CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 065286

Name: Aztreonam for Injection USP, packaged in 1 g and 2 g Single-dose Vials

Sponsor: Bedford Laboratories

Approval Date: March 23, 2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065286

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065286

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 065286

Bedford Laboratories
Attention: Molly Rapp
Executive Director, Compliance and Regulatory Affairs
300 Northfield Road
Bedford, OH 44146

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 23, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Aztreonam for Injection USP, packaged in 1 g and 2 g Single-dose Vials.

Reference is also made to your amendments dated May 31, and June 23, 2006; March 16 (2), July 27, August 7, August 30, and October 18, 2007; February 8, June 25, and September 5, 2008; May 26, 2009; and June 17, August 25, September 24, November 4, and December 21, 2010.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Aztreonam for Injection USP, 1 g and 2 g per vial to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Azactam® for Injection, 1 g and 2 g per vial, of Bristol Myers Squibb.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/U_CM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
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/

ROBERT L WEST

03/23/2011

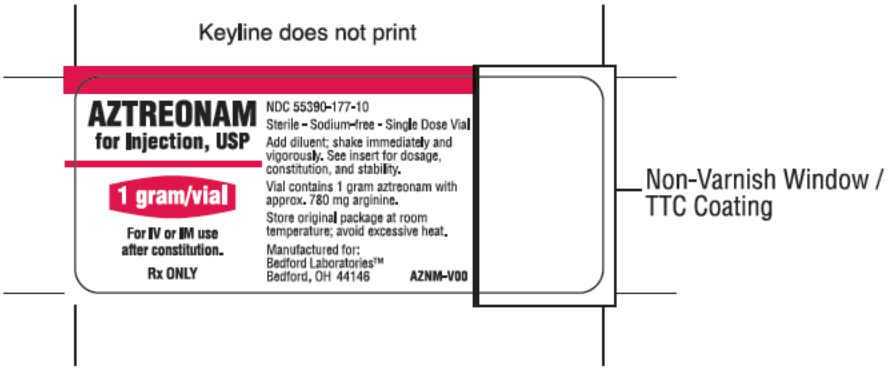
Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065286

LABELING



Electronic Art Hard Copy	**Date:** 08/28/07	**cGMP**	**YES** ☒ **NO** ☐
Art File: 27497	**Format:** 055002 #051A	**Colors:**	
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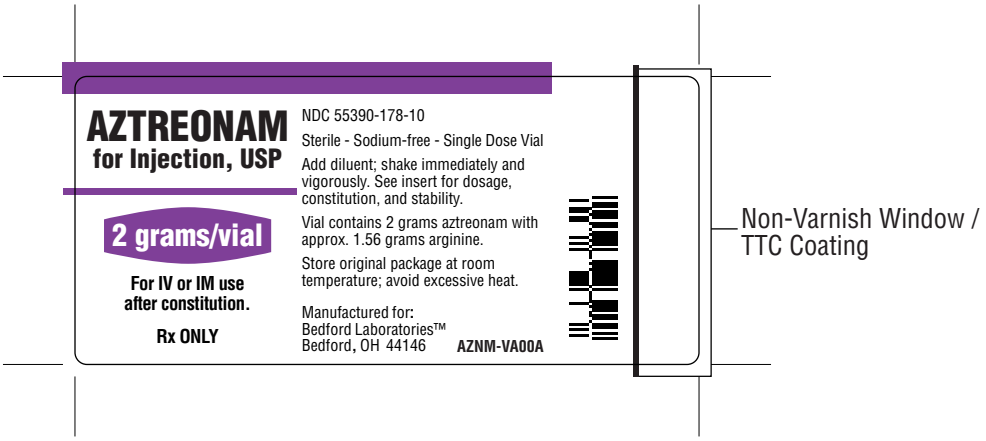
WTP Proofread: /			

BEDFORD LABORATORIES™
ANDA 065286
Aztreonam for Injection USP - 1 gram and 2 grams per vial

Proposed Vial Label - 2 grams

Note: Keyline does not print.



142

NDC 55390-177-10 10 Sterile Single Dose Vials

AZTREONAM FOR INJECTION, USP

For IV or IM use after constitution.

Rx ONLY

1 gram/vial

BEDFORD LABORATORIES™

011185

Glue

Glue

DIV-AZNM-C00

AZTREONAM
FOR INJECTION, USP
1 gram/vial

N 3 55390-177-10 9

AZTREONAM
FOR INJECTION, USP
1 gram/vial

56

Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146

BEDFORD LABORATORIES™

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

EXP
LOT

Each vial contains 1 gram aztreonam with approximately 780 mg arginine.
Sodium-free
Add diluent; shake immediately and vigorously. See insert for dosage, constitution, and stability.
Store original package at 20° to 25°C (68° to 77°F). See USP controlled room temperature; avoid excessive heat.

Glue

Glue

61.5

NDC 55390-177-10 10 Sterile Single Dose Vials

AZTREONAM FOR INJECTION, USP

For IV or IM use after constitution.

Rx ONLY

1 gram/vial

BEDFORD LABORATORIES™

55390-177-10

Ben Venue
Printed Side
#M022601J

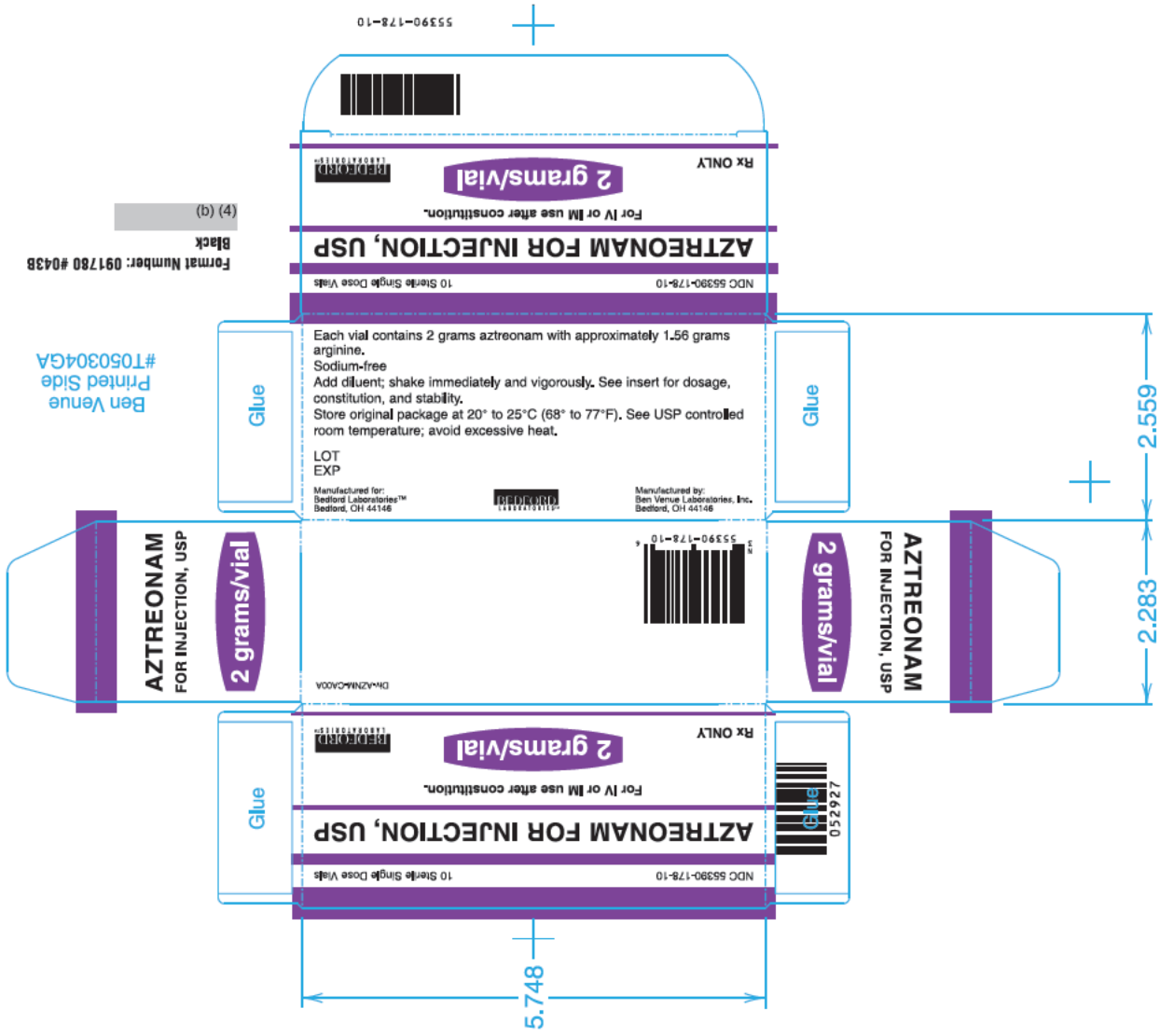
(b) (4)

Format Number: 054971 #036A
Black

Reference ID: 2908178

BEDFORD LABORATORIES™
ANDA 065286
Aztreonam for Injection USP - 1 gram and 2 grams per vial

Proposed Carton - 2 grams



BEDFORD LABORATORIES

Div-AZNM-P00

AZTREONAM FOR INJECTION, USP

Rx ONLY

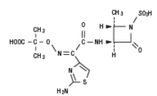
To reduce the development of drug-resistant bacteria and maintain the effectiveness of aztreonam and other antibacterial drugs, aztreonam should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Aztreonam for Injection, USP contains the active ingredient aztreonam, a monobactam. It was originally isolated from *Chromobacterium violaceum*. It is a synthetic bactericidal antibiotic.

The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other beta-lactam antibiotics (e.g., penicillins, cephalosporins, cephamycins). The sulfonic acid substituent in the 1-position of the ring activates the beta-lactam moiety; an aminothiazolyl oxime side chain in the 3-position and a methyl group in the 4-position confer the specific antibacterial spectrum and beta-lactamase stability.

