicenter, randomized, placebo-controlled study designed to assess the safety and efficacy of a 28-day treatment with Aztreonam lysinate for inhalation (AI, Cayston™) in cystic fibrosis (CF) patients with lung disease due to *Pseudomonas aeruginosa* (PA) infection. Patients were randomized to receive 28 days of treatment with 75 mg AI or volume-matched placebo administered twice or three times daily by the eFlow® Electronic Nebulizer, following an initial run in treatment period of a 28 day course of TSI. The study was conducted February 24, 2005 to September 7, 2006 (original database lock on December 1, 2006, database unlocked February 15, 2007 and relocked February 28, 2007).

The primary efficacy endpoint of the study was the time to need for a course of inhaled or IV antipseudomonal antibiotics, with documented physician assessment of need for antibiotics, following start of AI/placebo therapy (Visit 3). The time to need antibiotic was to be documented based on the presence of at least one of the following four symptoms predictive of pulmonary exacerbation: decreased exercise tolerance, increased cough, increased sputum/chest congestion, or decreased appetite.

Key secondary efficacy endpoints include: 1) change in FEV<sub>1</sub>, 2) clinical symptoms as assessed by the CFQ-R Respiratory Domain, and 3) change in PA colony forming units (CFU) in expectorated sputum. Safety endpoints defined by the protocol include: 1) adverse events, 2) airway reactivity following study drug administration (acute decrease in FEV<sub>1</sub> of  $\geq 15\%$ ), clinical chemistry and hematology, and 4) vital signs.

B. Protocol CP-AI-007: Title: A Phase 3, Double-Blind, Multicenter, Multinational, Randomized, Placebo-Controlled Trial Evaluating Aztreonam Lysinate for Inhalation in Cystic Fibrosis Patients with Pulmonary *P. aeruginosa* (AIR-CF1)

This was a double-blind, randomized, placebo-controlled, multinational, multicenter study designed to assess the safety and efficacy of a 28-day treatment with Aztreonam lysinate for inhalation (AI, Cayston™) in cystic fibrosis (CF) patients with lung disease due to *Pseudomonas aeruginosa* (PA) infection that was conducted June 10, 2005 to April 3, 2007 (database lock on May 15, 2007). Patients were to receive 28 days of treatment with 75 mg AI or volume-matched placebo administered three times daily by the eFlow® Electronic Nebulizer (eFlow).

In the original protocol dated, February 15, 2005, the primary efficacy endpoint stated was change in FEV<sub>1</sub> from Day 0 through Day 42. In Version 2 of the protocol, dated October 10, 2005, change in respiratory clinical symptoms as assessed by the CFQ-R (Respiratory Domain) was designated as the key secondary efficacy endpoint in the study and the sample size was increased to adequately power the study for this key secondary endpoint. In Version 4 of the protocol, dated August 11, 2006, the primary efficacy endpoint was changed from change in FEV<sub>1</sub> from Day 0 through Day 42, to clinical symptoms as assessed by the respiratory domain of the Cystic Fibrosis Questionnaire-Revised [CFQ-R] at Day 28 (as a result to discussions with the FDA).

Key secondary efficacy endpoints (as defined in Version 4 of the protocol) include: 1) change in FEV<sub>1</sub> and change in PA colony forming units (CFU) in expectorated sputum. Safety endpoints defined by the protocol include: 1) adverse events, 2) airway reactivity following study drug administration (acute decrease in FEV<sub>1</sub> of  $\geq 15\%$ ), clinical chemistry and hematology, and 4) vital signs.

The Clinical Investigators (CI) chosen for inspection are the two centers with the largest number of enrolled patients in each of the pivotal multicenter studies, CP-AI-005 and CP-AI-007. Of note, the actual numbers enrolled at each site appear relatively small; however, given that Cystic Fibrosis is a relatively rare disease, each study center is generally expected to enroll and randomize a small number of patients. The NDA review team was concerned that any site specific factors involving these centers (with their relatively large numbers of enrollees) could potentially affect overall study results and thus approvability of the Application.

**II. RESULTS (by Site):**

<b>Name of CI City, State or Country</b>	<b>Protocol # # of Subjects</b>	<b>Inspection Dates</b>	<b>Interim Classification</b>	<b>Final Classification</b>
			NAI/VAI/ OAI	NAI/VAI/ OAI/ Pending
Center 104 Craig T. Nakamura, M.D. Las Vegas, NV 89144	CP-AI-005 Enrolled 14 (+2 screen failures)	04/03/2008- 04/08/2008	NAI	NAI
Center 013 Carlos E. Milla, M.D./Joanne L. Billings, M.D. Minneapolis, MN 55455	CP-AI-005 Enrolled 9 (+1 screen failure)	04/17/2008- 04/23/2008	NAI	NAI
Center 098 Theodore Geh-Lu Liou, M.D. Salt Lake City, UT 84132	CP-AI-007 Enrolled 11 (+9 screen failures)	04/21/2008- 04/25/2008	NAI	Pending
Center 160 Cori L. Daines, MD/Bruce C. Trapnell, MD Cincinnati, OH 45229	CP-AI-007 Enrolled 10 (+13 screen failures)	04/15/2008- 04/22/2008	NAI	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI-No Response Requested= Deviations(s) from regulations.

