CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-632/S-010

ADMINISTRATIVE DOCUMENTS

HFD-520

APR 10 1998

MEMORANDUM
CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

Date: April 8, 1998

To: Stephen Trostle
Consumer Safety Officer HFD-520

Subm. dated: 12.19.97
SE1-010

Subject: NDA 50-632 Aztreonam (Azactam) (010)

From: Dr. Kenneth A. Seethaler
Pharmacologist/Toxicologist HFD-520

Through: Dr. Robert E. Osterberg
Pharmacology Team Leader HFD-520

Aztreonam was originally classified in Pregnancy Category B based on the results of animal reproduction/teratogenicity studies on the compound. Later aztreonam was reclassified into Pregnancy Category C because of concerns expressed by FDA with regard to the possibility of potential teratogens leaching from the plastic packaging that was being used for the product.

The original packaging that was the source of concern is no longer being used. Aztreonam is now packaged in Galaxy (PL 2040) plastic containers, which are not thought to be a teratogenic hazard. For this reason, aztreonam should once again be returned to Pregnancy Category B.

This portion of the label should read as follows:

Pregnancy Category B

/S/

Kenneth Seethaler, R.Ph., Ph.D., D.A.B.T.
Pharmacologist/Toxicologist
HFD-520/CDER/FDA

Copy:
NDA 50-632
HFD-520/K.Seethaler
HFD-520/M.Albuerne
HFD-520/S.Trostle
HFD-520/R.Osterberg
HFD-520/L.Gavrilovich
HFD-520/G.Chikami

RDD 4/10/98
MB 4/12/98

EXCLUSIVITY SUMMARY FOR NDA # 50-632 SUPPL # 010

Trade Name Azactam I.V. Generic Name aztreonam

Applicant Name Bristol-Myers Squibb Co. HFD # 520

Approval Date If Known DEC 24 1998

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?

YES /___/ NO /✓/

b) Is it an effectiveness supplement?

YES /✓/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

(By reference) (50-590/SE1-008, Azactam for Inj. AP 11.01.96)

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /✓/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____ _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 50-632 AZACTAM I.V.

NDA# 50-580 AZATAM for INJECTION

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /√/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "NO," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____ _____

_____ _____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /✓/ NO /___/

Investigation #2 YES /✓/ NO /___/

Investigation #3 YES ✓

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Study 18554-58 50-580 (for SE1-008)

Study 18554-16A 50-580 (for SE1-008)

Study 18554-64 50-580 (for SE1-008)

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 NO ___

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____

! _____

Investigation #2 !

IND # _____ YES /___/ ! NO /___/ Explain: _____

! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

/S/
Signature
Title: Regulatory Health Project Manager

11.02.1998
Date

/S/
Signature of Office/
Division Director

12/23/98
Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	50632	**Trade Name:**	AZACTAM IV BAGS, FROZEN
Supplement Number:	10	**Generic Name:**	AZTREONAM
Supplement Type:	SE1	**Dosage Form:**	Injectable; Intravenous
Regulatory Action:	AP	**Proposed Indication:**	ADD "PEDIATRIC USE," ADVERSE REACTIONS, AND DOSAGE AND ADMINISTRATION.

Original

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? YES

What are the INTENDED Pediatric Age Groups for this submission?

___NeoNates (0-30 Days) _X_Children (25 months-12 Years)
_X_Infants (1-24 Months) ___Adolescents (13-16 Years)

Label Status	ADEQUATE Labeling for SOME PEDIATRIC ages
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, STEPHEN TROSTLE

/S/
Signature

11.02.1998
Date

DEBARMENT CERTIFICATION NOT NEEDED
REFERENCED APPLICATION, NDA 50-580/SE1-008, SUBMITTED
PRIOR TO JUNE 1, 1992

CENTER FOR DRUG EVALUATION AND RESEARCH

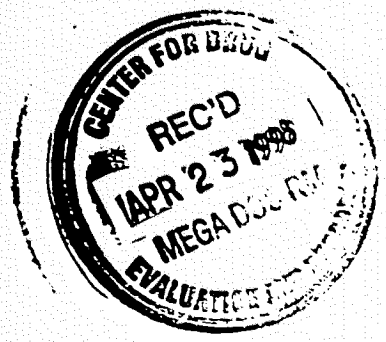
APPLICATION NUMBER: NDA 50-632/S-010

CORRESPONDENCE

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5761 Fax: 609 252-6000
Internet: Joseph_A._Linkewich@ccmail.bms.com

Joseph A. Linkewich, Pharm.D.
Director
U.S. Regulatory Liaison
Worldwide Regulatory Affairs



NDA 50-632/S-010
AZACTAM® (aztreonam injection)

April 20, 1998

Gary K. Chikami, M.D.
Director, Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Chikami:

Reference is made to our approved New Drug Application 50-632 for AZACTAM® (aztreonam injection) and to the following pending supplemental applications:

- S-010 which provides for labeling changes requested by the Agency on August 20, 1996, with additional changes outlined in my letter of December 19, 1997.