Aztreonam is designated chemically as (Z)-2-[[[(2-amino-4-thiazolyl)[(2*S*,3*S*)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]carbamoyl]methylene]amino]oxy]-2-methylpropionic acid. The structural formula is shown below:



Molecular Formula - $C_{13}H_{17}N_6O_8S_2$ MW= 435.43

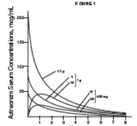
Aztreonam for injection is a sterile, nonpyrogenic, sodium-free, white powder containing approximately 780 mg arginine per gram of aztreonam. Following constitution, the product is for intramuscular or intravenous use. Aqueous solutions of the product have a pH in the range of 4.5 to 7.5.

CLINICAL PHARMACOLOGY

Single 30-minute intravenous infusions of 500-mg, 1-g and 2-g doses of aztreonam for injection in healthy subjects produced aztreonam peak serum levels of 54, 90 and 204 mcg/mL, respectively, immediately after administration; at eight hours, serum levels were 1, 3 and 6 mcg/mL, respectively (Figure 1). Single 3-minute intravenous injections of the same doses resulted in serum levels of 58, 125 and 242 mcg/mL at five minutes following completion of injection.

Serum concentrations of aztreonam in healthy subjects following completion of single intramuscular injections of 500-mg and 1-g doses are depicted in Figure 1; maximum serum concentrations occur at about one hour. After identical single intravenous or intramuscular doses of aztreonam, the serum concentrations of aztreonam are comparable at one hour (1.5 hours from start of intravenous infusion) with similar slopes of serum concentrations thereafter.

FIGURE 1



The serum levels of aztreonam following single 500-mg or 1-g (intramuscular or intravenous) or 2-g (intravenous) doses of aztreonam exceed the MIC_{90} for *Neisseria* sp., *Haemophilus influenzae* and most genera of the *Enterobacteriaceae* for eight hours (for *Enterobacter* sp., the eight-hour serum levels exceed the MIC for 80 percent of strains). For *Pseudomonas aeruginosa*, a single 2-g intravenous dose produces serum levels that exceed the MIC_{90} for approximately four to six hours. All of the above doses of aztreonam result in average urine levels of aztreonam that exceed the MIC_{90} for the same pathogens for up to 12 hours.

When aztreonam pharmacokinetics were assessed for adult and pediatric patients, they were found to be comparable (down to 9-months old). The serum half-life of aztreonam averaged 1.7 hours (1.5 to 2.0) in subjects with normal renal function, independent of the dose and route of administration. In healthy subjects, based on a 70 kg person, the serum clearance was 91 mL/min and renal clearance was 56 mL/min; the apparent mean volume of distribution at steady-state averaged 12.6 liters, approximately equivalent to extracellular fluid volume.

In elderly patients, the mean serum half-life of aztreonam increased and the renal clearance decreased, consistent with the age-related decrease in creatinine clearance.[1 4] The dosage of aztreonam should be adjusted accordingly (see **DOSAGE AND ADMINISTRATION: Renal Impairment in Adult Patients**).

In patients with impaired renal function, the serum half-life of aztreonam is prolonged (See **DOSAGE AND ADMINISTRATION: Renal Impairment in Adult Patients.**) The serum half-life of aztreonam is only slightly prolonged in patients with hepatic impairment since the liver is a minor pathway of excretion.

Average urine concentrations of aztreonam were approximately 1100, 3500 and 6600 mcg/mL within the first 2 hours following single 500-mg, 1-g and 2-g intravenous doses of aztreonam (30-minute infusions), respectively. The range of average concentrations for aztreonam in the 8- to 12-hour urine specimens in these studies was 25 to 120 mcg/mL. After intramuscular injection of single 500 mg and 1 g doses of aztreonam for injection, urinary levels were approximately 500 and 1200 mcg/mL, respectively, within the first two hours, declining to 180 and 470 mcg/mL in the 6- to 8-hour specimens. In healthy subjects, aztreonam is excreted in the urine about equally by active tubular secretion and glomerular filtration. Approximately 60 to 70% of an intravenous or intramuscular dose was recovered in the urine by eight hours. Urinary excretion of a single parenteral dose was essentially complete by 12 hours after injection. About 12% of a single intravenous radiolabeled dose was recovered in the feces. Unchanged aztreonam and the inactive beta-lactam ring hydrolysis product of aztreonam were present in feces and urine.

Intravenous or intramuscular administration of a single 500-mg or 1-g dose of aztreonam every 8 hours for 7 days to healthy subjects produced no apparent accumulation of aztreonam or modification of its disposition characteristics; serum protein binding averaged 56% and was independent of dose. An average of about 6% of a 1-g intramuscular dose was excreted as a microbiologically inactive open beta-lactam ring hydrolysis product (serum half-life approximately 26 hours) of aztreonam in the 0 to 8 hour urine collection on the last day of multiple dosing.

Renal function was monitored in healthy subjects given aztreonam; standard tests (serum creatinine, creatinine clearance, BUN, urinalysis and total urinary protein excretion) as well as special tests (excretion of N-acetyl-β-glucosaminidase, alanine aminopeptidase and β_2-microglobulin) were used. No abnormal results were obtained.

Aztreonam achieves measurable concentrations in the following body fluids and tissues:

EXTRAVASCULAR CONCENTRATIONS OF AZTREONAM AFTER A SINGLE PARENTERAL DOSE*

Fluid or Tissue	Dose (g)	Route	Hours Post-injection	Number of Patients	Mean Concentration (mcg/mL or mcg/g)
Fluids					
bile	1	IV	2	10	39
blister fluid	1	IV	1	6	20
bronchial secretion	2	IV	4	7	5
cerebrospinal fluid (inflamed meninges)	2	IV	0.9-4.3	16	3
pericardial fluid	2	IV	1	6	33
pleural fluid	2	IV	1.1-3.0	3	51
synovial fluid	2	IV	0.8-1.9	11	83
Tissues					
atrial appendage	2	IV	0.9-1.6	12	22
endometrium	2	IV	0.7-1.9	4	9
fallopian tube	2	IV	0.7-1.9	8	12
fat	2	IV	1.3-2.0	10	5
femur	2	IV	1.0-2.1	15	16
gallbladder	2	IV	0.8-1.3	4	23
kidney	2	IV	2.4-5.6	5	67
large intestine	2	IV	0.8-1.9	9	12
liver	2	IV	0.9-2.0	6	47
lung	2	IV	1.2-2.1	6	22
myometrium	2	IV	0.7-1.9	9	11
ovary	2	IV	0.7-1.9	7	13
prostate	1	IM	0.8-2.0	8	8
skeletal muscle	2	IV	0.3-0.7	6	16
skin	2	IV	0.0-1.0	8	25
sternum	2	IV	1	6	6

*Tissue penetration is regarded as essential to therapeutic efficacy, but specific tissue levels have not been correlated with specific therapeutic effects.

The concentration of aztreonam in saliva at 30 minutes after a single 1-g intravenous dose (9 patients) was 0.2 mcg/mL; in human milk at 2 hours after a single 1-g intravenous dose (6 patients), 0.2 mcg/mL, and at 6 hours after a single 1-g intramuscular dose (6 patients), 0.3 mcg/mL; in amniotic fluid at 6 to 8 hours after a single 1-g intravenous dose (5 patients), 2 mcg/mL. The concentration of aztreonam in peritoneal fluid obtained 1 to 6 hours after multiple 2-g intravenous doses ranged between 12 and 90 mcg/mL in 7 of 8 patients studied.

Aztreonam given intravenously rapidly reaches therapeutic concentrations in peritoneal dialysis fluid; conversely, aztreonam given intraperitoneally in dialysis fluid rapidly produces therapeutic serum levels.

Concomitant administration of probenecid or furosemide and aztreonam for injection causes clinically insignificant increases in the serum levels of aztreonam. Single-dose intravenous pharmacokinetic studies have not shown any significant interaction between aztreonam and concomitantly administered gentamicin, nafcillin sodium, cephradine, clindamycin or metronidazole. No reports of disulfiram-like reactions with alcohol ingestion have been noted; this is not unexpected since aztreonam does not contain a methyl-tetrazole side chain.

Microbiology

Aztreonam exhibits potent and specific activity *in vitro* against a wide spectrum of gram-negative aerobic pathogens including *Pseudomonas aeruginosa*. The bactericidal action of aztreonam results from the inhibition of bacterial cell wall synthesis due to a high affinity of aztreonam for penicillin binding protein 3 (PBP3). Aztreonam, unlike the majority of beta-lactam antibiotics, does not induce beta-lactamase activity and its molecular structure confers a high degree of resistance to hydrolysis by beta-lactamases (i.e., penicillinases and cephalosporinases) produced by most gram-negative and gram-positive pathogens; it is, therefore, usually active against gram-negative aerobic microorganisms that are resistant to antibiotics hydrolyzed by beta-lactamases. It is active against many strains that are multiply-resistant to other antibiotics, such as certain cephalosporins, penicillin, and aminoglycosides. Aztreonam maintains its antimicrobial activity over a pH range of 6 to 8 *in vitro*, as well as in the presence of human serum and under anaerobic conditions.

Aztreonam has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in **INDICATIONS AND USAGE.**

Aerobic gram-negative microorganisms:
Citrobacter species, including *C. freundii*
Enterobacter species, including *E. cloacae*
Escherichia coli
Haemophilus influenzae (including ampicillin-resistant and other penicillinase-producing strains)
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa
Serratia species, including *S. marcescens*

The following *in vitro* data are available, **but their clinical significance is unknown.**

Aztreonam exhibits *in vitro* minimal inhibitory concentrations (MIC_s) of 8 mcg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of aztreonam in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-negative microorganisms:
Aeromonas hydrophila
Morganella morganii
Neisseria gonorrhoeae (including penicillinase-producing strains)
Pasteurella multocida
Proteus vulgaris
Providencia stuartii
Providencia rettgeri
Yersinia enterocolitica

Aztreonam and aminoglycosides have been shown to be synergistic *in vitro* against most strains of *P. aeruginosa*, many strains of *Enterobacteriaceae*, and other gram-negative aerobic bacilli.