VAI-R = Response Requested = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

**1. Craig T. Nakamura, MD**

1112 Golden Age Court  
Las Vegas, NV 89144  
(CP-AI-005, Center 104)

**a. What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 04/03/2008-04/08/2008. For Center 104 a total of 16 patients were screened, 14 were randomized, and 5 completed the study. The inspection evaluated informed consent and included review of source documents and hard copy reporting for 100% of subjects. All study subject files were reviewed for verification of: 1) subject consent/assent, 2) inclusion and exclusion criteria, 3) primary and secondary endpoints, 4) adverse events, 5) serious adverse events, 6) protocol deviations, 7) subject randomization, 8) subject discontinuation (when present), 9) concomitant medications, and 10) subject compliance with study drug dosing. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

**b. General observations/commentary:**

The inspection of Dr. Nakamura's site revealed that the study was conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations,

was not issued to this investigator and the ORA investigator recommended No Action Indicated (NAI) for the site. Two minor issues identified by the field investigator were noted in the Establishment Inspection Report:

1. Concerning the Sponsor, for patient 10404 the data line listing provided in the background package (From original NDA, Protocol CP-AI-005, Final Clinical Trial Report, Listing 16.2.3.5 Baseline Criteria Review) recorded that at baseline *P. aeruginosa* was not present in sputum, but patient was recorded as having met inclusion criteria, which required *P. aeruginosa* to be present. Based on review of source data, *P. aeruginosa* was present in baseline sputum; therefore, this patient did meet inclusion criteria for the study and was appropriately enrolled.
2. The investigator identified several write-overs in source documentation and discussed with study personnel at the site how to properly make corrections (i.e. to correct errors by drawing a single line through the entry with initials and date, then to write the correct information next to the original entry).

c. **Assessment of data integrity:**

Based on the EIR report, data derived from Dr. Nakamura's site are considered reliable.

2. **Carlos E. Milla, M.D./Joanne L. Billings, M.D.**

Pediatric Pulmonary and Critical Care Medicine  
Room 413 VCRC  
401 East River Road  
Minneapolis, MN 55455  
(CP-AI-005, Center 013)

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 04/17/2008-04/23/2008. For Center 013 a total of 10 patients were screened, 10 were randomized, and 3 completed the study. One patient was randomized, but never received study therapy and six patients failed to complete the study due to need for off-study inhaled or intravenous antibiotic therapy. The inspection evaluated informed consent and included review of source documents and hard copy reporting for 100% of subjects. All study subject files were reviewed for verification of: 1) subject consent/assent, 2) inclusion and exclusion criteria, 3) primary and secondary endpoints, 4) adverse events, 5) serious adverse events, 6) protocol deviations, 7) subject randomization, 8) subject discontinuation (when present), 9) concomitant medications, and 10) subject compliance with study drug dosing. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary:**

Dr. Billings took over all remaining PI responsibilities for this study in March 2007, after enrollment in the study was closed. She had been a sub-investigator from the start on the study. The original principal investigator was Dr. Carlos

E. Milla; Dr. Milla left the University of Minnesota in March 2007 to move to Stanford, CA.

The inspection of Dr. Billing's site revealed that the study was conducted in accordance with the investigational plan. An FDA Form 483, Inspectional Observations, was not issued to this investigator and the ORA investigator recommended No Action Indicated (NAI) for the site. Several minor issues identified by the field investigator were noted in the Establishment Inspection Report and discussed with the study site personnel:

1. A single Safety Report/Medwatch form for subject 02754 (enrolled at a different center) was reported from the sponsor on 10/30/06, but not reported from this site to their IRB until 04/06/07. Center staff stated that this may not have been handled as urgently as it should have been because all study subjects at their center had completed by the time the Safety Report was received. Center staff acknowledged that all safety reports are to be reported expeditiously in the future.
2. Patient #2 had a last visit on 9/23/05 and started "TOBI" on 9/26/05 per the Concomitant Medications and Therapies Log/source worksheet. The study site Research Nurse Clinician (b) (4) stated that she had talked to the subject by phone to determine this and recorded it on the study worksheet. Center staff were informed by the ORA inspector that they should write and maintain phone notes for all such patient interactions.
3. Several minor data entry errors were noted between source data and NDA line listings. Center staff acknowledged these errors.
4. Concerning the sponsor, the inspector noted that subject #4 was reported as having a negative sputum in the data line listing provided in the background package (From original NDA, Protocol CP-AI-005, Final Clinical Trial Report, Listing 16.2.3.5 Baseline Criteria Review). The line listing recorded that at baseline *P. aeruginosa* was not present in sputum, but patient was recorded as having met inclusion criteria, which required *P. aeruginosa* to be present. Based on review of source data, *P. aeruginosa* was present in baseline sputum; therefore, this patient did meet inclusion criteria for the study and was appropriately enrolled.

d. **Assessment of data integrity:**

Based on observations made on the Form FDA 483 for this Clinical Investigator, in general, efficacy and safety data from the site appear to be reliable.

3. **Theodore Geh-Lu Liou, M.D.**

50 North Medical Drive  
Salt Lake City, UT 84132  
(CP-AI-007, Center 098)

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 04/21/2008-04/25/2008. For Center 098 a total of 20 patients were screened,

11 were randomized, and 8 completed the study. The inspection evaluated informed consent and verification that all source documentation and CRFs were present for 100% of subjects. Four subject records were reviewed in depth for verification of: 1) subject consent/assent, 2) inclusion and exclusion criteria, 3) primary and secondary endpoints, 4) adverse events, 5) serious adverse events, 6) protocol deviations, 7) subject randomization, 8) subject discontinuation (when present), 9) concomitant medications, and 10) subject compliance with study drug dosing. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

**b. General observations/commentary:**

The inspection of Dr. Liou's site revealed that the study was conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was not issued to this investigator and the ORA investigator recommended No Action Indicated (NAI) for the site. The field investigator did note in her draft Establishment Inspection Report that she had discussed on several occasions with Dr. Liou the need to ensure that he "be attentive to review of records and the dating of such." These discussions were triggered by the finding of occasional study documents (lab report, PFT report, chest x-ray) that had either been signed but not dated by the PI or that had not been signed or dated by PI, but for which there was a note to file from the site study coordinator stating that he had reviewed the document during the appropriate study visit.

**c. Assessment of data integrity:**

Based on preliminary communication with the field investigator, the data appear reliable.

