CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
50-814/S001

**Trade Name:** Cayston

**Generic Name:** aztreonam

**Sponsor:** Gilead

**Approval Date:** 08/20/2010
# CONTENTS

Reviews / Information Included in this NDA Review.

<table>
<thead>
<tr>
<th>Reviews / Information</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
<td>✓</td>
</tr>
<tr>
<td>Other Action Letters</td>
<td></td>
</tr>
<tr>
<td>Labeling</td>
<td>✓</td>
</tr>
<tr>
<td>REMS</td>
<td></td>
</tr>
<tr>
<td>Summary Review</td>
<td></td>
</tr>
<tr>
<td>Officer/Employee List</td>
<td></td>
</tr>
<tr>
<td>Office Director Memo</td>
<td></td>
</tr>
<tr>
<td>Cross Discipline Team Leader Review</td>
<td></td>
</tr>
<tr>
<td>Medical Review(s)</td>
<td>✓</td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
<td>✓</td>
</tr>
<tr>
<td>Environmental Assessment</td>
<td></td>
</tr>
<tr>
<td>Pharmacology Review(s)</td>
<td></td>
</tr>
<tr>
<td>Statistical Review(s)</td>
<td></td>
</tr>
<tr>
<td>Microbiology Review(s)</td>
<td></td>
</tr>
<tr>
<td>Clinical Pharmacology/Biopharmaceutics Review(s)</td>
<td></td>
</tr>
<tr>
<td>Other Reviews</td>
<td></td>
</tr>
<tr>
<td>Risk Assessment and Risk Mitigation Review(s)</td>
<td></td>
</tr>
<tr>
<td>Proprietary Name Review(s)</td>
<td></td>
</tr>
<tr>
<td>Administrative/Correspondence Document(s)</td>
<td>✓</td>
</tr>
</tbody>
</table>
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring  MD  20993

NDA 50814/S-001

Gilead Sciences, Inc.
Attention: Jennifer Stephens
Director, Regulatory Affairs
199 E. Blaine St.
Seattle, WA  98102

Dear Ms. Stephens:


We acknowledge receipt of your amendment dated August 12, 2010.

We have completed our review of this supplemental application, containing new labeling text for the inside lid of the 28-day carton. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text submitted on August 12, 2010.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the content of carton and container labeling submitted on August 12, 2010 as soon as they are available, but no more than 30 days after they are printed.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

   MedWatch Program
   Office of Special Health Issues
   Food and Drug Administration
   10903 New Hampshire Ave
   Building 32, Mail Stop 5353
   Silver Spring, MD 20993
REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Katherine Laessig, M.D.
Deputy Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
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
08/20/2010
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
50-814/S001

LABELING
Contents

Includes 84 sterile single use vials of CAYSTON® and 88 sterile ampules of diluent for reconstitution. Each vial contains 75 mg aztreonam and 46.7 mg lysine lyophilized. Each diluent ampule contains 1 mL of 0.17% sodium chloride solution.

Dosage and Administration

Each 75 mg dose consists of one vial of CAYSTON reconstituted with one ampule of diluent. Reconstituted solution must be used immediately. For oral inhalation use only.

Storage

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.

See package insert for dosage and administration.

© 2011 Gilead Sciences, Inc.

75 mg/vial
For Oral Inhalation Only

Store Refrigerated, 2 °C to 8 °C (36 °F to 46 °F)
Contains:
- 84 Single Use Vials of Aztreonam for Inhalation Solution
- 88 Diluent Ampules of Sodium Chloride 0.17%, 1 mL
- 4 extra ampules provided in case of spillage

28-Day Supply
For use only with the Altera® Nebulizer System

Die in earn sh Free
for lear 2 n se l & g ue)
(l o ppear on p oof on y)
**How should I take CAYSTON?**

- You should take a CAYSTON dose three (3) times a day at least four (4) hours apart as directed by your physician.
- Each dose consists of one vial of CAYSTON mixed with one ampule of diluent to be administered with the Atera® Nebulizer System.
- Be sure to take your full 28 day course of treatment with CAYSTON in order to obtain the full treatment effect.