Alterations of the anaerobic intestinal flora by broad spectrum antibiotics may decrease colonization resistance, thus permitting overgrowth of potential pathogens, e.g., *Candida* and *Clostridium* species. Aztreonam has little effect on the anaerobic intestinal microflora *in in vitro* studies. *Clostridium difficile* and its cytotoxin were not found in animal models following administration of aztreonam. (See **ADVERSE REACTIONS:** *Gastrointestinal.*)

Susceptibility Tests
Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC_s). These MIC_s provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC_s should be determined using a standardized procedure. Standardized procedures are based on a dilution method[5] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of aztreonam for powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus influenzae*:

MIC (mcg/mL)	Interpretation
≤8	Susceptible (S)
16	Intermediate (I)
≥32	Resistant (R)

When testing *Haemophilus influenzae*[a]:

MIC (mcg/mL)	Interpretation[b]
≤2	Susceptible (S)

[a]Interpretative criteria applicable only to tests performed by broth microdilution method using *Haemophilus* Test Medium (HTM).[5]

[b]The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard aztreonam powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
Escherichia coli ATCC 25922	0.06-0.25
Haemophilus influenzae[a] ATCC 49247	0.12-0.5
Pseudomonas aeruginosa ATCC 27853	2.0-8.0

[a]Range applicable only to tests performed by broth microdilution method using *Haemophilus* Test Medium (HTM).[5]

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[6] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30-mcg aztreonam to test the susceptibility of microorganisms to aztreonam.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-mcg aztreonam disk should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus influenzae*:

Zone diameter (mm)	Interpretation
≥22	Susceptible (S)
16-21	Intermediate (I)
≤15	Resistant (R)

When testing *Haemophilus influenzae*[a]:

Zone diameter (mm)	Interpretation[b]
≥26	Susceptible (S)

[a]Interpretative criteria applicable only to tests performed by disk diffusion method using *Haemophilus* Test Medium (HTM).[6]

[b]The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for aztreonam.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-mcg aztreonam disk should provide the following zone diameters in these laboratory test quality control strains.

Microorganism	Zone diameter (mm)
Escherichia coli ATCC 25922	28-36 mm
Haemophilus influenzae[a] ATCC 49247	30-38 mm
Pseudomonas aeruginosa ATCC 27853	23-29 mm

[a]Range applicable only to tests performed by disk diffusion method using *Haemophilus* Test Medium (HTM).[6]

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of aztreonam and other antibacterial drugs, aztreonam should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Aztreonam for injection is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms:

Urinary Tract Infections (complicated and uncomplicated), including pyelonephritis and cystitis (initial and recurrent) caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Klebsiella oxytoca**, *Citrobacter* species* and *Serratia marcescens**.

Lower Respiratory Tract Infections, including pneumonia and bronchitis caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Proteus mirabilis*, *Enterobacter* species and *Serratia marcescens**.

Septicemia caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis**, *Serratia marcescens** and *Enterobacter* species.

Skin and Skin-Structure Infections, including those associated with postoperative wounds, ulcers and burns caused by *Escherichia coli*, *Proteus mirabilis*, *Serratia marcescens*, *Enterobacter* species, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Citrobacter* species*.

Intra-abdominal Infections, including peritonitis caused by *Escherichia coli*, *Klebsiella* species including *K. pneumoniae*, *Enterobacter* species including *E. cloacae**, *Pseudomonas aeruginosa*, *Citrobacter* species* including *C. freundii** and *Serratia* species* including *S. marcescens**.

Gynecologic Infections, including endometritis and pelvic cellulitis caused by *Escherichia coli*, *Klebsiella pneumoniae**, *Enterobacter* species* including *E. cloacae** and *Proteus mirabilis**.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Aztreonam is indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscus perforations, cutaneous infections and infections of serous surfaces. Aztreonam is effective against most of the commonly encountered gram-negative aerobic pathogens seen in general surgery.

Concurrent Therapy
Concurrent initial therapy with other antimicrobial agents and aztreonam for injection is recommended before the causative organism(s) is known in seriously ill patients who are also at risk of having an infection due to gram-positive aerobic pathogens. If anaerobic organisms are also suspected as etiologic agents, therapy should be initiated using an anti-anaerobic agent concurrently with aztreonam (see **DOSAGE AND ADMINISTRATION**). Certain antibiotics (e.g., cefoxitin, imipenem) may induce high levels of beta-lactamase *in vitro* in some gram-negative aerobes such as *Enterobacter* and *Pseudomonas* species, resulting in antagonism to many beta-lactam antibiotics including aztreonam. These *in vitro* findings suggest that such beta-lactamase inducing antibiotics not be used concurrently with aztreonam. Therapy with aztreonam and susceptibility testing of the causative organism(s), appropriate antibiotic therapy should be continued.

CONTRAINDICATIONS

This preparation is contraindicated in patients with known hypersensitivity to aztreonam or any other component in the formulation.

WARNINGS

Both animal and human data suggest that aztreonam is rarely cross-reactive with other beta-lactam antibiotics and weakly immunogenic. Treatment with aztreonam can result in hypersensitivity reactions in patients with or without prior exposure. (See **CONTRAINDICATIONS.**)

Careful inquiry should be made to determine whether the patient has any history of hypersensitivity reactions to any allergens.

While cross-reactivity of aztreonam with other beta-lactam antibiotics is rare, this drug should be administered with caution to any patient with a history of hypersensitivity to beta-lactams (e.g., penicillins, cephalosporins, and/or carbapenems). Treatment with aztreonam can result in hypersensitivity reactions in patients with or without prior exposure to aztreonam. If an allergic reaction to aztreonam occurs, discontinue the drug and institute supportive treatment as appropriate (e.g., maintenance of ventilation, pressor amines, antihistamines, corticosteroids). Serious hypersensitivity reactions may require epinephrine and other emergency measures. (See **ADVERSE REACTIONS.**)

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including aztreonam, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicro-

bial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Rare cases of toxic epidermal necrolysis have been reported in association with aztreonam in patients undergoing bone marrow transplant with multiple risk factors including sepsis, radiation therapy and other concomitantly administered drugs associated with toxic epidermal necrolysis.

PRECAUTIONS

General

Prescribing aztreonam in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy.

If an aminoglycoside is used concurrently with aztreonam, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics.

The use of antibiotics may promote the overgrowth of nonsusceptible organisms, including gram-positive organisms (*Staphylococcus aureus* and *Streptococcus faecalis*) and fungi. Should superinfection occur during therapy, appropriate measures should be taken.

Information for Patients

Patients should be counseled that antibacterial drugs including aztreonam should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When aztreonam is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by aztreonam or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of antibiotic. If this occurs, patients should contact their physician as soon as possible.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies in animals have not been performed.

Genetic toxicology studies performed *in vivo* and *in vitro* with aztreonam in several standard laboratory models revealed no evidence of mutagenic potential at the chromosomal or gene level.

Two-generation reproduction studies in rats at daily doses up to 20 times the maximum recommended human dose, prior to and during gestation and lactation, revealed no evidence of impaired fertility. There was a slightly reduced survival rate during the lactation period in the offspring of rats that received the highest dosage, but not in offspring of rats that received 5 times the maximum recommended human dose.

Pregnancy: Pregnancy Category B

Aztreonam crosses the placenta and enters the fetal circulation.

Studies in pregnant rats and rabbits, with daily doses up to 15 and 5 times, respectively, the maximum recommended human dose, revealed no evidence of embryo- or fetotoxicity or teratogenicity. No drug induced changes were seen in any of the maternal, fetal, or neonatal parameters that were monitored in rats receiving 15 times the maximum recommended human dose of aztreonam during late gestation and lactation.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed.

Nursing Mothers

Aztreonam is excreted in human milk in concentrations that are less than 1% of concentrations determined in simultaneously obtained maternal serum; consideration should be given to temporary discontinuation of nursing and use of formula feedings.

Pediatric Use

The safety and effectiveness of intravenous aztreonam for injection have been established in the age groups 9 months to 16 years. Use of aztreonam in these age groups is supported by evidence from adequate and well-controlled studies of aztreonam in adults with additional efficacy, safety, and pharmacokinetic data from non-comparative clinical studies in pediatric patients. Sufficient data are not available for pediatric patients under 9 months of age or for the following treatment indications/pathogens: septicemia and skin and skin-structure infections (where the skin infection is believed or known to be due to *H. influenzae* type b). In pediatric patients with cystic fibrosis, higher doses of aztreonam may be warranted. (See **CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION,** and **CLINICAL STUDIES.**)

Geriatric Use

Clinical studies of aztreonam did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.[7,10] In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

In elderly patients, the mean serum half-life of aztreonam increased and the renal clearance decreased, consistent with the age-related decrease in creatinine clearance.[1,4] Since aztreonam is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments made accordingly (see **DOSAGE AND ADMINISTRATION: Renal Impairment in Adult Patients** and **Dosage in the Elderly**).

Aztreonam contains no sodium.

ADVERSE REACTIONS

Local reactions such as phlebitis/thrombophlebitis following IV administration, and discomfort/swelling at the injection site following IM administration occurred at rates of approximately 1.9% and 2.4%, respectively.

