CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050814Orig1s000

MICROBIOLOGY REVIEW(S)

Division of Anti-Infective and Ophthalmology Products

APPLICANT:
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SUBMISSION REVIEWED: NDA 50-814 SN040

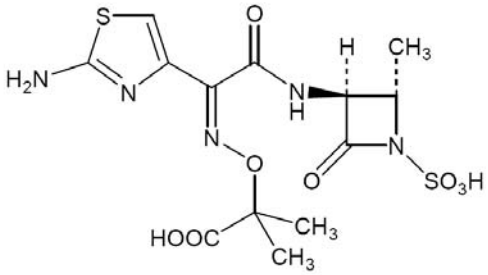
PROVIDING FOR: The management of cystic fibrosis (CF) patients with *Pseudomonas aeruginosa* to improve respiratory symptoms.

PRODUCT NAME:
Proprietary: CAYSTON
Non-proprietary: Aztreonam Lysine for Inhalation

CHEMICAL NAME: (Z)-2-[[[(2-Amino-4-thiazolyl)[[(2S, 3S)-2 methyl-4-oxo-1-sulfo-3-azetidinyl]carbomoyl]methylene]amino]oxy]-2-ethylpropionic acid

MOLECULAR FORMULA: $C_{13}H_{17}N_5O_8S_2$, MW 453.43 (anhydrous, β-form)

STRUCTURAL FORMULA:



ROUTE OF ADMINISTRATION, DOSAGE AND FORMULATION:

- ***Dosage Form:*** Aerosol (nebulization) NOTE: A device called the PARI eFlow will be used to deliver the dose. Patients will receive either 75 mg aztreonam for inhalation (AI) [1 ml] twice daily for 14 days.
- ***Formulation:*** Aztreonam for inhalation (75 mg/ml pyrogen-free aztreonam lysinate) dissolved in sterile 0.17% saline to result in a pH of 4.2—7.0 and osmolarity of 300—550 mOsmol/kg

PHARMACOLOGICAL CATEGORY: Antimicrobial

DISPENSED: Rx

INITIAL SUBMISSION DATES:

Received by CDER:	11 August 2009
Received by Reviewer:	13 August 2009
Review Completed:	29 December 2009

REMARKS:
The Applicant submits a resubmission intended to be a complete response to the deficiencies outlined by the Division in the Complete Response Letter (CRL). In addition, the Applicant requested this NDA 50-814 be presented to the Anti-Infective Drugs Advisory Committee as part of the review. This request was granted.

On 10 December 2009, the Anti-Infective Drugs Advisory Committee convened to discuss aztreonam, the subject of this NDA. Presentations were made by the Applicant, the Agency and the Public. It should be noted that one of the three public speakers was a 44-year old attorney afflicted with cystic fibrosis who is being treated with AZLI via an EAP program. This speaker made a compelling, emotional plea for approval of AZLI due to the lack of antimicrobials available for cystic fibrosis.

Following the presentations by the Applicant, the Agency and Public individuals, the committee addressed the following two questions posed by the Agency.

1. Has the Applicant provided substantial evidence of the efficacy and safety of 75 mg three times daily of AZLI for the requested indication of improvement of respiratory symptoms and pulmonary function in cystic fibrosis patients with *Pseudomonas aeruginosa*? In your response, discuss the rationale for your answer.

   a. If you voted YES, are there any specific issues that should be addressed in labeling?
   b. If you voted NO, what additional information is necessary?

2. Has the Applicant identified the correct dose and regimen for AZLI for the requested indication? In your response, discuss the rationale for your answer and discuss the rationale for your answer and discuss if there is any additional information that should be generated regarding the dose and regimen.

In response to question #1 regarding evidence of efficacy and safety, the committee voted as follows:

YES—15 members
NO — 2 members

The two dissenting voters did not elaborate on the rationale for their dissention other than saying the Applicant did not show sufficient data for efficacy, which did not show statistical significance. The other member believed that AZLI was not "durable" and that aztreonam resistance could be a potential safety problem.

While there were a variety of reasons given, many of the 15 assenting voters gave similar rationale for their vote.

- The bar should be low for approval for this drug due to the lack of alternative drugs for the treatment of this disease.
- New drugs are needed for this disease.
- The risk to benefit ratio is low for this drug.
- There was overriding evidence for the safety and efficacy of this drug.

- The CP-AI-006 study presented the necessary evidence to demonstrate safety and efficacy of this drug.

Some members of the committee did express concerns. One member was concerned about the time-to-need (TTN) data suffering from the lack of data. By far, the most common concern was the "durability" of AZLI compared to that of TOBI.