**How should I store CAYSTON?**

- Always keep your CAYSTON and saline together.
- Store CAYSTON and saline in a refrigerator at 2 °C to 8 °C (or 36 °F to 46 °F) until needed.
- If refrigeration is not available (for example, during the school or work day or when traveling), CAYSTON may be stored at room temperature (up to 25 °C/77 °F) for up to 28 days. Do not use any CAYSTON that has been stored at room temperature for more than 28 days.
- These CAYSTON bags have 14 days.
- Do not use CAYSTON after the expiration date on the vial.
- Do not use the saline if it looks or feels different than the ampule.
- Mix each vial of CAYSTON with saline for only when needed during or before a dose. Store CAYSTON tight away after you mix with the saline. Do not mix more than one dose of CAYSTON at a time.

**Important information about using CAYSTON®**

- Enclosed is:
  - Your 28 day supply of CAYSTON treatment
  - Your 28 day supply of diluent for CAYSTON
  - There are 4 trays holding 7 days of CAYSTON treatment each for a total of 28 vials of CAYSTON. There are 4 ampules holding 14 days of saline each for a total of 4 ampules of saline.

- There are 2 trays holding 14 days of diluent each for a total of 28 ampules of diluent. Also, there are 4 ampules of diluent in case of spillage for a total of 32 ampules of diluent.

- Mix (reconstitute) CAYSTON with saline only when ready to take a dose. Use CAYSTON right away after you mix with the saline. Do not mix more than one dose of CAYSTON at a time.

- CAYSTON is an inhalation solution.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
50-814/S001

MEDICAL REVIEW(S)
CAYSTON, aztreonam for inhalation solution (AZLI), was approved in Feb. 2010 for the treatment of respiratory symptoms in cystic fibrosis (CF) patients colonized with *Pseudomonas aeruginosa*. Safety and effectiveness have not been established for patients <7 years old and for patients with an FEV1 % predicted <25% or >75%. On Feb. 24, 2010, the sponsor submitted proposed labeling for its 28 day carton (inside lid of carton). The labeling focuses on description of contents, instructions for use, and storage information. This document represents a review of the proposed labeling as well as recommended changes.
1. Carton Labeling Column #1

Medical Reviewer Comments: Overall, the sponsor’s proposal is acceptable. However, further specification of the quantity of vials and ampules in each carton might be helpful to the patient. The MO recommends that the text be revised as follows:

Important information about using CAYSTON®
Enclosed is:
- your 28 day supply of CAYSTON treatment
- your 28 day supply of diluent for CAYSTON.
There are 4 trays holding 7 days of CAYSTON treatment each for a total of 84 vials of CAYSTON. Also, there are 2 trays holding 14 days of diluent each, plus 4 extra ampules of diluent in case of spillage, for a total of 88 ampules of diluent.

1a. Carton labeling Column #1 (continued)

How should I take CAYSTON?

Medical Reviewer Comments: Overall, the sponsor’s proposal is acceptable. However, it would be helpful to specify to the patient what exactly constitutes one dose. The MO recommends that the labeling text be revised as follows:

How should I take CAYSTON?
You should take a CAYSTON dose three (3) times a day at least four (4) hours apart as directed by your physician. Each dose consists of one vial of Cayston mixed with one ampule of diluent. Be sure to take your full 28-day course of treatment with CAYSTON in order to obtain the full treatment effect.

2. Carton Labeling Column # 2
Medical Reviewer Comments: We would recommend removing this section as it is self-evident and is overly promotional.

4. Carton Labeling Column # 3

How should I store CAYSTON?

Medical Reviewer Comments: This proposal might be somewhat confusing to the patient. We would avoid using terms such as that may be difficult for patients to understand, particularly children. We would recommend using language similar to that contained in the current label (shown below):

How should I store CAYSTON?