Systemic reactions (considered to be related to therapy or of uncertain etiology) occurring at an incidence of 1 to 1.3% include diarrhea, nausea and/or vomiting, and rash. Reactions occurring at an incidence of less than 1% are listed within each body system in order of decreasing severity:

Hypersensitivity – anaphylaxis, angioedema, bronchospasm

Hematologic – pancytopenia, neutropenia, thrombocytopenia, anemia, eosinophilia, leukocytosis, thrombocytosis

Gastrointestinal – abdominal cramps; rare cases of *C. difficile*-associated diarrhea, including pseudomembranous colitis, or gastrointestinal bleeding have been reported. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See **WARNINGS.**)

Dermatologic – toxic epidermal necrolysis (see **WARNINGS**), purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis

Cardiovascular – hypotension, transient ECG changes (ventricular bigeminy and PVC), flushing

Respiratory – wheezing, dyspnea, chest pain

Hepatobiliary – hepatitis, jaundice

Nervous System – seizure, confusion, vertigo, paresthesia, insomnia, dizziness

Musculoskeletal – muscular aches

Special Senses – tinnitus, diplopia, mouth ulcer, altered taste, numb tongue, sneezing, nasal congestion, halitosis

Other – vaginal candidiasis, vaginitis, breast tenderness

Body as a Whole – weakness, headache, fever, malaise

Pediatric Adverse Reactions

Of the 612 pediatric patients who were treated with aztreonam in clinical trials, less than 1% required discontinuation of therapy due to adverse events. The following systemic adverse events, regardless of drug relationship, occurred in at least 1% of treated patients in domestic clinical trials: rash (4.3%), diarrhea (1.4%), and fever (1%). These adverse events were comparable to those observed in adult clinical trials.

In 343 pediatric patients receiving intravenous therapy, the following local reactions were noted: pain (12%), erythema (2.9%), induration (0.9%), and phlebitis (2.1%). In the US patient population, pain occurred in 1.5% of patients, while each of the remaining three local reactions had an incidence of 0.5%.

The following laboratory adverse events, regardless of drug relationship, occurred in at least 1% of treated patients: increased eosinophils (6.3%), increased platelets (3.6%), neutropenia (3.2%), increased AST (3.8%), increased ALT (6.5%), and increased serum creatinine (5.8%).

In US pediatric clinical trials, neutropenia (absolute neutrophil count less than 1000/mm³) occurred in 11.3% of patients (8/71) younger than 2 years receiving 30 mg/kg q6h. AST and ALT elevations to greater than 3 times the upper limit of normal were noted in 15 to 20% of patients aged 2 years or above receiving 50 mg/kg q8h. The increased frequency of these reported laboratory adverse events may be due to either increased severity of illness treated or higher doses of aztreonam for injection administered.

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hepatic – elevations of AST (SGOT), ALT (SGPT), and alkaline phosphatase; signs or symptoms of hepatobiliary dysfunction occurred in less than 1% of recipients (see above).

Hematologic – increases in prothrombin and partial thromboplastin times, positive Coombs' test.

Renal – increases in serum creatinine.

OVERDOSAGE

If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

Dosage in Adult Patients

Aztreonam may be administered intravenously or by intramuscular injection. Dosage and route of administration should be determined by susceptibility of the causative organisms, severity and site of infection, and the condition of the patient.

The intravenous route is recommended for patients requiring single doses greater than 1 g or those with bacterial septicemia, localized parenchymal abscess (e.g., intra-abdominal abscess), peritonitis or other severe systemic or life-threatening infections.

The duration of therapy depends on the severity of infection. Generally, aztreonam should be continued for at least 48 hours after the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. Persistent infections may require treatment for several weeks. Doses smaller than those indicated should not be used.

Renal Impairment in Adult Patients

Prolonged serum levels of aztreonam may occur in patients with transient or persistent renal insufficiency. Therefore, the dosage of aztreonam should be halved in patients with estimated creatinine clearances between 10 mL/min/1.73 m² and 30 mL/min/1.73 m² after an initial loading dose of 1 g or 2 g.

When only the serum creatinine concentration is available, the following formula (based on sex, weight, and age of the patient) may be used to approximate the creatinine clearance (Clcr). The serum creatinine should represent a steady state of renal function.

$$\text{Males: Clcr} = \frac{\text{weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: 0.85 x above value

In patients with severe renal failure (creatinine clearance less than 10 mL/min/1.73 m²), such as those supported by hemodialysis, the usual dose of 500 mg, 1 g or 2 g should be given initially. The maintenance dose should be one-fourth of the usual initial dose given at the usual fixed interval of 6, 8 or 12 hours. For serious or life-threatening infections, in addition to the maintenance doses, one-eighth of the initial dose should be given after each hemodialysis session.

Dosage in the Elderly

Renal status is a major determinant of dosage in the elderly; these patients in particular may have diminished renal function. Serum creatinine may not be an accurate determinant of renal status. Therefore, as with all antibiotics eliminated by the kidneys, estimates of creatinine clearance should be obtained, and appropriate dosage modifications made if necessary.

Dosage in Pediatric Patients

Aztreonam for injection should be administered intravenously to pediatric patients with normal renal function. There are insufficient data regarding intramuscular administration to pediatric patients or dosing in pediatric patients with renal impairment. (See **PRECAUTIONS: Pediatric Use.**)

AZTREONAM FOR INJECTION DOSAGE GUIDELINES

Type of Infection	Dose	Frequency (hours)
ADULTS*		
Urinary tract infections	500 mg or 1 g	8 or 12
Moderately severe systemic infections	1 g or 2 g	8 or 12
Severe systemic or life-threatening infections	2 g	6 or 8
*Maximum recommended dose is 8 g per day.		
PEDIATRIC PATIENTS**		
Mild to moderate infections	30 mg/kg	8
Moderate to severe infections	30 mg/kg	6 or 8
**Maximum recommended dose is 120 mg/kg/day.		

Because of the serious nature of infections due to *Pseudomonas aeruginosa*, dosage of 2 g every 6 or 8 hours is recommended, at least upon initiation of therapy, in systemic infections caused by this organism in adults.

CLINICAL STUDIES

A total of 612 pediatric patients aged 1 month to 12 years were enrolled in uncontrolled clinical trials of aztreonam in the treatment of serious gram-negative infections, including urinary tract, lower respiratory tract, skin and skin-structure, and intra-abdominal infections.

Preparation of Parenteral Solutions

General

Upon the addition of the diluent to the container, contents should be shaken **immediately** and **vigorously.** Constituted solutions are not for multiple-dose use; should the entire volume in the container not be used for a single-dose, the unused solution must be discarded.

Depending upon the concentration of aztreonam and diluent used, constituted aztreonam yields a colorless to light straw yellow solution which may develop a slight pink tint on standing (potency is not affected).

Parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit.

Admixtures with Other Antibiotics

Intravenous infusion solutions of aztreonam not exceeding 2% w/v prepared with Sodium Chloride Injection 0.9% or Dextrose Injection 5%, to which clindamycin phosphate, gentamicin sulfate, tobramycin sulfate, or cefazolin sodium have been added at concentrations usually used clinically, are stable for up to 48 hours at room temperature or 7 days under refrigeration. Ampicillin sodium admixtures with aztreonam in Sodium Chloride Injection 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection 5% is 2 hours at room temperature and 8 hours under refrigeration.

Aztreonam-clavacillin sodium and aztreonam-vancomycin hydrochloride admixtures are stable in Dianeal® 137* (Peritoneal Dialysis Solution) with 4.25% Dextrose for up to 24 hours at room temperature.

Aztreonam is incompatible with nafcillin sodium, cephradine, and metronidazole.

Other admixtures are not recommended since compatibility data are not available.

Intravenous (IV) Solutions

For Bolus Injection: The contents of the aztreonam for injection vial should be constituted with 6 to 10 mL Sterile Water for Injection.

For Infusion: If the contents of the vial are to be transferred to an appropriate infusion solution, each gram of aztreonam should be initially constituted with at least 3 mL Sterile Water for Injection. Further dilution may be obtained with one of the following intravenous infusion solutions:

Sodium Chloride Injection, 0.9%
Ringer's Injection
Lactated Ringer's Injection
Dextrose Injection, 5% or 10%
Dextrose and Sodium Chloride Injection, 5%-0.9%, 5%-0.45% or 5%-0.2%
Sodium Lactate Injection (M/6 Sodium Lactate)
Ionosol® B and 5% Dextrose
Isolyte® M with 5% Dextrose
Normosol®-R
Normosol®-R and 5% Dextrose
Normosol®-M and 5% Dextrose
Mannitol Injection, 5% or 10%
Lactated Ringer's and 5% Dextrose Injection

Intramuscular (IM) Solutions

The contents of an aztreonam vial should be constituted with at least 3 mL of an appropriate diluent per gram aztreonam. The following diluents may be used:

Sterile Water for Injection
Sterile Bacteriostatic Water for Injection (with benzyl alcohol or with methyl- and propylparabens)
Sodium Chloride Injection, 0.9%
Bacteriostatic Sodium Chloride Injection (with benzyl alcohol)

Stability of IV and IM Solutions

Aztreonam solutions for IV infusion at concentrations not exceeding 2% w/v must be used within 48 hours following constitution if kept at 20° to 25°C (68° to 77°F) (see USP controlled room temperature) or within seven days if refrigerated 2° to 8°C (36° to 46°F).

Aztreonam solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection or Sodium Chloride Injection, should be used promptly after preparation; the two excepted solutions must be used within 48 hours if stored at controlled room temperature or within seven days if refrigerated.

Intravenous Administration

Bolus Injection: A bolus injection may be used to initiate therapy. The dose should be **slowly** injected directly into a vein, or the tubing of a suitable administration set, over a period of 3 to 5 minutes (see next paragraph regarding flushing of tubing).

Infusion: With any intermittent infusion of aztreonam and another drug with which it is not pharmaceutically compatible, the common delivery tube should be flushed before and after delivery of aztreonam with any appropriate infusion solution compatible with both drug solutions; the drugs should not be delivered simultaneously. Any aztreonam for injection infusion should be completed within a 20 to 60 minute period. With use of a *Y-type administration set*, careful attention should be given to the calculated volume of aztreonam solution required so that the entire dose will be infused. A volume control administration set may be used to deliver an initial dilution of aztreonam (see **Preparation of Parenteral Solutions - Intravenous (IV) Solutions:** *For Infusion*) into a compatible infusion solution during administration; in this case, the final dilution of aztreonam should provide a concentration not exceeding 2% w/v.

