CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050814Orig1s000

SUMMARY REVIEW

M E M O R A N D U M

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

DATE: 02-22-10

FROM: Katherine A. Laessig, M.D.
Deputy Director
Division of Anti-infective and Ophthalmology Products

SUBJECT: Addendum to Deputy Division Director's Decisional Memo for NDA 50-814, lyophilized aztreonam lysine 75 mg for inhalation (Tradename CAYSTON®); Class II resubmission, second cycle

Please refer to my memorandum dated 2/13/10 in which I recommended issuance of a complete response letter to the applicant, Gilead Sciences Inc., pending the clearance of the 510(k) application K100380 for the nebulizer system Altera®. DAIOP has consulted on the label for Altera, and today CDRH is clearing the device, which allows DAIOP to take a concurrent approval action for this NDA. The coordination of the NDA approval and 510(k) clearance was discussed with the Office of Combination Products.

NDA 50-814, CAYSTON, aztreonam lysine for inhalation is recommended for approval.

Katherine A. Laessig, MD

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHERINE A LAESSIG
02/22/2010

M E M O R A N D U M

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

DATE: 02-13-10

FROM: Katherine A. Laessig, M.D.
Deputy Director
Division of Anti-infective and Ophthalmology Products

SUBJECT: Deputy Division Director's Decisional Memo for NDA 50-814, lyophilized aztreonam lysine 75 mg for inhalation (Tradename CAYSTON®); Class II resubmission, second cycle

1.0 Background

The applicant, Gilead Sciences Inc., has resubmitted NDA 50-814 in support of 75 mg lyophilized aztreonam lysine for inhalation (AZLI), administered using the PARI eFlow electronic nebulizer (Tradename ALTERA®). The nebulizer, Altera, was the subject of a separate 510(k) (b) (4) The sponsor of the nebulizer, PARI, has been instructed to resubmit the 510(k) after the NDA for CAYSTON has been approved. However, DAIOP has been coordinating with CDRH, Office of Combination Products (OCP), Gilead, and PARI for the 510(k) to be resubmitted sooner. In addition, Gilead has allowed right of cross-reference to PARI to the CAYSTON NDA, and the Altera package insert has been submitted to DAIOP by Gilead. When the 510(k) has been resubmitted, CDRH will consult DAIOP to review the device product labeling. Once the labeling has been agreed to by DAIOP, CDRH, and PARI, the 510(k) can be cleared, and the NDA for AZLI approved.

This NDA is submitted under Section 505(b)(2) of the FD&C Act, and relies on the Agency's previous findings of safety and effectiveness for the reference listed drug product, aztreonam (AZACTAM®, NDA 50-580, approved December 31, 1986). However, the original application did contain new clinical studies to support the requested indication of improvement of respiratory symptoms and pulmonary function in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa* (PA).

The original NDA was submitted on November 16, 2007. Approval was not recommended and a complete response letter was issued on September 16, 2008, citing a lack of substantial evidence of efficacy from two adequate and well-controlled studies as well as some product quality issues. The division concluded that one of the Phase 3 studies was uninterpretable, due to the presence of a regimen effect in study CP-AI-005 (hereafter referred to as study 005). The second study, CP-AI-007 (Study 007), was found to demonstrate the safety and efficacy of AZLI for the treatment of respiratory symptoms in CF patients with PA, based on an endpoint using a patient reported outcome tool, the Cystic Fibrosis Questionnaire-Revised (CFQ-R). However, 007 was not sufficient to stand on its own as the basis of approval because of the absence of replication of the treatment effect on respiratory symptoms from another trial. Please refer to my summary memo from the first cycle, as well as reviews from all disciplines and the CDTL memo from September 2008 for additional details.

After the division's action, the applicant submitted a request for Formal Dispute Resolution (FDR), first to the Office of Antimicrobial Products (OAP), and then to the Office of New Drugs (OND). The division's action was upheld because the applicant was making an argument that Study 005 provided evidence of efficacy based on analyses that were not submitted as part of the NDA. OND recommended that GSI resubmit the new analyses as a complete response, and that the application be presented at a meeting of the Anti-Infective Drugs Advisory Committee.

This memo will briefly summarize elements of all reviews by discipline. For detailed discussions, please refer to the respective CMC, product quality microbiology, pharmacology/toxicology, microbiology, clinical pharmacology, clinical, and biometrics reviews, and related consults.