- Always keep your CAYSTON and saline together
- Store CAYSTON and saline in the refrigerator at 36 ° F to 46° F (or 2° C to 8° C) until needed
- When you remove CAYSTON and saline from the refrigerator they may be stored at room temperature (up to 77° F) for up to 28 days. Do not use any CAYSTON that has been stored at room temperature for more than 28 days.
- Keep CAYSTON away from light
- Do not use CAYSTON after the expiration date on the vial
- Do not use the saline diluent after the expiration date on the ampule
- Mix (reconstitute) CAYSTON with the saline only when ready to take a dose. Use CAYSTON right away after you mix with the saline. Do not mix more than one dose of CAYSTON at a time
Carton Labeling Note below Columns 2 and 3:

NOTE: Please review the enclosed FDA-Approved Patient Labeling for CAYSTON insert carefully before you or the person in your care start taking CAYSTON. Also, please refer to the manufacturer’s instructions for use provided with your AlteraNebulizer System for complete details on the assembly, preparation, use and care of your Altera Nebulizer System.

If you need additional information or have other questions, please call 1-877-7CAYSTON (1-877-722-9786).

*Medical Reviewer Comments: The sponsor’s proposal is acceptable.*

*Medical Officer Recommendations:*

The sponsor’s proposed labeling is overall acceptable provided the revisions outlined above are made. These recommendations should be conveyed to the sponsor.
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-50814</td>
<td>SUPPL-1</td>
<td>GILEAD SCIENCES INC</td>
<td>CAYSTON(AZTREONAM FOR INHALATION SOL)</td>
</tr>
</tbody>
</table>

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

/s/

SHRIMANT MISHRA
07/20/2010
Changes made

JOHN J ALEXANDER
07/21/2010
<table>
<thead>
<tr>
<th>Chemistry Review</th>
<th>1. Division:</th>
<th>2. NDA Number:</th>
</tr>
</thead>
<tbody>
<tr>
<td># 1</td>
<td>HFD-520</td>
<td>50-814</td>
</tr>
</tbody>
</table>

3. **Name and Address of Applicant:**
   Gilead Sciences  
   2025 East 1st avenue, Suite PH  
   Seattle, WA 98121

4. **Supplement(s):**
   - **Number:** SLR-001  
   - **Date(s):** February 24, 2010

5. **Name of Drug:** Cayston
6. **Nonproprietary name:** Aztreonam for inhalation solution

7. **Supplement Provides for:** Revised Drug Substance Test Method, Draft Labeling

8. **Amendment(s):** None

9. **Pharmacological Category:** Synthetic, monocyclic beta-lactam antibacterial

10. **How Dispensed:** 
    R

11. **Related Documents:** None

12. **Dosage Form:**
    For inhalation solution

13. **Potency:** 75 mg aztreonam/vial; diluted with 1 mL sodium chloride, 0.17% w/v diluent

14. **Chemical Name and Structure:**
    Aztreonam: (1) Propanoic acid, 2-[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]oxy]-2-methyl-, [2S-[2(®(Z))]];
    C₁₃H₁₇N₅O₈S₂, M.W. 435.43

![Chemical Structure Image]

15. **Comments:**
    This supplement is for revision and validation of the Organic Volatile Impurity (OVI) test procedure for determination of contents. The proposed revision is for improved performance of the method.

    The supplement also contains new labeling text for the inside lid of the 28 days carton providing important information for administration and storage of Cayston drug product. The new labeling text was submitted to the Medical Officer (MO) in Division HFD-520 for evaluation, the MO, Dr. Mishra, recommended text revisions as a result of his evaluation.

    A new corporate address for Gilead and updated contact for NDA 58-814 is included in this submission. That is:

        Gilead Sciences, Inc.  
        333 Lakeside Drive, Building 300  
        Foster City, CA 94404  
        Contact: Carla Fiankan  
        Associate Director, Regulatory Affairs, CMC  
        Carla.Fiankan@gilead.com  
        Phone: 650-522-5393  
        Fax: 650-522-5816

    Batch analysis of six lots of Aztreonam drug substance was conducted using the revised GC analytical method for among the methods for analysis. The results provided indicate that the batches analyzed conform with the acceptance criteria and that the revised analytical method is suitable for its intended...
16. Conclusions and Recommendations: The validation data demonstrates that the proposed, revised method is suitable for its intended purposes, from the CMC point of view this supplement is recommended for approval. However, the clinical review of the labeling changes recommends some revisions to the proposed labeling, therefore, the final recommendation for this supplements is for a complete response (CR) letter.