Intramuscular Administration

The dose should be given by deep injection into a large muscle mass (such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh). Aztreonam is well tolerated and should not be admixed with any local anesthetic agent.

HOW SUPPLIED

Aztreonam for Injection, USP, single-dose vials, is supplied as follows:
NDC 55390-177-10; 1 g/vial; 10 mL capacity vial; carton of 10
NDC 55390-178-10; 2 g/vial; 15 mL capacity vial; carton of 10

Storage

Store original packages at 20° to 25°C (68° to 77°F). See USP controlled room temperature; avoid excessive heat.

*Dianeal® 137 is a registered trademark of Baxter International Inc.

Ionosol® and Normosol® are registered trademarks of Abbott Laboratories Corporation.
Isolyte® is a registered trademark of McGaw Inc.

REFERENCES

1. Naber KG, Dette GA, Kees F, Kocthe H, Grobecker H. Pharmacokinetics, *in vitro* activity, therapeutic efficacy, and clinical safety of aztreonam vs. cefotaxime in the treatment of complicated urinary tract infections. *J Antimicrob Chemother* 1986; 17:517-527.
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3. Meyers BR, Wilkinson P, Mendelson MH, *et al.* Pharmacokinetics of aztreonam in healthy elderly and young adult volunteers. *J Clin Pharmacol* 1993; 33:470-474.
4. Sattler FR, Schramm M, Swabb EA. Safety of aztreonam and SQ 26,992 in elderly patients with renal insufficiency. *Rev Infect Dis* 1985; 7 (suppl 4):S622-S627.
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8. Knockaert DC, Dejaeger E, Nestor L, *et al.* Aztreonam-flucloxacillin double beta-lactam treatment as empirical therapy of serious infections in very elderly patients. *Age and Aging* 1981; 20:135-139.
9. Roelandts F. Clinical use of aztreonam in a psychogeriatric population. *Acta Clin Belg* 1992; 47:251-255.
10. Andrews R, Fasoli R, Scoggins WG, *et al.* Combined aztreonam and gentamicin therapy for pseudomonal lower respiratory tract infections. *Clin Therap* 1994; 16:236-252.
11. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Susceptibility Testing* – Eleventh Informational Supplement, NCCLS Document M100-S11, Vol. 21, No. 1, NCCLS, Wayne, PA, January 2001.

Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

February 2010

Div-AZNM-P00

Reference ID: 2908178

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065286

LABELING REVIEWS

THIS APPROVAL SUMMARY SUPERSEDES THE APPROVAL SUMMARY DATED MAY 26, 2009

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-286

Date of Submission: June 17, 2010

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram and 2 grams

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BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? See EDR.
- REMS required? No.

MedGuides and/or PPIs (505-1(e))	☐ Yes	☒ No
Communication plan (505-1(e))	☐ Yes	☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☒ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☒ No
Timetable for assessment (505-1(d))	☐ Yes	☒ No

- ANDA REMS acceptable? ☐ Yes ☐ No ☒ n/a

1. CONTAINER:
   -1 gram
   Satisfactory in final as of the August 30, 2007 submission.
   - 2 grams
   Satisfactory in final as of the June 17, 2010 submission.

2. CARTON:
   - 1 gram - 10s
   Satisfactory in final as of the August 30, 2007 submission.
   - 2 grams - 10s
   Satisfactory in final as of the June 17, 2010 submission.

3. INSERT:
   Satisfactory in final as of the June 17, 2010 submission.
   Insert code: Div.AZNM-P00 Revised February 2010

Revisions needed post-approval:
1. CONTAINER: 1 gram and 2 grams
   a. Front Panel
      Print “for Injection” using the same font size as “Aztreonam”.

b. Side panel
    i. Revise to read, "…solution stability".
    ii. Include the temperature range in the storage statement.

2. CARTON: 10s
   See comments under CONTAINER.
3. INSERT
   a. General Comments:
      i. Increase the size of the asterisks and superscripts.
      ii. Decrease the prominence of the company logo appearing prior to the TITLE.
   b. DESCRIPTION
      i. Revise the last paragraph to read, "…of aztreonam. Each 1 gram vial contains 1 gram aztreonam with approximately ... arginine. Each 2 gram vial contains….".
   c. CLINICAL PHARMACOLOGY
      i. Following the second paragraph, increase the size of Figure 1.
      ii. If you are not able to print the entire table on the same page, then reprint the title at the top of the second portion of the table with the entire heading following by "(continued)" at the end of title.
   d. DOSAGE AND ADMINISTRATION
      Intravenous (IV) Solutions
      Upon further review, retain the IV solutions, "Isolyte® E" and "Isolyte® E with 5% Dextrose". In addition, Plasma-Lyte M and 5% Dextrose should also be retained.

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Azactam

NDA Number: NDA 050580

NDA Drug Name: Azactam

NDA Firm: Bristol Myers Squibb Company

Date of Approval of NDA Insert and supplement #:S-040 approved 1/22/08

Has this been verified by the Drugs @FDA Yes

Was this approval based upon an OGD labeling guidance? No

-----Original Message-----
From: Nguyen, Ryan
Sent: Wednesday, February 01, 2006 4:37 PM
To: Takiar, Neeru B
Cc: Zuk, Susan; Park, Sarah Soojung
Subject: FW: 65-286.

Hi Neeru,

Please respond to Jackie's questions below. Thanks.

Ryan

-----Original Message-----
From: Council, Jacqueline
Sent: Wednesday, February 01, 2006 4:36 PM
To: Nguyen, Ryan
Subject: 65-286.

Good afternoon Ryan,

I completed the review [with deficiencies]. Please see below.

Thanks,
Jacqueline

ANDA Number: 65-286

Dates of Submission: December 23, 2004

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

NOTES/QUESTIONS TO THE CHEMIST [chemist response copied from previous reviewer].

1. The innovator's vial size is "15 mL" and the ANDA vial size is "10 mL" We plan to inform the ANDA that the vial size should be the same as the innovator's, "15 mL".

That is fine.

Neeru's email dated 4/19/07:

> As per comment 6 (see below) in my review #2,10 mL size is not acceptable.
>
> Please note that it is recommended in your labeling that for intravenous solutions (bolus injection), the contents of the aztreonam for injection 1 gram vial should be are constituted with 6 to 10 mL Sterile Water for Injection. Therefore, we recommend that you revise your vial size to same as the innovator "15 mL" because the proposed vial size "10 mL" may not be an adequate size for constituting IV solutions. Please revise your labels and labeling accordingly.
>
> Neeru

2. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION SECTION, [i.e., dilution volumes, concentration, admixture with other ant biotics and diluents]? See text from insert labeling below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam not exceeding 2% w/v prepared with Sodium Chloride Injection 0.9% or Dextrose Injection 5%, to which clindamycin phosphate, gentamicin sulfate, tobramycin sulfate, or cefazolin sodium have been added at concentrations usually used clinically, are stable for up to 48 hours at room temperature or seven days under refrigeration. Ampicillin sodium admixtures with aztreonam in Sodium Chloride Injection 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection 5% is two hours at room temperature and eight hours under refrigeration.

Aztreonam-cloxacillin sodium and aztreonam-vancomycin hydrochloride admixtures are stable in Dianeal® 137 (Peritoneal Dialysis Solution) with 4.25% Dextrose for up to 24 hours at room temperature.

Aztreonam is incompatible with nafcillin sodium, cephradine, and metronidazole.

Other admixtures are not recommended since compatibility data are not available.

Intravenous (IV) Solutions

For Bolus Injection: The contents of the aztreonam for injection 1 gram vial should be constituted with 6 to 10 mL Sterile Water for Injection.

For Infusion (b) (4) Each gram of aztreonam should be initially constituted with at least 3 mL Sterile Water for Injection and transferred to an appropriate infusion solution. Further dilution may be obtained with one of the following intravenous infusion solutions:

Sodium Chloride Injection, 0.9%
Ringer's Injection
Lactated Ringer's Injection
Dextrose Injection, 5% or 10%
Dextrose and Sodium Chloride Injection, 5%:0.9%, 5%:0.45% or 5%:0.2%
Sodium Lactate Injection (M/6 Sodium Lactate)
Ionosol® B and 5% Dextrose
Isolyte® M with 5% Dextrose
Normosol®-R
Normosol®-R and 5% Dextrose
Normosol®-M and 5% Dextrose
Mannitol Injection, 5% or 10%
Lactated Ringer's and 5% Dextrose Injection
Plasma-Lyte® M and 5% Dextrose

Intramuscular (IM) Solutions

The contents of an aztreonam vial should be constituted with at least 3 mL of an appropriate diluent per gram aztreonam. The following diluents may be used:

Sterile Water for Injection
Sterile Bacteriostatic Water for Injection (with benzyl alcohol or with methyl- and propylparabens)

Sodium Chloride Injection, 0.9%
Bacteriostatic Sodium Chloride Injection (with benzyl alcohol)

Stability Of IV And IM Solutions

Aztreonam solutions for IV infusion at concentrations not exceeding 2% w/v must be used within 48 hours following constitution if kept at 20° to 25°C (68° to 77°F) (see USP controlled room temperature) or within seven days if refrigerated 2° to 8°C (36° to 46°F).

(b) (4)

Aztreonam solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection or Sodium Chloride Injection, should be used promptly after preparation; the two excepted solutions must be used within 48 hours if stored at controlled room temperature or within seven days if refrigerated.

Yes

Thanks

From: Takiar, Neeru B
Sent: Saturday, January 22, 2011 10:39 AM
To: Council, Jacqueline
Subject: RE: 65-286

Hi Jacqueline,

The chemistry portion of review is complete and found acceptable. The chemistry revisions do not affect any portion of the labeling. See Attached review below for details.