***Note: Observations noted above are based on the draft Establishment Inspection Report provided by the field investigator, an inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR and associated exhibits.***

**4. Cori L. Daines, M.D./Bruce C. Trapnell, M.D.**

Pediatric Pulmonary  
CCHMC ML 2021  
3333 Burnet Avenue  
Cincinnati, OH 45229  
(CP-AI-007, Center 160)

**a. What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 04/15/2008-04/22/2008. For Center 160 a total of 20 patients were screened, 10 were randomized, and 9 completed the study. One patient withdrew after study visit 3 due to hospitalization for exacerbation of cystic fibrosis. Informed consents for all patients were reviewed and the study records for all randomized patients were audited. In addition, drug accountability

records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

**b. General observations/commentary:**

Dr. Trapnell took over as principal investigator during the course of the study. The original principal investigator was Dr. Cori L. Daines. During the course of this study, Dr. Daines was recruited by the Arizona University Medical Center (Tuscon, AZ) and accepted a position at that institution.

The inspection of Dr. Trapnell's site revealed that the study was conducted in accordance with the investigational plan. An FDA Form 483, Inspectional Observations, was not issued to this investigator and the ORA investigator recommended No Action Indicated (NAI) for the site. Two minor issues identified by the field investigator were noted in the Establishment Inspection Report and discussed with the study site personnel:

1. Patients 16066 and 16077 (originally consented on 7/6/06 and 7/10/06, respectively) were due to be re-consented on a revised consent form (approved on 7/11/06); however, the patient signatures were not obtained until after the study ended. The only change between the two versions of the consent form was an increase in the number of patients permitted to be enrolled at the study site and there was no increased risk to the study participants.
2. Patient 16067 was placed on Vicodin and Flexeril for back pain on 8/17/06, which was noted at study visit 4 on 8/23/06. The Flexeril was not transferred to the concomitant medications list in the source document and consequently not reported in the electronic case report form. This medication was not on the protocol list of restricted medications.

**c. Assessment of data integrity:**

Based on the EIR report, data derived from Drs. Daines'/Trapnell's site are considered reliable.

### **III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

In general, the studies appear to have been conducted adequately and the data in support of the NDA appear reliable. Final classifications of Clinical Investigator inspections of Dr. Nakamura, Dr. Billings, and Dr. Trapnell are No Action Indicated (NAI). Safety and efficacy data from these clinical investigators is considered reliable. The preliminary classification of Dr. Liou is NAI, which suggests that safety and efficacy data from this site may also be considered reliable; however, final classification is pending for this site and will be determined when the final EIR and associated exhibits are received. Should the final classification for Dr. Liou be different from the current preliminary classification of NAI, the Division will be notified and an inspection summary addendum will be generated.

*{See appended electronic signature page}*

Jean M. Mulinde, M.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations  
Office of Compliance

CONCURRENCE:

*{See appended electronic signature page}*

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## STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2008.002.A.00022
APPLICATION NUMBER	NDA 050814
LETTER DATE/SUBMISSION NUMBER	11-16-2007
REQUESTED DUE DATE	03-31-2008
DATE OF CONSULT REQUEST	02-14-2008
REVIEW DIVISION	DAIOP
MEDICAL REVIEWER/TEAM LEADER	Menfo Imoisili /John Alexander
REVIEW DIVISION PM	Kyong Hyon
SEALD REVIEWER	Elektra J. Papadopoulos
REVIEW COMPLETION DATE	June 12, 2008
ESTABLISHED NAME	aztreonam lysine for inhalation
APPLICANT	Gilead Sciences Inc
ENDPOINT(S) CONCEPT(S)	respiratory symptoms
INSTRUMENT(S)	CFQ-R
INDICATION	Improve respiratory symptoms and pulmonary function in cystic fibrosis patients with P. aeruginosa
INTENDED POPULATION	Patients ages 6 years and older with cystic fibrosis

### A. EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the DAIOP regarding NDA 050814, aztreonam lysine for inhalation (AI) to improve respiratory symptoms and pulmonary function in cystic fibrosis (CF) patients 6 years and older with *Pseudomonas aeruginosa*. The Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain was used to measure respiratory symptoms in the phase 3 clinical studies. It is important to note that the CFQ-R was developed as a health-related quality of life instrument, and it was not developed as a stand-alone measure of respiratory symptoms in CF. The instrument was not tested for its ability to measure individual symptoms.

Of primary concern, is its 2-week recall period. This is of particular concern given that children as young as 6-years old were included in the clinical studies. Another concern, especially for young children, is the respondent burden of the instrument, a 50-item questionnaire, because of the potential for missing data. It is also unclear why the adult version of the CFQ-R included an item about wheezing, but “wheezing” was absent from the version of the instrument for children ages 13-years and younger. It is important to note that PRO measures for the respiratory symptoms of cystic fibrosis are in development that are expected to be an improvement over the methods used in these studies. The adequacy of the CFQ-R for this application should not be used as a firm precedent that the CFQ-R represents a standard for efficacy measurement in CF. For that reason, SEALD recommends excluding reference to the CFQ-R in labeling.

The instrument as a measure of respiratory symptoms also has had uncertain reliability in this patient population. According to the NDA submission, “the true variance for the key secondary endpoint (change in CFQ-R respiratory domain) was unknown in this patient population”. At the time of this development program, however, there were limited options of instruments to measure symptoms in this patient population. Despite these concerns, however, a statistically significant improvement in the respiratory symptom domain of the CFQ was detected in the phase 3 confirmatory studies. This review focuses on the implementation of the CFQ-R in the phase 3 study, CP-AI-007.

#### **Recommendations:**

This reviewer has noted the following concerns that might be addressed at the NDA stage.

- Each of the pediatric subjects age 13 years and under completed two versions of the CFQ-R that differed by method of administration. (See Section 4 of this review.) It may be helpful to include a side-by-side evaluation of these data by method of administration to determine whether any important differences resulted from the method of administration. For example, it may be helpful to check to see whether there any important difference observed when the parent/caregiver administered the questionnaire vs. the investigator/ trial coordinator in children ages 6-11.