17. Name: Libaniel Rodriguez, Ph.D., Review Chemist
    Signature: Date:

18. Concurrence: Hasmukh Patel, Ph.D., Branch Chief ONDQA VIII
    Signature: Date:
6 Page (s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(4) Draft Labeling

___ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry#1 -50-814/S001
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-50814</td>
<td>SUPPL-1</td>
<td>GILEAD SCIENCES INC</td>
<td>CAYSTON(AZTREONAM FOR INHALATION SOL)</td>
</tr>
</tbody>
</table>

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

/s/

LIBANIEL RODRIGUEZ  
06/23/2010

HASMUKH B PATEL  
06/23/2010
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
50-814/S001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
From: Jennifer Stephens [jennifer.Stephens@gilead.com]
Sent: Wednesday, August 11, 2010 4:43 PM
To: Hyon, Kyong
Subject: RE: Labeling Proposal and comments for NDA 50814, submission dated 24Feb10

Thanks Kyong! We will get the formal submission out as soon as possible.

Best regards,
Jennifer

-----Original Message-----
From: Hyon, Kyong [mailto:Kyong.Hyon@fda.hhs.gov]
Sent: Wednesday, August 11, 2010 1:16 PM
To: Jennifer Stephens
Subject: RE: Labeling Proposal and comments for NDA 50814, submission dated 24Feb10

Hi Jennifer,

We accept your proposed changes to our proposals. Please submit it formally as an amendment to the labeling supplement submitted on February 25, 2010.

Thanks! ---- Kyong

-----Original Message-----
From: Jennifer Stephens [mailto:jennifer.Stephens@gilead.com]
Sent: Tuesday, August 10, 2010 11:23 PM
To: Hyon, Kyong
Subject: RE: Labeling Proposal and comments for NDA 50814, submission dated 24Feb10
Importance: High

Hi Kyong,

The Gilead team accepted all the changes requested by the Division, and we proposed a few additional edits. I have attached a track change Word version of our proposed edits, as well as a PDF file of the layout of the text on the inside lid of the carton. If the Division is in agreement with our proposed changes, we will send the PDF file to the NDA in a formal submission.
Important information about using CAYSTON®

Enclosed is:

- Your 28 day supply of CAYSTON treatment
- Your 28 day supply of diluent for CAYSTON

There are 4 trays holding 7 days of CAYSTON treatment each for a total of 84 vials of CAYSTON. Also, there are 2 trays holding 14 days of diluent each, plus 4 extra ampules of diluent in case of spillage, for a total of 88 ampules of diluent.

How should I take CAYSTON?

You should take a CAYSTON dose three (3) times a day at least four (4) hours apart as directed by your physician. Each dose consists of one vial of Cayston mixed with one ampule of diluent to be administered with the Altera® Nebulizer System. Be sure to take your full 28-day course of treatment with CAYSTON in order to obtain the full treatment effect.

How should I store CAYSTON?

- Always keep your CAYSTON and saline together.
- Store CAYSTON and saline in the refrigerator at 36 °F to 46 °F (or 2 °C to 8 °C) until needed.

- If refrigeration is not available (for example, during the school or work day, or when traveling), When you remove CAYSTON and saline from the refrigerator they may be stored at room temperature (up to 25 °C/77 °F) for up to 28 days. Do not use any CAYSTON that has been stored at room temperature for more than 28 days.
• Keep CAYSTON away from light.
• Do not use CAYSTON after the expiration date on the vial.
• Do not use the saline diluent after the expiration date on the ampule.
• Mix (reconstitute) CAYSTON with the saline only when ready to take a dose. Use CAYSTON right away after you mix with the saline. Do not mix more than one dose of CAYSTON at a time.

NOTE: Please review the enclosed FDA-Approved Patient Labeling for CAYSTON insert carefully before you or the person in your care start taking CAYSTON. Also, please refer to the manufacturer’s instructions for use provided with your Altera Nebulizer System for complete details on the assembly, preparation, use and care of your Altera Nebulizer System.

If you need additional information or have other questions, please call 1-877-7CAYSTON (1-877-722-9786).

Please let me know if you have any questions.