Neeru

From: Council, Jacqueline
Sent: Friday, January 21, 2011 1:22 PM
To: Takiar, Neeru B
Subject: FW: 65-286

Good afternoon Neeru,

Any update? Please see below.

Thanks,
Jacqueline

From: Takiar, Neeru B
Sent: Monday, August 24, 2009 1:15 PM
To: Council, Jacqueline
Subject: RE: 65-286

Hi Jacqueline,

The firm has not responded to minor amendment yet (issued in June 2008). Thanks.

Neeru

From: Council, Jacqueline
Sent: Tuesday, August 11, 2009 1:33 PM
To: Takiar, Neeru B
Subject: FW: 65-286

Good afternoon Neeru,

I am not sure if you have completed your chemistry review yet. If you have completed the review can you please inform me of the following?

Thanks,
Jacqueline

1. Does the chemistry revision effect any of the information below from the firm's Description section?

DESCRIPTION

Aztreonam for Injection, USP contains the active ingredient aztreonam, a monobactam. It was originally isolated from Chromobacterium violaceum. It is a synthetic bactericidal antibiotic.

The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other betalactam antibiotics (e.g., penicillins, cephalosporins, cephamycins). The sulfonic acid substituent in the 1-position of the ring activates the beta-lactam moiety; an aminothiazolyl oxime side chain in the 3-position and a methyl group in the 4-position confer the specific antibacterial spectrum and beta-lactamase stability.

Aztreonam is designated chemically as (Z)-2-[[[(2-amino-4-thiazolyl)[[(2S,3S)-2methyl-4-oxo-1-sulfo-3-azetidinyl] carbamoyl]methylene]amino]oxy]-2-methylpropionic acid. The structural formula is shown below:

Molecular Formula - C13H17N508S2 MW= 435.43

Aztreonam for injection is a sterile, nonpyrogenic, sodium-free, white powder containing approximately 780 mg arginine per gram of aztreonam. Following constitution, the product is for intramuscular or intravenous use.

Aqueous solutions of the product have a pH in the range of 4.5 to 7.5.

2. Does the chemistry revision effect any other portion of the labeling?

From: Takiar, Neeru B
Sent: Monday, March 16, 2009 3:29 PM
To: Council, Jacqueline
Cc: Iser, Robert
Subject: RE: 65-286

This is a first generic, I cannot say for sure about the changes until the review is complete.

From: Council, Jacqueline
Sent: Monday, March 16, 2009 3:24 PM
To: Takiar, Neeru B
Subject: RE: 65-286

Does the chemistry revision effect any of the information below from the firm's Description section?

Thanks

DESCRIPTION
Aztreonam for Injection, USP contains the active ingredient aztreonam, a monobactam. It was originally isolated from Chromobacterium violaceum. It is a synthetic bactericidal antibiotic.
The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other betalactam antibiotics (e.g., penicillins, cephalosporins, cephamycins). The sulfonic acid substituent in the 1-position of the ring activates the beta-lactam moiety; an aminothiazolyl oxime side chain in the 3-position and a methyl group in the 4-position confer the specific antibacterial spectrum and beta-lactamase stability.
Aztreonam is designated chemically as (Z)-2-[[[(2-amino-4-thiazolyl)[[(2S,3S)-2methyl-4-oxo-1-sulfo-3-azetidinyl] carbamoyl]methylene]amino]oxy]-2-methylpropionic acid. The structural formula is shown below:
Molecular Formula - C13H17N508S2 MW= 435.43
Aztreonam for injection is a sterile, nonpyrogenic, sodium-free, white powder containing approximately 780 mg arginine per gram of aztreonam. Following constitution, the product is for intramuscular or intravenous use.
Aqueous solutions of the product have a pH in the range of 4.5 to 7.5.

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Sent: Monday, March 16, 2009 3:18 PM
To: Council, Jacqueline
Subject: RE: 65-286

This change is in the drug substance.

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Subject: RE: 65-286

Can you please inform what the chemistry change is for, then I can determine if the labeling will require a revision.

Thanks.

From: Takiar, Neeru B
Sent: Monday, March 16, 2009 3:13 PM
To: Council, Jacqueline
Subject: RE: 65-286

The firm will be required to make changes.

From: Council, Jacqueline
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To: Takiar, Neeru B
Subject: RE: 65-286

Is okay as is or will the firm be required to make any revisions?

From: Takiar, Neeru B
Sent: Monday, March 16, 2009 3:11 PM
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I have not seen the monograph in the current USP.

Neeru

From: Council, Jacqueline
Sent: Monday, March 16, 2009 2:03 PM
To: Takiar, Neeru B
Subject: 65-286

Good afternoon Neeru.

Is there still a USP issue regarding this drug product? Please refer to your comment below. [This ANDA is getting close to approval].

Thanks,
Jacqueline

From: Takiar, Neeru B
Sent: Thursday, July 24, 2008 11:06 AM
To: Vu, Thuyanh (Ann)
Subject: RE: Labeling comment for 65-286 (Bedford's aztreonam)
Ann,
(b) (4)

Neeru

From: Vu, Thuyanh (Ann)
Sent: Thursday, July 24, 2008 11:29 AM
To: Takiar, Neeru B
Subject: RE: Labeling comment for 65-286 (Bedford's aztreonam)
Neeru, until the USP becomes official, I could not comment to the firm. Could you also email me when you have "comment to the labeling reviewer"?
Thanks
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(b) (4)

Neeru

From: Vu, Thuyanh (Ann)
Sent: Thursday, July 24, 2008 10:30 AM
To: Takiar, Neeru B
Subject: Labeling comment for 65-286 (Bedford's aztreonam)
Neeru,
I found this statement for 65-286 from your review #3
Comment to the Labeling reviewer:
(b) (4). Please contact the firm (b) (4)
recommended
labeling (b) (4).
From your review, the proposed (b) (4)
(b) (4)
I do not understand the meaning of (b) (4)

Thanks
Ann

FOR THE RECORD: (portions taken from previous review)

1. Labeling model

- Azactam®, by Bristol-Myers Squibb Company
NDA 50-580/S-040 approved 1/22/08

- DOSAGE AND ADMINISTRATION section

The firm indicated that they omitted the following infusion solutions because they are no longer commercially available. The new drug division concurred. We plan to allow the ANDAs to omit these infusion solutions. See e-mail below.

10% Travert Injection
10% Travert Injection and Electrolyte No. 1 Injection
10% Travert Injection and Electrolyte No. 2 Injection
10% Travert Injection and Electrolyte No. 3 Injection

From: Samanta, Susmita
Sent: Tuesday, July 28, 2009 2:19 PM
To: Council, Jacqueline
Subject: RE: ...NDA 50-580 Azactam

Good afternoon Dr. Council,

Thank you for the reminder. It is true that these products are not available any more. The sponsor is going to change the label. As soon as I hear from them when that is, I will let you know.

Regards

Susmita

From: Samanta, Susmita
Sent: Tuesday, June 23, 2009 2:27 PM
To: Council, Jacqueline
Subject: RE: NDA 50-580 Azactam

Good afternoon Dr. Council,

I have contacted the innovator company about this and as soon as they get back to me, I will let you know.

Have a nice day.

Susmita

Susmita Samanta, MD
Regulatory Project Manager
Division of Anti-Infective and Ophthalmology Products
301-796-0803

From: Council, Jacqueline
Sent: Tuesday, June 23, 2009 11:41 AM
To: Samanta, Susmita
Subject: NDA 50-580 Azactam

Good morning Dr. Samanta,

A generic firm with an ANDA for Aztreonam for Injection informed us that the following infusion solutions are no longer commercially available. Do you have any information regarding this issue? Can you please inform me if there are any plans to ask the innovator to delete these solutions from the package insert labeling?

10% Travert Injection
10% Travert Injection and Electrolyte No. 1 Injection
10% Travert Injection and Electrolyte No. 2 Injection
10% Travert Injection and Electrolyte No. 3 Injection

Thanks for your assistance,
Dr. Council

2. The listing of the active and inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the composition listed in the application. [Vol. 1.2, p. 96]
NOTE: The USP indicates that Aztreonam for Injection is a dry mixture of sterile Aztreonam and Arginine. This is consistent with the RLD. (b) (4)

3. Physical Description

Dry: White to off-white powder
(b) (4) [per chemist review]
Solution: clear, colorless to yellow solution
[Vol 2.1, p. 86, 201]

4. Manufacturing Facility

Ben Venue Laboratories, Inc.
300 Northfield Road
Bedford, OH 44146
[Vol. 1.2, p. 217]

5. Patent/ Exclusivities..

Patent Data – 50-521

No	Expiration	Use Code	Use	File
None				I

Exclusivity Data –

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

6. Package Sizes

RLD- Single-dose 15 mL capacity vials:
500 mg/vial – 10s
1 g/vial – 10s
2 g/vial - 10s

ANDA - 1 g/vial; 10 mL capacity vial; carton of 10

In AM dated 7/27/07, Bedford provided a justification to the 10 mL vial for 1 gram. To recap, Beford has developed a 2 gram dosage in a 15 mL vial and has chosen to use a 10 mL vial for the 1 gram dosage to differentiate the two products. There is enough volume in the 10 mL vial to allow for the reconstitution using the maximum amount of diluent. The stability testing was conducted in a 10 mL vial and the results are within the allowable limits. Thus, the 10 mL vial should not present any problems in the market for reconstitution of the DP according to the PI labeling. From the labeling standpoint, the difference in vial sizes between the RLD and innovator is acceptable (please read the email between Lilly and Carol about the difference in vial sizes).

From: Holquist, Carol A
Sent: Thursday, July 26, 2007 5:10 PM
To: Golson, Lillie D
Cc: Toyer, Denise P
Subject: RE: Vial size differences

Lillie,

Denise is on leave this week. It appears from your e-mail that there is no direct correlation to the size of vial per strength. If there is no pre-existing correlation then I don't see much of a problem with this proposal. I would just hope they differentiate the strengths adequately.