## STUDY ENDPOINT REVIEW

- According to the submission, a change of five points represents the minimum change (indicative of either improvement or decline) that can be reliably detected by an individual patient on the respiratory domain scale. This was determined from data obtained from study AI-005. In study AI-007, it may also be helpful in determining clinical relevance, if changes in symptoms as measured by the CFQ-R respiratory domain were linked to improvements in respiratory function and microbiology in individual patients.
- The Agency should clarify what were the training method/materials (patient, investigator and other study site personnel).
- An assessment of missing data should be done that includes both missing assessments as well as incomplete responses to items in the respiratory domain of the CFQ-R. This is more important for the self-administered versions of the CFQ-R, as interviewer-administered versions are less likely to have substantial missing data.
- It is important to document the responses to the individual items of the CFQ-R respiratory domain by treatment group to evaluate whether each of the items responded or whether the overall response appeared to be driven by a single item.

### B. STUDY ENDPOINT REVIEW

Cystic fibrosis (CF) is the most common, life-shortening genetic disorder in Caucasians, with approximately 60,000 affected persons worldwide. *Pseudomonas aeruginosa* (PA) is the most commonly isolated pathogen in CF. According to the sponsor's submission, CF patients infected with PA experience progressive obstruction of the airways and loss of lung function. The majority of CF patients ultimately succumb to respiratory failure due to damage resulting from chronic pulmonary infection. Aztreonam is a monocyclic  $\beta$ -lactam that binds primarily to PBP3 in Enterobacteriaceae, *Pseudomonas* and other Gram-negative bacteria. The inhaled antibiotic therapy is intended to be delivered to the site of the infection minimizing systemic absorption. According to the submission, the most widely used aerosolized treatment for treatment of CF patients in the U.S. is tobramycin, which has been shown to produce improvement in pulmonary function.

Antibiotics are used in several ways to treat infections in CF patients:

- Prophylactic treatment to delay/avoid chronic pulmonary infection (primarily for *S. aureus*),
- Early treatment following bacterial colonization to eradicate pulmonary infection
- Treatment of acute pulmonary exacerbations to stabilize patients and reduce sputum bacterial loads,
- Regularly scheduled treatment of chronically infected patients (regardless of symptomatology) to reduce inflammation and slow lung function decline.

The sponsor has submitted an NDA application for aztreonam lysine and seeks two claims in the indication statement for the target patient population:

- (1) to improve respiratory symptoms; and
- (2) improved pulmonary function.

Respiratory symptoms were measured using the CFQ-R. The review division requested that SEALD review CFQ-R to determine whether the instrument was properly validated, properly applied in the primary efficacy endpoint determination in Study SP-AI-007, and properly applied in the secondary efficacy endpoint determination in patients in all 3 studies.

The study under review that used the CFQ-R as a primary efficacy endpoints is CP-AI-007: *A Phase 3, Double-Blind, Multicenter, Multinational, Randomized, Placebo-Controlled Trial Evaluating Aztreonam Lysinate for Inhalation in Cystic Fibrosis Patients with Pulmonary P. aeruginosa.*

Primary Endpoint: Clinical Symptoms assessed by respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R)

### 1 INSTRUMENT

Four versions of the questionnaire were used during this trial:

- Children ages 6 to 11 years (interviewer format; administered by the research nurse or trial coordinator)
- Children ages 12 and 13 years (child format; completed by the patient)
- Adolescents and adults, ages 14 years and older (teen/adult format; completed by the patient)
- Parents/caregivers for children ages 6 to 13 years (parent format; completed by the patient's parent/caregiver)

For children aged 6 to 11 years, two questionnaires were to be completed at each time point: one completed by the trial coordinator and one completed by the parent/caregiver.

For children aged 12 and 13, two questionnaires were completed at each time point: one completed by the child and one completed by the parent/caregiver.

The same parent/caregiver was to complete the CFQ-R at every visit.

*Reviewer's comment: A concern, especially for young children, is the respondent burden of the instrument, a 50-item questionnaire. It seems unlikely that young children could easily and reliably complete a 50-item questionnaire. In the phase 3 study, children under the age of 14 were to complete two versions of the questionnaire.*

The CFQ-R was administered at Days 0 (baseline), 14, 28, and 42/Early Termination. The CFQ-R was given to the respondent before any other procedure or clinical examination was performed, with the exception of weight measurement.

Specific instructions were given to the trial coordinator about how to administer the questionnaire so that the results accurately reflected the child's symptoms from his/her perspective. Similarly, specific instructions were provided on how to administer the questionnaires completed by the patients. These instructions are outlined in Section 3.2.6 of protocol version 4. If there were any missing responses, the trial coordinator was to point them out to the respondent so they could be completed.

Spirometry was performed at all scheduled visits. At Days 0, 14, and 28, spirometry was performed before administration of trial drug treatment and 30 minutes after treatment completion.

A user manual and scoring algorithm was noted in the submission. This included instructions for copying the item-by-item responses onto a worksheet, reverse coding and instructions for inserting median values for missing values. The subject's median response for that domain was to be inserted for a missing values. If more than half of the answers are missing, then the investigator was not to calculate the scaled score.

## STUDY ENDPOINT REVIEW

### 2 PROPOSED LABELING

The proposed indication statement is as follows.

(b) (4)

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The proposed clinical studies section includes the following language.

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill, covering the proposed clinical studies section.

## STUDY ENDPOINT REVIEW

(b) (4)



## STUDY ENDPOINT REVIEW

(b) (4)



## STUDY ENDPOINT REVIEW

(b) (4)



## STUDY ENDPOINT REVIEW

(b) (4)

Although this is not a labeling review, this reviewer has several comments regarding the proposed label with regard to the CRQ-R as follows:

**Line 518:** I recommend deleting the word (b) (4).

**Line 521-525:** I recommend deleting the sentence, (b) (4)

**Line 530:** Add the scale as follows: (b) (4)

### 3 ENDPOINT MODEL

The objectives of Study 007 was to assess the safety and efficacy of a 28-day treatment with AI (75mg TID) compared to placebo in CF patients with lung disease due to PA.

The primary endpoint is the change at Day 28 from baseline in clinical symptoms as assessed by the respiratory domain of the CFQ.