2.0 Summary of Chemistry, Manufacturing, and Controls

During the first and second review cycles, this application is recommended for approval by the CMC reviewer, Mark R. Seggel, PhD. The Office of Compliance issued an overall recommendation of acceptable for the NDA 50-814 facilities inspections on February 2, 2010.

3.0 Summary of Product Quality Microbiology

The product quality microbiology deficiencies in the CR letter included the need for additional information on solution (b) (4), sterilization/depyrogenation, media fill procedures, specifications at manufacturing sites, and endotoxin testing for the aztreonam lysine product. The applicant submitted the requested information, and the Product Quality Microbiology review by Dr. Vinayak Pawar, dated November 9, 2009, recommends approval from his standpoint.

4.0 Summary of Pharmacology/Toxicology

This application was recommended for approval during the first cycle by the pharmacology/toxicology reviewer, Dr. Amy Ellis. The resubmission included new pharm/tox reports for safety pharmacology studies in dogs and several genotoxicity studies. After review of these reports, Dr. Ellis continues to recommend approval. She made recommendations for inclusion of additional genotoxicity information in the product labeling that have been accepted by the applicant.

5.0 Summary of Clinical Pharmacology

During the first cycle, the application was found to be acceptable from the standpoint of the clinical pharmacology reviewer, Sarah Robertson, PharmD. However, she noted that the proposed dose of 75 mg tid may not be the most efficacious dose for the requested indication based on data from the Phase 2 and 3 studies. She recommended should another Phase 3 trial be conducted, that a dose of 150 mg bid be evaluated.

No new clinical pharmacology information was submitted with the CR. Dr. Yongheng Zhang reviewed the resubmission, (b) (4) Of note, the AIDAC voted that the applicant had demonstrated that 75 mg tid was an effective dose and regimen, but not necessarily the most effective dose and regimen.

6.0 Summary of Clinical Microbiology

The clinical microbiology reviewer, Dr. Peter Coderre, was unable to support approval during the first cycle because neither he nor the applicant could demonstrate any correlations of microbiologic outcomes to clinical outcomes. Therefore, he deferred to the recommendations of the statistical and clinical reviewers.

New microbiology information was included in the resubmission in the final study report of the open label, follow-on study of 005 and 007, Study CP-AI-006. His conclusion, based on review of the new information, and consideration of the discussion at the December 2009 meeting of the AIDAC, is that the application is recommended for approval based on the medical need for new therapies for CF, the acceptable safety profile, and the efficacy of the drug on reduction in $\log_{10}$ CFUs of *P. aeruginosa*, and the overwhelming vote by the AIDAC supporting both the safety and efficacy of AZLI for the proposed indication.

He also proposed a post-marketing requirement (PMR) to address his concern, and that of many of the AIDAC members, that the applicant should conduct a 5 year study to evaluate the effect of AZLI on the susceptibility of *P. aeruginosa* to AZLI in CF patients. The applicant has agreed to this PMR.

7.0 Summary of Clinical Efficacy

As noted previously, the statistical and medical reviewers concluded after the first cycle that the applicant had not demonstrated substantial evidence of effectiveness from adequate and well-controlled studies because the results of 005 were not interpretable due to a strong regimen effect. However, study 007 was determined to demonstrate the effect of AZLI on the treatment of respiratory symptoms, despite the limitations of the CFQ-R as noted in earlier reviews. Please refer to those reviews for a complete description of the trials and their findings.

In this resubmission, the applicant presented post hoc analyses of study 005 in an attempt to explain biases in the primary endpoint of "time to need" by examining the influence of a decline in FEV_1 on the occurrence of a pulmonary exacerbation and consequent decision to initiate antibacterial therapy. According to the protocol, the presence of at least one of the four following symptoms was used to define an exacerbation: increased cough, increased sputum/chest congestion, decreased exercise tolerance, or decreased appetite. The statistical reviewer, Dr. Christopher Kadoorie, and the CDTL, Dr. John Alexander, have found the applicant's post hoc analyses to be inadequate given the highly robust regimen effect and significant amount of dependent missing data. As noted by Dr. Alexander, "while decline in pulmonary function after treatment in the AZLI TID group might contribute to greater numbers of patients in this arm receiving treatment for a pulmonary exacerbation, it does not explain the reasons for the differences between the two placebo groups." However, Dr. Alexander recommends approval based on the evidence from studies 006 and 007.

Dr. Kadoorie was also concerned with the rapid loss of benefit in between treatment cycles, which was not seen with the TOBI application. However, aminoglycosides are well known to have a post antibiotic effect, which AZLI does not. This may, in part, explain the lack of a sustained post-treatment effect. In addition, it is likely that AZLI will be alternated with TOBI monthly in some CF patients. As in his recommendation from the first cycle, Dr. Kadoorie continues to recommend a second adequate and well-controlled study be conducted.