Thanks,
Carol

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 3:57 PM
To: Holquist, Carol A
Cc: Toyer, Denise P
Subject: Vial size differences

Hi Guys,

Quick question. What are your thoughts on a firm proposing a different vial size for a powder for injection product. The RLD for an antibiotic packages its 500 mg, 1 g, and 2 g products in 15 mL size vials. A generic firm is proposing to package its products in 20 mL and 30 mL vials. Rationale, their product is lyophilized. Another generic firm is proposing a 10 mL vial. No rationale provided. In speaking with a couple of pharmacists, they see no problem with this since a syringe is used to draw up the diluent and would be measuring the amount added so vial size shouldn't matter. What are your thoughts on this?

Thanks much.

7. Container/Closure

The configuration of container/closure system used for packaging the drug product (is summarized in the table below:
[Vol. 1.2, p. 96]

Container/Closure	Description
10 mL vial	10 cc, 20 mm, Type I Flint Tubing Vials
Closure	20 mm Gray Lyo stoppers
Seal	Mist gray 20 mm, Flip-off Aluminum Seals
(b) (4)	(b) (4)

* The firm indicates that this (b) (4)

8. Storage, Packaging and/or Dispensing:

USP - Preserve in *Containers for Sterile Solids* as described under *Injections*

NDA - Store original packages at room temperature: avoid excessive heat

ANDA - Store original packages at 20° to 25° C (68° to 77° F). See USP controlled room temperature; avoid excessive heat.

9. This is the first generic.

10. The June 17, 2010 amendment is for the addition of a new strength, “2 grams”.

Primary Reviewer: Jacqueline Council, Pharm.D. Date:

Team Leader: Captain Lillie Golson Date:

cc: ANDA: 65-286
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSAM\BEDFORD\LTRS&REV\65286ap.3.l.doc
Review

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

/s/

JACQUELINE D COUNCIL
02/18/2011

LILLIE D GOLSON
02/22/2011

THIS APPROVAL SUMMARY SUPERSEDES THE APPROVAL SUMMARY DATED AUGUST 30, 2007.

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-286

Date of Submission: May 26, 2009

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? See EDR.

1. CONTAINER: 1 gram
   Satisfactory in final as of the August 30, 2007 submission.
   .
2. CARTON: 10s
   Satisfactory in final as of the August 30, 2007 submission.

3. INSERT:
   Satisfactory in final as of the May 26, 2009 submission.
   Insert code: Div.AZNM-P00 Revised May 2009

Revisions needed post-approval:
1. CONTAINER: 1 gram
   i. Add an asterisk after the strength, "1 gram*/vial" and immediately prior to the "*Each vial contains…" statement.
   ii. Side panel
   Revise to read, "…solution stability".
2. CARTON: 10s
   See comments under CONTAINER.
3. INSERT:
   General Comment: Increase the size of the asterisks and superscripts.

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Azactam

NDA Number: NDA 50-580

NDA Drug Name: Azactam

NDA Firm: Bristol Myers Squibb Company

Date of Approval of NDA Insert and supplement #:S-040 approved 1/22/08

Has this been verified by the Drugs @FDA/ Yes

Was this approval based upon an OGD labeling guidance? No

Appears this way on original.

NOTES/QUESTIONS TO THE CHEMIST

From: Takiar, Neeru B
Sent: Monday, August 24, 2009 1:15 PM
To: Council, Jacqueline
Subject: RE: 65-286

Hi Jacqueline,

The firm has not responded to minor amendment yet (issued in June 2008). Thanks.

Neeru

From: Council, Jacqueline
Sent: Tuesday, August 11, 2009 1:33 PM
To: Takiar, Neeru B
Subject: FW: 65-286

Good afternoon Neeru,

I am not sure if you have completed your chemistry review yet. If you have completed the review can you please inform me of the following?

Thanks,
Jacqueline

1. Does the chemistry revision effect any of the information below from the firm's Description section?

DESCRIPTION
Aztreonam for Injection, USP contains the active ingredient aztreonam, a monobactam. It was originally isolated from Chromobacterium violaceum. It is a synthetic bactericidal antibiotic.
The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other betalactam antibiotics (e.g., penicillins, cephalosporins, cephamycins). The sulfonic acid substituent in the 1-position of the ring activates the beta-lactam moiety; an aminothiazolyl oxime side chain in the 3-position and a methyl group in the 4-position confer the specific antibacterial spectrum and beta-lactamase stability.
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Neeru

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Subject: 65-286

Good afternoon Neeru.

Is there still a USP issue regarding this drug product? Please refer to your comment below. [This ANDA is getting close to approval].

Thanks,
Jacqueline

From: Takiar, Neeru B
Sent: Thursday, July 24, 2008 11:06 AM
To: Vu, Thuyanh (Ann)
Subject: RE: Labeling comment for 65-286 (Bedford's aztreonam)
Ann,

(b) (4)

USP monograph will be updated soon.
Neeru

NOTES/QUESTIONS TO THE CHEMIST

PI see below.

-----Original Message-----
From: Nguyen, Ryan
Sent: Wednesday, February 01, 2006 4:37 PM
To: Takiar, Neeru B
Cc: Zuk, Susan; Park, Sarah Soojung
Subject: FW: 65-286.

Hi Neeru,

Please respond to Jackie's questions below. Thanks.

Ryan

-----Original Message-----
From: Council, Jacqueline
Sent: Wednesday, February 01, 2006 4:36 PM
To: Nguyen, Ryan
Subject: 65-286.

Good afternoon Ryan,

I completed the review [with deficiencies]. Please see below.

Thanks,
Jacqueline

ANDA Number: 65-286

Dates of Submission: December 23, 2004

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

NOTES/QUESTIONS TO THE CHEMIST [chemist response copied from previous reviewer].

1. The innovator's vial size is "15 mL" and the ANDA vial size is "10 mL" We plan to inform the ANDA that the vial size should be the same as the innovator's, "15 mL".

That is fine.

Neeru's email dated 4/19/07:

> As per comment 6 (see below) in my review #2,10 mL size is not acceptable.
>
> Please note that it is recommended in your labeling that for intravenous solutions (bolus injection), the contents of the aztreonam for injection 1 gram vial should be are constituted with 6 to 10 mL Sterile Water for Injection. Therefore, we recommend that you revise your vial size to same as the innovator "15 mL" because the proposed vial size "10 mL" may not be an adequate size for constituting IV solutions. Please revise your labels and labeling accordingly.
>
> Neeru

2. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION SECTION, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]? See text from insert labeling below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam not exceeding 2% w/v prepared with Sodium Chloride Injection 0.9% or Dextrose Injection 5%, to which clindamycin phosphate, gentamicin sulfate, tobramycin sulfate, or cefazolin sodium have been added at concentrations usually used clinically, are stable for up to 48 hours at room temperature or seven days under refrigeration. Ampicillin sodium admixtures with aztreonam in Sodium Chloride Injection 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection 5% is two hours at room temperature and eight hours under refrigeration.

Aztreonam-cloxacillin sodium and aztreonam-vancomycin hydrochloride admixtures are stable in Dianeal® 137 (Peritoneal Dialysis Solution) with 4.25% Dextrose for up to 24 hours at room temperature.

Aztreonam is incompatible with nafcillin sodium, cephradine, and metronidazole.

Other admixtures are not recommended since compatibility data are not available.

Intravenous (IV) Solutions

For Bolus Injection: The contents of the aztreonam for injection 1 gram vial should be constituted with 6 to 10 mL Sterile Water for Injection.

For Infusion (b) (4) Each gram of aztreonam should be initially constituted with at least 3 mL Sterile Water for Injection and transferred to an appropriate infusion solution. Further dilution may be obtained with one of the following intravenous infusion solutions:

Sodium Chloride Injection, 0.9%
Ringer's Injection
Lactated Ringer's Injection
Dextrose Injection, 5% or 10%
Dextrose and Sodium Chloride Injection, 5%:0.9%, 5%:0.45% or 5%:0.2%
Sodium Lactate Injection (M/6 Sodium Lactate)
Ionosol® B and 5% Dextrose
Isolyte® M with 5% Dextrose
Normosol®-R
Normosol®-R and 5% Dextrose
Normosol®-M and 5% Dextrose
Mannitol Injection, 5% or 10%
Lactated Ringer's and 5% Dextrose Injection

Plasma-Lyte® M and 5% Dextrose

Intramuscular (IM) Solutions

The contents of an aztreonam vial should be constituted with at least 3 mL of an appropriate diluent per gram aztreonam. The following diluents may be used:

Sterile Water for Injection

Sterile Bacteriostatic Water for Injection (with benzyl alcohol or with methyl- and propylparabens)

Sodium Chloride Injection, 0.9%

Bacteriostatic Sodium Chloride Injection (with benzyl alcohol)

Stability Of IV And IM Solutions

Aztreonam solutions for IV infusion at concentrations not exceeding 2% w/v must be used within 48 hours following constitution if kept at 20° to 25°C (68° to 77°F) (see USP controlled room temperature) or within seven days if refrigerated 2° to 8°C (36° to 46°F).

(b) (4)

Aztreonam solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection or Sodium Chloride Injection, should be used promptly after preparation; the two excepted solutions must be used within 48 hours if stored at controlled room temperature or within seven days if refrigerated.

Yes

Thanks

In the 3/16/07 amendment, Bedford added Isolyte E and Isolyte E with 5% Dexrose to DOSAGE AND ADMINISTRATION. Bedford also submitted stability studies in support. A copy of the stability studies was submitted to chemistry.

PENDING USP ISSUE- USP will be official on December 1, 2008, also see item #8 in the FTR below.