Secondary Efficacy Endpoints:

- Change in FEV1, FVC and FEF25-75
- Change in the non-respiratory domains of the CFQ-R
- Number of days of hospitalization
- Use of non-study drug antipseudomonal antibiotics (including IV, inhaled, or oral)
- Change in CF symptoms and severity
- Missed school/work days
- Change in patient's ability to produce sputum.

## **STUDY ENDPOINT REVIEW**

The CF symptoms review was to be administered at screening, baseline, Day 14, Day 28 and Day 42.

### 4 CONCEPTUAL FRAMEWORK

Information regarding the conceptual framework of the adult/teen questionnaire is shown in the following table.

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The CFQ-R is a multidomain instrument intended to measure health-related quality of life in cystic fibrosis. Domains include the following: physical, role, emotion, social, body image, treatment, eating, weight, respiratory symptoms, digestive symptoms and health perceptions. The number of domains varies depending on the CFQ-R version. The sponsor has chosen a single domain, the respiratory symptoms domain, as the primary endpoint measurement. There are a total of 7 questions related to respiratory symptoms (questions #40, 41, 42, 43, 44, 45, and 46). The recall period is over the previous 2 weeks. Responses are based on a 4-point Likert scale.

*Reviewer's comment: The two middle response options, "somewhat" and "a little" are very close and do not appear meaningfully different.*

As stated earlier in this review, four versions of the CFQ-R were used in Study 007:

- Children ages 6 to 11 years (interviewer format)
- Children ages 12 and 13 years (child format; completed by the patient)
- Adolescents and adults, ages 14 years and older (teen/adult format; completed by the patient)
- Parents/caregivers for children ages 6 to 13 years (parent format)

For children aged 6 to 11 years, two questionnaires were to be completed at each time point (one completed by the trial coordinator and one completed by the parent/caregiver). For children aged 12 and 13, two questionnaires were completed at each time point (one completed by the child and one completed by the parent/caregiver). The same parent/caregiver was to complete the CFQ-R at every visit.

## STUDY ENDPOINT REVIEW

According to the SAP, the primary analysis is based on combining the respiratory domains of the following CFQ-R versions:

- A. Children ages 6 to 11 (Interviewer Format)
- B. Children Ages 12 and 13 (Self-report Format)
- C. Adolescents and Adults (Patients 14 years and Older)

Note that A and B are identical, and the results from these two formats will be combined and referred to as “Child” version for the reporting purposes.

There is also the Parent/Caregiver Ages 6-13 that was to be summarized, but will not be statistically analyzed.

*Reviewer’s comment: Note that two questionnaires were used at each timepoint for children ages 6-11 and children ages 12 and 13 years old. However, only the interviewer format questionnaire for children 6-11 and the self-report format instrument for children ages 12 and 13 were to be used in the primary analysis.*

### 5 CONTENT VALIDITY

The NDA submission included the questionnaires that were handed to patients as well as a manual describing the scoring methods. Evidence of content validity with respect to the claimed concept-respiratory symptoms-was not provided.

The submission did not describe the following items.

- Literature review and documentation of expert input
- Qualitative study protocols and interview guides for focus group testing, patient interviews, cognitive debriefing)
- Chronology of events for item generation, modification and finalization (e.g., item tracking matrix)
- Qualitative study summary with evidence of saturation
- Justification for response options, recall period, scoring
- Availability of transcripts

For the adolescent and adult questionnaire (patients 14 years old and older), item stems related to the respiratory domain are as follows:

Indicate how you have been feeling during the past two weeks.

- Have you been congested?
- Have you been coughing during the day?
- Have you had to cough up mucus?
- Have you been wheezing?
- Have you had trouble breathing?
- Have you woken up during the night because you were coughing?

Response options ranged from 0 (not at all) to 3 (a great deal).

## STUDY ENDPOINT REVIEW

For children ages 6-13, the item stems related to respiratory symptoms are as follows:  
Let us know how often in the past two weeks:

- You coughed during the day
- You woke up during the night because you were coughing
- You had to cough up mucus
- You had trouble breathing

Response options were on a scale from 0 (never) to 3 (always).

*Reviewer's comments:*

*Patients are unlikely to be able to reliably average their symptoms over a two-week time period. This may be particularly true for young children.*

*Some of the items appeared vague (e.g., "You had trouble breathing" could mean trouble due to congestion or a feeling of shortness of breath).*

*The respondent burden appeared high given that the questionnaire was comprised of a total of 50 items and two methods of administration were used in pediatric patients under the age of 13.*

*This instrument was developed as a health-related quality of life instrument.*

(b) (4)

## 6 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The same version of instrument to be used in clinical trials was used to identify measurement properties and a similar population and testing situation used in clinical trials was used to identify measurement properties.

- Scores are stable over time when no change has occurred in the concept of interest (test-retest reliability)
- If interviewer administered: evidence of agreement between responses when administered by 2 or more different interviewers (inter-rater reliability)
- Hypotheses concerning the relationships among items, domains, and measures of related concepts are confirmed (construct validity).
- Evidence that scores change in the predicted direction when there has been a notable change in patient status (longitudinal construct validity).

## 7 INTERPRETATION OF SCORES

The CFQ-R respiratory symptoms domain consists of 4 (child) or 6 (adolescent/adult) questions evaluating respiratory symptoms on a 4-point scale. Total scores for the domain are normalized on a 100-point scale, where 0 is the worst possible and 100 is the best possible score. According to the submission, it was determined that a change of  $\geq 5$  points (increase or decrease) represents the minimal clinically important difference (MCID) in patients with stable disease.

## STUDY ENDPOINT REVIEW

The instructions for scoring in the statistical analysis plan for study AI-007 (pages 244, 245 of 246) was similar to the instructions found in the user manual for the instrument. Specifically, it stated that if a question was skipped, then the response was to be set to missing. Missing values were to be imputed with the median value of all completed responses in the relevant domain. If more than half of the responses in a domain were missing, then no domain score was to be calculated.