Members expressed concerns about the approval of the drug that should be addressed in the labeling of the drug. Due to the concern regarding durability of AZLI, the development of AZLI resistance should be tracked over time. This is based on the belief that the 28 day treatment period was not sufficient to address the chronic effect on resistance. Another committee member stated that the label should be crafted such that only the device described in this application could be used to deliver AZLI to cystic fibrosis patients.

In response to question #2 regarding identification of the correct dose and regimen for AZLI, the committee voted as follows:

YES—17 members
NO — 0 members

There was less discussion of the rationale for the answers given by the committee for this question as compared to the first question. Several members favored the TID regimen, due to the favorable time above MIC for the TID regimen versus the BID regimen. One member would consider the BID regimen as appropriate treatment while another member was skeptical that the BID regimen was an appropriate treatment.

The recommendations of the Anti-Invective Advisory Committee were considered along with the microbiological outcomes in the determination of a recommendation by this Reviewer.

This review describes the findings and recommendations of the Clinical Microbiology Reviewer. These recommendations are for evaluation by the Division Director for the determination of a decision regarding the approval of this new drug application.

CONCLUSION AND RECOMMENDATIONS:
The Applicant seeks approval of AZLI for the improvement of respiratory symptoms and pulmonary function in CF patients with *Pseudomonas aeruginosa*.

AI is intended as a suppressive therapy and is not expected to eradicate *P. aeruginosa* in CF patients with established airway infections. Consequently, in the Phase 2 and three Phase 3 clinical trials, there are no definitive endpoints for microbiological eradication or clinical cure. Under these circumstances, the objective of the review team is to determine ***what constitutes microbiological or clinical success?*** While it is not the place for this Reviewer to define clinical success, he shall attempt to define microbiological success.

There are two ways to evaluate the data from this submission. First, the microbiological efficacy endpoints were compared to the most common clinical efficacy endpoint, improvement in FEV_1. Second, the results of the microbiological

and primary clinical efficacy endpoint data were compared to the corresponding data derived from the package insert for TOBI Solution for Inhalation (TSI), a drug for which AI is intended to be an alternative treatment for CF. TOBI is the only other Agency-approved drug for the management of cystic fibrosis and also is administered in a similar manner.

There are three measures of microbiological outcome:

1. Change in log10 *P. aeruginosa* CFUs/g sputum specimens from patients;
2. Appearance of other pathogens, specifically *S. aureus*, *B. cepacia*, *S. maltophilia* or *A. xylosoxidans* in CF patients; and
3. Changes in aztreonam MIC50s and MIC90s of *P. aeruginosa* isolates from CF patients.

However, none of the data from the three microbiology outcomes correlated with clinical outcomes.

In the original NDA submission, to investigate the possible correlation between microbiological and clinical endpoints, scatterplots were produced. Scatterplots examining these endpoints showed the following:

- Changes in numbers of PA in sputum were not associated with changes in FEV_1 or aztreonam concentrations in study CP-AI-003, CP-AI-005 and slightly negatively associated in study CP-AI-007.
- Changes in numbers of PA in sputum were not associated with changes in aztreonam concentrations in study CP-AI-003.
- Changes in aztreonam MIC for the PA isolate with the highest MIC from each patient were slightly positively associated with changes in FEV_1 in study CP-AI-003 but slightly negatively associated in study CP-AI-007.
- Changes in numbers of PA in sputum were not associated with changes in aztreonam MIC for the PA isolate with the highest MIC in study CP-AI-005 and CP-AI-007.
- Changes in numbers of PA in sputum were not associated with changes in CFQ-R respiratory domain score in study CP-AI-007.
- The Applicant did not present scattergrams to explain relationships between microbiological to clinical outcomes.

The lack of correlation of microbiology outcomes with clinical outcomes for the treatment of cystic fibrosis with aztreonam is not unprecedented. In the Microbiology subsection of the package insert for TOBI for the management of cystic fibrosis patients with *P. aeruginosa*, the Agency states "The relationship between *in vitro* susceptibility test results and clinical outcome with TOBI therapy is not clear".

The efficacy of AZLI for CF caused by *P. aeruginosa* is not entirely clear in terms of clinical outcomes. *While none of the three microbiology responses correlated with clinical responses, AZLI treated patients demonstrated positive microbiological outcomes by all three measures.* In addition, the Applicant has demonstrated the safety of AZLI from the Microbiology standpoint as demonstrated by the lack of the development of aztreonam resistance in patients during therapy.

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