Best regards,
Jennifer

From: Hyon, Kyong [Kyong.Hyon@fda.hhs.gov]
Sent: Wednesday, August 04, 2010 12:11 PM
To: Jennifer Stephens
Subject: RE: Labeling Proposal and comments for NDA 50814, submission dated 24Feb10

Hello Ms. Stephens,

Based on our review of your Labeling Supplement submitted on February 25, 2010, we are proposing the following labeling text changes for the inside lid of the 28-day carton for Cayston® (aztreonam for inhalation solution), NDA 50814:

1. Carton Labeling Column #1
Division Comment: Overall, your proposal is acceptable. However, further specification of the quantity of vials and ampules in each carton might be helpful to the patient. Therefore, we recommend that the text be revised as follows:

Important information about using CAYSTON®
Enclosed is:

* your 28 day supply of CAYSTON treatment
* your 28 day supply of diluent for CAYSTON.

There are 4 trays holding 7 days of CAYSTON treatment each for a total of 84 vials of CAYSTON. Also, there are 2 trays holding 14 days of diluent each, plus 4 extra ampules of diluent in case of spillage, for a total of 88 ampules of diluent.

1a. Carton labeling Column #1 (continued)

How should I take CAYSTON?

Division Comment: Overall, your proposal is acceptable. However, it would be helpful to specify to the patient what exactly constitutes one dose. Therefore, we recommend that the labeling text be revised as follows:

How should I take CAYSTON?
You should take a CAYSTON dose three (3) times a day at least four (4) hours apart as directed by your physician. Each dose consists of one vial of Cayston mixed with one ampule of diluent. Be sure to take your full 28-day course of treatment with CAYSTON in order to obtain the full treatment effect.

2. Carton Labeling Column # 2

Division Comment: We would recommend removing this section as it is self-evident and is overly promotional.
4. Carton Labeling Column # 3

How should I store CAYSTON?

* Always keep your CAYSTON and saline together
* Store CAYSTON and saline in the refrigerator at 36 °F to 46 °F (or 2 °C to 8 °C) until needed
* When you remove CAYSTON and saline from the refrigerator they may be stored at room temperature (up to 77 °F) for up to 28 days. Do not use any CAYSTON that has been stored at room temperature for more than 28 days.
* Keep CAYSTON away from light
* Do not use CAYSTON after the expiration date on the vial
* Do not use the saline diluent after the expiration date on the ampule
* Mix (reconstitute) CAYSTON with the saline only when ready to take a dose. Use CAYSTON right away after you mix with the saline. Do not mix more than one dose of CAYSTON at a time

Best regards,
Kyong Hyon, CDR
Regulatory Project Manager
Food and Drug Administration (CDER)
Division of Anti-Infective Ophthalmology Products, HFD-520
10903 New Hampshire Ave.
BLDG #22/Room 6345
Silver Spring, MD 20993-0002
Tel: 301-796-0734
Fax: 301-796-9881
kyong.hyon@fda.hhs.gov
Please note: My e-mail address is now kyong.hyon@fda.hhs.gov. If you have a different address, please change it.
This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at kyong.hyon@fda.hhs.gov.
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-50814</td>
<td>SUPPL-1</td>
<td>GILEAD SCIENCES INC</td>
<td>CAYSTON(AZTREONAM FOR INHALATION SOL)</td>
</tr>
</tbody>
</table>

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

/s/

KYONG M HYON
08/18/2010
Dear Ms. Stephens:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Cayston (aztreonam for inhalation solution)

NDA Number: 50-814

Supplement number: 001

Date of supplement: February 24, 2010

Date of receipt: February 24, 2010

This supplemental application proposes the following: revision of the organic volatile impurity (OVI) test procedure for that includes provision for determining content (unspecified OVI).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 25, 2010, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 24, 2010.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-infective and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call me at (301) 796-4061.

Sincerely,

{See appended electronic signature page} 

Althea Cuff
Regulatory Health Project Manager
Branch VIII, Division of Post-Marketing Evaluation
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-50814</td>
<td>SUPPL-1</td>
<td>GILEAD SCIENCES INC</td>
<td>CAYSTON(AZTREONAM FOR INHALATION SOL)</td>
</tr>
</tbody>
</table>

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

/s/

ALTHEA CUFF
03/12/2010