The scaled score was to be calculated as follows (identical to the methods in the CFQ-R user manual):

$$100 \left( \frac{\text{Sum of responses in domain} - \text{number of questions in domain (n)}}{\text{Maximum possible sum for domain (4n) - n}} \right)$$

It may be helpful for the sponsor to describe the methods that were used to benchmark change scores. For example, in the confirmatory studies, a description of whether improvements in respiratory symptoms linked to improvements in respiratory function and microbiology in individual patients may be helpful in determining clinical relevance and aid in interpreting study results.

### 8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

In Study-007, patients were enrolled at 53 sites in total: 40 in the United States, 5 in Canada, 7 in Australia, and 1 in New Zealand.

*Reviewer's comment: It was noted that there was a higher magnitude of the treatment effect in New Zealand and Australia. This may have been attributable to the difference in seasons (spring/summer in New Zealand and Australia vs. fall winter in U.S. and Canada).*

*As stated in the draft PRO guidance, measurement of PRO concepts across culture or language group can introduce challenges. It would therefore be important to document whether any adaptation to the CFQ-R was needed for use in the investigational sites outside of the U.S..*

### 9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not Applicable: The instrument has not been reformatted for new method or mode of administration.

### 10 PROTOCOL AND ANALYSIS PLAN

Protocol version 2 to study CP-AI-007, issued in October 2005, changed the method of analysis of the primary endpoint, FEV1, and identified the CFQ-R respiratory domain as a key secondary efficacy endpoint. As a result, the sample size was re-calculated for sufficient power for the study endpoints. The original sample size of 66 patients was increased to 116 patients.

## STUDY ENDPOINT REVIEW

The true variance for the key secondary endpoint (change in CFQ-R respiratory domain) was unknown in this patient population and, therefore, the planned interim analysis was adjusted to include a review the sample size assumptions of variability.

Protocol version 4 was issued in August 2006 and changed the primary endpoint (change in FEV1) to change in CFQ-R respiratory domain. In addition, the planned sample size re-estimation had been performed and indicated that there was more variability in the results than previously assumed and that an increased number of patients would be required to achieve the desired power for the trial. The increase in sample size (from 116 to 140 patients) was added in this amendment. An additional country (New Zealand) was added. The inclusion criterion regarding PA isolation at Day -14 was changed to allow enrollment of patients who had 2 documented cultures of PA within the previous 12 months, with at least 1 of the 2 cultures testing positive in the previous 3 months. The exclusion criterion was also changed, reducing the antibiotic-free window before enrollment from 28 to 14 days. Protocol version 4 was the final version of the protocol.

*Reviewer's comment: It is possible that the precision of the instrument might have been improved with the use of a shorter recall period.*

This Phase 3 trial included a 28-day course of therapy and TID dosing of 75mg aztreonam lysine was administered. Randomization was stratified by disease severity (FEV1 percent of predicted  $\geq 25\%$  to  $\leq 50\%$  and  $> 50\%$  to  $\leq 75\%$ ).

### Entry criteria were as follows:

Patients  $\geq 6$  years of age.

- Documentation of CF diagnosis as evidenced by one or more clinical features consistent with the CF phenotype and one or more of the following criteria:
  - sweat chloride  $\geq 60$  mEq/L by quantitative pilocarpine iontophoresis test, or
  - two well characterized mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene, or
  - abnormal nasal potential difference.
- PA present in expectorated sputum or throat swab culture at Visit 1, for patients enrolled under protocol versions 1, 2, and 3.
- PA present in expectorated sputum or throat swab culture at Visit 1 or documented PA in 2 expectorated sputum or throat swab cultures within the 12 months prior to Visit 1 (one of the previous PA positive cultures had to be no more than 3 months prior to Visit 1), for patients enrolled under protocol version 4.

### Number of Patients:

There were 166 patients randomized to a treatment group (83 AI, 83 placebo). Two patients randomized to AI withdrew before receiving drug. In addition, one patient randomized to receive AI received placebo in error. Thus, 80 patients received AI and 84 patients received placebo.

## STUDY ENDPOINT REVIEW

### Duration of Treatment:

The trial lasted 56 days (14-day Screening period, a 28-day course of AI/placebo, and a 14-day follow-up period).

### Data Collection and Management:

An electronic case report form was used for data collection for much of the study assessments. However, the CFQ-R was to be recorded on paper forms and sent to the sponsor for processing that included double data entry. Missing data on the CFQ-R were not to be queried.

*Reviewer's comment: It would be important to ascertain whether a copy of the CFQ-R were retained at the site as source documentation.*

### Results:

Efficacy Endpoint or Evaluation	Placebo N = 84	75 mg AI N = 80	Treat. Diff.	p- value
Clinical symptoms as assessed by CFQ-R respiratory domain				
Mean* change in CFQ-R respiratory domain score Day 14	-0.98	7.01	7.98	0.0006
Mean* change in CFQ-R respiratory domain score Day 28	-2.63	7.08	9.71	0.0005
Categorical result: % of patients who improved at Day 28	37.3	56.3	-	0.0055
% of patients who worsened at Day 28	44.6	25.0	-	
Mean* change in CFQ-R respiratory domain score Day 42	-5.71	0.62	6.33	0.0154

\* adjusted

*Reviewer's comment: The treatment effect (active-placebo) was on average a change of 8 at day 14 and a change of 10 at day 28. The sponsor proposes a change in score of 5 as a clinically meaningful inpatient change. This was on a scale from 0-100.*

Overall, there was a higher magnitude of treatment effect in the CFQ-R respiratory domain score for patients <18 years old compared with adults ( $\geq 18$  years). At Day 28, adult patients (aged  $\geq 18$  years; n = 126: 59 AI and 67 placebo) showed an adjusted mean change of 4.82 on AI compared with -1.53 on placebo for the CFQ-R respiratory domain scores (treatment difference: 6.35; p = 0.0495). The changes for younger patients (aged < 18 years; n = 37: 21 AI and 16 placebo) were greater than for adults; adjusted mean changes were 12.73 on AI and -6.19 on placebo (treatment difference: 18.91; p = 0.0006).