Although limited by lack of randomization and the open-label nature of the study, 006 does provide supportive evidence of efficacy for the improvement of respiratory symptoms endpoint. In this study, there were two groups of subjects; those who received AZLI or placebo BID from 005 (n=85) and were all rolled over to AZLI BID, and those who received AZLI or placebo TID from either 005 or 007

(n=189) and were rolled over to AZLI TID. Subjects in this study received up to 9 courses of AZLI, and analyses of mean change in FEV_1 and CFQ-R score over multiple visits demonstrate responses to treatment. A fair degree of variability in the CFQ-R responses was noted; however this may be related to the fact that subjects from study 005 were more treatment experienced than those from 007. Several members of the AIDAC committee found the data from 006 to be compelling, although the FEV_1 data, i[redacted] (b) (4) The AIDAC voted 15:2 that the applicant had demonstrated the safety and efficacy of AZLI 75 mg tid.

My conclusion based on these data is that there is a treatment effect on respiratory symptoms based on the results of studies 006 and 007, which may be modest and most pronounced in younger, and/or less treatment experienced patients. However, given the limited availability of treatments for this orphan indication, restricting the indication to some subpopulation of CF patients is not appropriate. In addition, this NDA is a 505(b)2 which relies on the Agency's previous finding of safety and efficacy for AZACTAM, which was approved in 1986 and among its approved indications includes treatment of lower respiratory tract infection caused by susceptible isolates of *P. aeruginosa.* The requested indication of treatment of respiratory symptoms in CF patients is clearly less serious than that of treatment of LRTI, and therefore the efficacy data for the treatment of pneumonia with AZACTAM are relevant and supportive.

8.0 Summary of Safety

Dr. Menfo Imoisili's medical officer review from the first cycle provides an extensive discussion of the safety of AZLI and concludes that adequate safety data have been presented by the applicant to support the safe use of AZLI in patients with CF. For complete information, please refer to his review. Adverse events known to be associated with Azactam use and described in the label include pseudomembranous colitis, toxic epidermal necrolysis, hypersensitivity, and thrombophlebitis, among others.

As part of this resubmission, the applicant included the final study report for 006, and Dr. Imoisili has reviewed the safety information from that study. His conclusions are that the frequency of adverse events and serious adverse events increased as the subjects received more cycles of AZLI. Rates of these events were higher in the TID arm compared to the BID arm. The most common AEs seen in the TID arm included: productive cough, decreased appetite, dyspnea, nausea, sinus congestion, and asthenia. The types of AEs seen in 006 do not appear to differ from those seen in 005 and 007. This new information safety information did not change Dr. Imoisili's conclusion that the safety profile of AZLI TID is acceptable in the context of treatment of CF subjects.

9.0 Summary of Other Regulatory Issues

DSI issued a warning letter (OAI) to Dr. Samya Nasr of Ann Arbor, MI that was related to this investigator's participation in 005 and 007 and recommended that DAIOP not rely on data from this site. This investigator contributed very few subjects to either of the controlled studies and exclusion of the patients from this site does not change the interpretation of the study results and the data were excluded from our analyses. .

OSE has provided comments regarding the patient package insert, as well as the carton and container labeling that have been conveyed to the applicant and incorporated. The name CAYSTON has also been determined to be acceptable.

10.0 Recommendation

I concur with the findings of all reviewers, with the exception of the biometrics reviewer, that the applicant has demonstrated substantial evidence of the safety and efficacy of AZLI 75 mg TID for the treatment of respiratory symptoms in CF patients with PA based on study 007, supportive evidence from study 006, and the Agency's previous finding of safety and efficacy of AZACTAM in the treatment of LRTI. The Agency and the applicant have agreed upon the product labeling. In addition, the applicant has agreed to conduct the following postmarketing studies/trials: a resistance surveillance study, a randomized trial of CAYSTON vs. TOBI, and a prospective trial comparing BID vs. TID administration of AZLI to evaluate the impact of a treatment effect. However, until the 510(k) for the Altera nebulizer can be cleared by CDRH simultaneously, GSI will be issued a CR letter describing this outstanding deficiency. As noted above, DAIOP is working with OCP, CDRH, and both companies to accomplish NDA approval and 510(k) clearance as soon as possible.

Katherine A. Laessig, MD

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHERINE A LAESSIG
02/12/2010