Additional reference is made to phone conversations with Mr. Stephen Trostle of March 17, 18 and 23, 1998 during which we agreed that we would submit revised AZACTAM® insert text in Word® format to incorporate the following:

- all revisions as included in FPL previously provided to the Agency on December 19, 1997 (S-010)

- revisions to the PRECAUTIONS – Pregnancy subsection of labeling to make this subsection consistent with the approved labeling for NDA 50-580 AZACTAM (aztreonam for injection, USP) text

- minor editorial revisions

Herewith please find the revised draft AZACTAM® insert text in hard copy and on diskette. Highlighted on the hard copy are the aforementioned Pregnancy subsection changes and the very minor editorial changes that were made to the approved AZACTAM® text as the Word® document was produced.

Should there be any questions concerning this submission, kindly contact me.

Sincerely,

Joseph A. Linkewich, Pharm. D.
Director
U.S. Regulatory Liaison
Worldwide Regulatory Affairs
(609) 252-5761

JAL/MP/dk
Attachments

Desk Copy: Mr. Stephen Trostle (letter, hard copy draft and diskette)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-632/S-010

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000

JAN 5 1998

Attention: Joseph A. Linkewich, Pharm. D.
Director, U.S. Regulatory Liaison

Dear Mr. Linkewich:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: AZACTAM® (aztreonam injection)

NDA Number: 50-632

Supplement Number: S-010

Date of Supplement: December 19, 1997

Date of Receipt: December 29, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on Februaray 27, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products, HFD-520
Office of Drug Evaluation IV
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/ 1/5/98

James D. Bona, R.Ph., M.P.H.
Chief, Project Management Staff
Division of Anti-Infective Drug Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 50-632/S-010
HFD-520/Div. Files
HFD-520/CSO/Trostle, S.

SUPPLEMENT ACKNOWLEDGEMENT

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5761 Fax: 609 252-6000
Internet: Joseph_A._Linkewich@ccmail.bms.com

NDA NO. 50632 REF. NO. SE1 SUPP 010

NDA SUPPL FOR Labeling

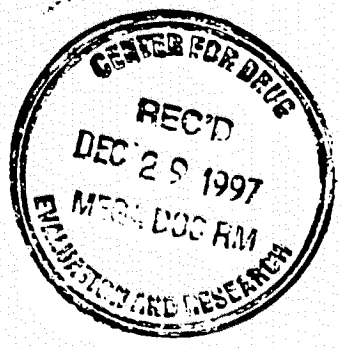
DUPLICATE

Joseph A. Linkewich, Pharm.D.
Director
U.S. Regulatory Liaison
Worldwide Regulatory Affairs

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

NDA 50-632
AZACTAM® (aztreonam injection)

December 19, 1997



Gary K. Chikami, M.D.
Acting Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Chikami:

Reference is made to our approved New Drug Application for AZACTAM® (aztreonam injection) and to the letter from the Division of August 20, 1996, (copy enclosed) approving supplemental applications S-006 and S-007 and requesting that additional changes be made to the insert for AZACTAM at its next printing.

Herewith, are copies of Final Printed Labeling that incorporates all revisions exactly as specified in the Division's letter. For ease of review, these revisions are depicted on the enclosed side-by-side text and are highlighted in yellow.

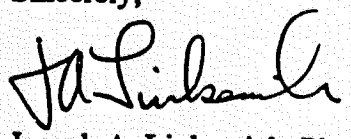
In addition, we are taking this opportunity to effect additional changes. Changes in the **CLINICAL PHARMACOLOGY, PRECAUTIONS (Pediatric Use subsection), ADVERSE REACTIONS (Pediatric Adverse Reactions subsection)** and **DOSAGE AND ADMINISTRATION** sections of the insert relate to pediatric use. These changes are found on the enclosed side-by-side and are not highlighted with color. These changes have been approved and implemented in the AZACTAM® (aztreonam for injection) package insert, NDA 50-580, S-008 (submitted May 18, 1987 approved, November 1, 1996; Final Printed Labeling submitted January 27, 1997 and approved June 10, 1997). This supplement provided for the expanded use of AZACTAM® in pediatric patients. Also included in this submission are changes that would otherwise be described in the annual report under 21 CFR 314.70.

We are providing sixteen copies of the final printed insert (code I-269-797). One copy of the insert is mounted and attached to the archival copy; the reviewer's copy has nine copies of the mounted insert attached; six copies are enclosed in an envelope. For the convenience of the FDA reviewer, we have included a copy of the package insert in a side-by-side format that identifies revisions made to the labeling.

Finally, we wish to acknowledge that additional revisions to the **CLINICAL PHARMACOLOGY** section of the AZACTAM® package insert are contained in our pending supplemental application S-009 submitted on June 5, 1996. This supplemental application provides for revisions to the package insert with changes in the **CLINICAL PHARMACOLOGY** section, **Microbiology** subsection according to the Agency's Notice to All NDA Holders of January 26, 1993. In a letter dated July 18, 1997, the Agency indicated that the supplement was approvable provided additional revisions were made to the labeling. These revisions will be submitted in a separate future amendment.

Should there by any questions concerning this submission, kindly contact me.

Sincerely,



Joseph A. Linkewich, Pharm. D.
Director
U.S. Regulatory Liaison
Worldwide Regulatory Affairs
(609) 252-5761

Desk Copy: Mr. Stephen Trostle
Ms. Maureen Dillon-Parker