*Reviewer's comment: The difference in magnitude of treatment effect (active-placebo) appears clinically meaningful. It is possible given that children on average have less advanced pulmonary disease may have a better response to treatment. It is also important, however, to exclude important differences that might arise from the PRO instrument version and any possible interviewer effects.*

According to the submission, the active treatment group also demonstrated significant improvements in the CFQ domains of physical functioning, emotional functioning, body image, eating disturbances, role limitations/school performance, weight disturbances, vitality, and treatment burden.

## STUDY ENDPOINT REVIEW

*Reviewer's comment: Although the sponsor reported treatment effect among the other domains, it is not known how we can interpret the clinical meaning of these results without a responder definition.*

## STUDY ENDPOINT REVIEW

### Study AI 005:

In study AI 005, the CFQ respiratory domain was measured as a secondary endpoint. The results are shown in the following table.

<b>Study AI 005: Change in CFQ-R Respiratory Domain Scores at Day 28 Child/Teen/Adult Combined (Source: Table 18 of CSR)</b>				
	Placebo	AI		
	Pooled (N = 76)	BID (N = 69)	TID (N = 66)	Pooled (N = 135)
Mean (SD)	-0.34 (10.96)	5.10 (17.99)	3.21 (17.65)	4.17 (17.78)
Adjusted mean	-0.66	5.10	3.56	4.34
Treatment difference: pooled AI – pooled placebo	5.01			
95% CI (p-value)	0.81, 9.21 (0.0196)			
ANCOVA. Baseline CFQ-R respiratory domain score included as a covariate.				

The adjusted mean change in CFQ-R respiratory domain scores from baseline at Day 28 was 4.34 for AI-treated patients and -0.66 for placebo-treated patients in this study. The difference was statistically significant.

*Reviewer's comment: These results are supportive of those seen in Study AI007.*

## 11 KEY REFERENCES FOR INSTRUMENT

1. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest*. 2005 Oct;128(4):2347-54.
2. Quittner AL, McCoy K, Montgomery AB. Inhaled antibiotics to treat stable patients with cystic fibrosis and *Pseudomonas aeruginosa* (PA): Measuring patient perception of symptom improvement. Abstract submitted and accepted. 21st Annual North American Cystic Fibrosis Conference, Oct. 3-6, 2007, Anaheim, CA.

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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: May 29, 2008

To: Wiley Chambers, M.D., Acting Director  
Division of Anti-Infective and Ophthalmology Products

Through: Todd Bridges, RPh, Team Leader  
Denise Toyer, Pharm.D., Deputy Director  
Carol Holquist, R.Ph., Director  
Division of Medication Error Prevention

From: Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator  
Division of Medication Error Prevention

Subject: Label and Labeling Review for Cayston

Drug Name(s): Cayston  
(Aztreonam Lysine for Inhalation)  
75 mg/vial

Application Type/Number: NDA 50-814 (IND 64,402)

Applicant: Gilead Sciences, Inc.

OSE RCM #: 2008-306

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## EXECUTIVE SUMMARY

The Division of Medication Error Prevention's analysis of the container label, carton and insert labeling noted areas of vulnerability that could lead to medication errors. Improvements should be made to the container label, carton and package insert labeling prior to approval to increase the readability of information presented on the labeling. Such improvements include revising the established name in accordance with current USP salt nomenclature, revising the net quantity statement, embossing only one side of the ampule and eliminating abbreviations in the package insert labeling. For full recommendations, we refer you to section 5 of this review.

## 1 BACKGROUND

### 1.1 INTRODUCTION

This review was written in response to a request from the Division of Anti-Infective and Ophthalmology Products for a review of the container labels, carton and insert labeling of Cayston.

### 1.2 PRODUCT INFORMATION

Cayston (Aztreonam Lysine) is indicated

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Cayston is specifically formulated to be administered by inhalation. The usual adult and pediatric dosage is 75 mg by aerosolization with the *eFlow*® *electronic nebulizer* three times daily for twenty-eight consecutive days. Cayston is available as a sterile, unit-of-use vial containing 75 mg of aztreonam as the lysine salt, which must be reconstituted before use. The product will be packaged as part of a kit with a 1 mL ampule of diluent containing 0.17% NaCl. The Cayston kit will contain a 28-day supply, which will include 84 Cayston vials and 88 diluent ampules. The four additional diluent ampules are provided in case of spillage. The vials and ampules will be packed in two side-by-side removable carton inserts each containing a 14-day supply of Cayston and diluent.

## 2 METHODS AND MATERIALS

This section describes the methods and materials used by our medication error staff to conduct a label, labeling and/or packaging risk assessment (see Section 3 Results). The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. We define a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>1</sup>

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error

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<sup>1</sup> National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>2</sup>

Because the Division of Medication Error Prevention staff analyzes reported misuse of drugs, we are able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. We use Failure Modes and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

## 2.1 PROPOSED LABEL/LABELING

For this product the Applicant submitted on November 30, 2007, via the FDA's Electronic Document Room (EDR) the following labels and labeling for our review (see Appendix A, B, C and D for images):

- Container Label for Cayston: 75 mg/vial
- Container for Saline Diluent (0.17% Sodium Chloride): 1 mL ampules
- Carton Labeling: 2 week kit
- Carton Labeling: 28 day kit
- Prescribing Information (no image)
- Patient Insert Labeling (no image)

In addition, on April 18, 2008, the Applicant sent a proposal requesting the following:

## 3 RESULTS

### 3.1 PACKAGE DESIGN

We had difficulty in opening two sample vials provided by the Applicant.

### 3.2 DILUENT AMPULE

The established name contains the salt (lysine), even though the product strength is based upon the active moiety.

(b) (4)

The phrase (b) (4) lacks prominence, as it is the same font size as aztreonam lysine.

### 3.3 CONTAINER LABEL

The established name contains the salt (lysine), even though the product strength is based upon the active moiety.

(b) (4)

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<sup>2</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

(b) (4)

### **3.4 CARTON LABELING (2 WEEK KIT AND 28 DAY KIT)**

(b) (4)

### **3.5 INSERT LABELING**

(b) (4)

We also noted the use of the error prone symbols (b) (4)

The storage recommendations are ambiguous.

### **3.6 PATIENT INSERT LABELING**

(b) (4)

## 4 DISCUSSION

Our analysis noted areas of needed improvements. Specifically, we were concerned with the package design, how the diluent is labeled, how the established name is presented, and the presentation of information on the labels and labeling.

### 4.1 PACKAGE DESIGN

[REDACTED] (b) (4)

### 4.2 DILUENT

Our review of the diluent ampule noted that the word [REDACTED] (b) (4)

[REDACTED]

### 4.3 CONTAINER LABEL AND CARTON LABELING

Our evaluation of the labels and labeling noted a few areas where information lacked prominence, was absent or ambiguous [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (b) (4)

The directions for storage recommendations are inconsistent and sometimes ambiguous. (b) (4)

Improper product storage may result from such ambiguous and conflicting statements.

Since product stability is dependent on proper storage, presentation of the recommended storage conditions in a manner that is readily comprehensible is essential. This includes expression of the recommended storage temperatures in degrees Celsius and degrees Fahrenheit as well as ensuring that storage statements such as “Refrigerate” or “Store in Refrigerator” are always accompanied by the corresponding temperature ranges (expressed in both degrees Celsius and degrees Fahrenheit).

#### 4.4 INSERT LABELING

Our analysis of the insert labeling noted the use of the symbols (b) (4). The symbols (b) (4) are included on the Institute for Safe Medication Practices (ISMP) List of Error-Prone Abbreviations. (b) (4)

#### 4.5 PRESENTATION OF THE ESTABLISHED NAME

We noted that the product strength is based upon the active moiety. (b) (4)  
Typically the established name should match the dosing instructions. In order to achieve this, (b) (4)  
Rik Lostritto, the chair of the CDER Labeling and Nomenclature Committee, would need to make this determination.

### 5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and layout design of the proposed container labels and carton labeling introduce vulnerability to confusion that could lead to medication errors with Cayston. The Division of Medication Error Prevention believes the risks we have identified can be addressed and mitigated prior to approval,

and provide recommendations in Section 5.2, below, that aim at reducing the risk of medication errors.

The Division of Medication Error Prevention would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any correspondence to the applicant pertaining to this review. If you have further questions or need clarification, please contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

## **5.1 COMMENTS TO THE DIVISION**

Based upon our assessment of the labels and labeling, DMETS has identified areas of needed improvement. We request a revision of the established name so that it is in accordance with current USP salt nomenclature. Consult Rik Lostritto, chair of the CDER Labeling and Nomenclature Committee for further guidance. Additionally, please consult the Division of Surveillance, Research, and Communication Support (DSRCS) for the comprehensibility of the language used in the patient insert labeling. We have provided recommendations in section 5.2 below and request that they be forwarded to the Applicant for implementation prior to approval of this application.

## **5.2 COMMENTS TO THE APPLICANT**

### **5.2.1 Package Design**

Ensure that the aluminum ring portion (pull tab) of the container closure system, which secures the rubber stopper in the vial, can be easily removed.

### **5.2.2 Diluent Ampule**

1. Revise the established name to read “Aztreonam for Inhalation”.
2. We recommend embossing only appears on one side of the ampule.
3. Revise so that “Sodium chloride 0.17%, 1 mL” and “Diluent for Aztreonam for Inhalation” appear on the same side of the ampule.
4. Ensure “Sodium chloride 0.17%, 1 mL” is the most prominent information on the label ampule.
5. Increase the prominence of the phrase “Diluent for”, so that the drug name does not compete with it (e.g. Diluent for Aztreonam for Inhalation).

### **5.2.3 Container Label**

1. Revise the established name to read “Aztreonam for Inhalation”.
2.  (b) (4)
3. Include the route of administration (i.e., For Oral Inhalation Only) to highlight this product is for inhalation.
4. Increase the size of the strength and delete  (b) (4) from the strength statement to read: “75 mg/vial”.
5. Include the statement “Single use vial”.

6. Include the Fahrenheit temperature. Revise the statement to read “Refrigerate 2 to 8° C (36 to 46° F)”.

#### 5.2.4 Carton Labeling (2 week/28 day)

1. Revise the established name to read “Aztreonam for Inhalation”.
2. Revise to include a prominent statement which clearly conveys that the product can only be used in the eFlow nebulizer specifically designed for the administration of Cayston.
3. Including the route of administration (i.e. For Oral Inhalation Only) per 21 CFR 201.100(b)(3).
4. Increase the prominence of the strength and revise the strength to read: “75 mg/vial”. Delete the words (b) (4) and (b) (4).
5. Relocate the net quantity statement away from the strength, preferably to the bottom portion of the display panel.
6. Revise the “Store in Refrigerator” statement on the principal display panel of the 28 day kit to read “Store in refrigerator 2° C to 8° C (36° F to 46° F)”. Additionally, revise to include this statement on the principle display panel of the 2 week kit.
7. In the storage section of each carton labeling revise the side panels to state: “Cayston vials and diluent ampules should be stored in the refrigerator at 2° C to 8° C (36° F to 46° F) until expiration date is reached or at room temperature (up to 25° C/77° F) for up to 28 days. Do not separate the Cayston vials from the diluent ampules.”
8. On the principle display panel and the top panel revise to state  
“Contains:  
84 Single-Use Vials of Aztreonam for Inhalation  
88 Diluent Ampules of Sodium Chloride 0.17%, 1mL (4 extra ampules provided in case of spillage)”

#### 5.2.5 Insert Labeling

1. Revise the established name to read “Aztreonam for Inhalation”.
2. Revise the (b) (4).
3. Revise the (b) (4).
4. In the ‘How Supplied/Storage and Handling Section revise the statement (b) (4) to state: “Cayston vials and diluent ampules should be stored in the refrigerator at 2° C to 8° C (36° F to 46° F) until expiration date is reached or at room temperature (up to 25° C/77° F) for up to 28 days. Do not separate the Cayston vials from the diluent ampules.”

#### 5.2.6 Patient Insert Labeling

Revise the established name to read “Aztreonam for Inhalation”.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

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