From: Vu, Thuyanh (Ann)
Sent: Thursday, July 24, 2008 11:29 AM
To: Takiar, Neeru B
Subject: RE: Labeling comment for 65-286 (Bedford's aztreonam)

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Thanks
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Subject: Labeling comment for 65-286 (Bedford's aztreonam)

Neeru,
I found this statement for 65-286 from your review #3

Comment to the Labeling reviewer:

(b) (4). Please contact the firm (b) (4) recommended labeling (b) (4).
From your review, the proposed (b) (4) (b) (4)
I do not understand the meaning of (b) (4)
Thanks
Ann

Appears this way on original.

FOR THE RECORD: (portions taken from previous review)

1. Labeling model

- Azactam®, by Bristol-Myers Squibb Company
NDA 50-580/S-040 approved 1/22/08

- DOSAGE AND ADMINISTRATION section

The firm indicated that they omitted the following infusion solutions because they are no longer commercially available. The new drug division concurred. We plan to allow the ANDAs to omit these infusion solutions. See e-mail below.

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10% Travert Injection and Electrolyte No. 1 Injection
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Have a nice day.

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Susmita Samanta, MD
Regulatory Project Manager
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Thanks for your assistance,
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2. The listing of the active and inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the composition listed in the application. [Vol. 1.2, p. 96]
NOTE: The USP indicates that Aztreonam for Injection is a dry mixture of sterile Aztreonam and Arginine. This is consistent with the RLD. (b) (4)

3. Physical Description

Dry: White to off-white powder
(b) (4) [per chemist review]
Solution: clear, colorless to yellow solution
[Vol 2.1, p. 86, 201]

4. Manufacturing Facility

Ben Venue Laboratories, Inc.
300 Northfield Road
Bedford, OH 44146
[Vol. 1.2, p. 217]

5. Patent/ Exclusivities..

Patent Data – 50-521

No	Expiration	Use Code	Use	File
None				I

Exclusivity Data –

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

6. Package Sizes

RLD- Single-dose 15 mL capacity vials:
500 mg/vial – 10s
1 g/vial – 10s
2 g/vial - 10s

ANDA - 1 g/vial; 10 mL capacity vial; carton of 10

In AM dated 7/27/07, Bedford provided a justification to the 10 mL vial for 1 gram. To recap, Beford has developed a 2 gram dosage in a 15 mL vial and has chosen to use a 10 mL vial for the 1 gram dosage to differentiate the two products. There is enough volume in the 10 mL vial to allow for the reconstitution using the maximum amount of diluent. The stability testing was conducted in a 10 mL vial and the results are within the allowable limits. Thus, the 10 mL vial should not present any problems in the market for reconstitution of the DP according to the PI labeling. From the labeling standpoint, the difference in vial sizes between the RLD and innovator is acceptable (please read the email between Lilly and Carol about the difference in vial sizes).

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Subject: RE: Vial size differences

Lillie,

Denise is on leave this week. It appears from your e-mail that there is no direct correlation to the size of vial per strength. If there is no pre-existing correlation then I don't see much of a problem with this proposal. I would just hope they differentiate the strengths adequately.

Thanks,
Carol

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 3:57 PM
To: Holquist, Carol A
Cc: Toyer, Denise P
Subject: Vial size differences

Hi Guys,

Quick question. What are your thoughts on a firm proposing a different vial size for a powder for injection product. The RLD for an antibiotic packages its 500 mg, 1 g, and 2 g products in 15 mL size vials. A generic firm is proposing to package its products in 20 mL and 30 mL vials. Rationale, their product is lyophilized. Another generic firm is proposing a 10 mL vial. No rationale provided. In speaking with a couple of pharmacists, they see no problem with this since a syringe is used to draw up the diluent and would be measuring the amount added so vial size shouldn't matter. What are your thoughts on this?

Thanks much.

7. Container/Closure

The configuration of container/closure system used for packaging the drug product (is summarized in the table below:
[Vol. 1.2, p. 96]

Container/Closure	Description
10 mL vial	10 cc, 20 mm, Type I Flint Tubing Vials
Closure	20 mm Gray Lyo stoppers
Seal	Mist gray 20 mm, Flip-off Aluminum Seals
(b) (4)	(b) (4)

* The firm indicates that this (b) (4)

8. Storage, Packaging and/or Dispensing:

USP - Preserve in *Containers for Sterile Solids* as described under *Injections*

NDA - Store original packages at room temperature: avoid excessive heat

ANDA - Store original packages at 20° to 25° C (68° to 77° F). See USP controlled room temperature; avoid excessive heat.

9. This is the first generic.

10. Post approval revisions:
CONTAINER and CARTON: acceptable in final as of the 8/30/07 submission.
    1. CONTAINER: 1 gram
        i. Add an asterisk after the strength, "1 gram*/vial" and immediately prior to the "*Each vial contains…" statement.
        ii. Side panel
        Revise to read, "…solution stability".
    2. CARTON: 10s
        See comments under CONTAINER.

Date of Review: 8/21/09

Date of Submission: 5/26/09

Primary Reviewer: Jacqueline Council, Pharm.D. Date:

Team Leader: Captain Lillie Golson Date:

cc: ANDA: 65-286
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSAM\BEDFORD\LTRS&REV\65286ap2.l.doc
Review

Following this page, 4 pages withheld in full (b)(4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-65286	ORIG-1	BEDFORD LABORATORIES DIV BEN VENUE LABORATORIES INC	AZTREONAM

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

/s/

JACQUELINE D COUNCIL
09/09/2009

MELAINE M SHIN
09/10/2009

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-286

Date of Submission: September 5, 2008

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

---

1 INSERT

a. General Comments

i. Delete the terminal zero, “1 instead of “1.0”.

ii. Increase the size of the asterisks.

b. DOSAGE AND ADMINISTRATION

i. Admixture with other Antibiotics

Add an asterisk following the trade name “Dianeal®137* (Peritoneal Dialysis Solution)”. Also, reference the manufacturer of the product in a footnote at the end of your insert.

ii. Preparation of Parenteral Solutions

Relocate the paragraph, “Parenteral drug products should…permit” to appear as the last paragraph of this subsection.

iii. Intravenous (IV) Solutions

A) For Bolus Injection

Revise to read, “… Injection vial should …”

B) For Infusion (b) (4)
Revise to read, “If the contents of the vial are to be transferred to an appropriate infusion solution, each gram…Injection (b) (4). Further …”.

C) We note that you omitted some of the intravenous infusion solutions”. Your insert is required to be the same as the innovator. Is your drug product incompatible with the solutions you omitted? Please comment and/or revise accordingly. .

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling reference listed drug's labeling with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTES/QUESTIONS TO THE CHEMIST

Pl see below.

-----Original Message-----
From: Nguyen, Ryan
Sent: Wednesday, February 01, 2006 4:37 PM
To: Takiar, Neeru B
Cc: Zuk, Susan; Park, Sarah Soojung
Subject: FW: 65-286.

Hi Neeru,

Please respond to Jackie's questions below. Thanks.

Ryan

-----Original Message-----
From: Council, Jacqueline
Sent: Wednesday, February 01, 2006 4:36 PM
To: Nguyen, Ryan
Subject: 65-286.

Good afternoon Ryan,

I completed the review [with deficiencies]. Please see below.

Thanks,
Jacqueline

ANDA Number: 65-286

Dates of Submission: December 23, 2004

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

NOTES/QUESTIONS TO THE CHEMIST [chemist response copied from previous reviewer].

1. The innovator's vial size is "15 mL" and the ANDA vial size is "10 mL" We plan to inform the ANDA that the vial size should be the same as the innovator's, "15 mL".

That is fine.

Neeru's email dated 4/19/07:

As per comment 6 (see below) in my review #2,10 mL size is not acceptable.

Please note that it is recommended in your labeling that for intravenous solutions (bolus injection), the contents of the aztreonam for injection 1 gram vial should be

are constituted with 6 to 10 mL Sterile Water for Injection. Therefore, we recommend that you revise your vial size to same as the innovator “15 mL” because the proposed vial size “10 mL” may not be an adequate size for constituting IV solutions. Please revise your labels and labeling accordingly.

Neeru

2. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION SECTION, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]? See text from insert labeling below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam not exceeding 2% w/v prepared with Sodium Chloride Injection 0.9% or Dextrose Injection 5%, to which clindamycin phosphate, gentamicin sulfate, tobramycin sulfate, or cefazolin sodium have been added at concentrations usually used clinically, are stable for up to 48 hours at room temperature or seven days under refrigeration. Ampicillin sodium admixtures with aztreonam in Sodium Chloride Injection 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection 5% is two hours at room temperature and eight hours under refrigeration.

Aztreonam-cloxacillin sodium and aztreonam-vancomycin hydrochloride admixtures are stable in Dianeal® 137 (Peritoneal Dialysis Solution) with 4.25% Dextrose for up to 24 hours at room temperature.

Aztreonam is incompatible with nafcillin sodium, cephradine, and metronidazole.

Other admixtures are not recommended since compatibility data are not available.

Intravenous (IV) Solutions

For Bolus Injection: The contents of the aztreonam for injection 1 gram vial should be constituted with 6 to 10 mL Sterile Water for Injection.

For Infusion (b) (4) Each gram of aztreonam should be initially constituted with at least 3 mL Sterile Water for Injection and transferred to an appropriate infusion solution. Further dilution may be obtained with one of the following intravenous infusion solutions:

Sodium Chloride Injection, 0.9%
Ringer's Injection
Lactated Ringer's Injection

Dextrose Injection, 5% or 10%
Dextrose and Sodium Chloride Injection, 5%:0.9%, 5%:0.45% or 5%:0.2%
Sodium Lactate Injection (M/6 Sodium Lactate)
Ionosol® B and 5% Dextrose
lsolyte® M with 5% Dextrose
Normosol®-R
Normosol®-R and 5% Dextrose
Normosol®-M and 5% Dextrose
Mannitol Injection, 5% or 10%
Lactated Ringer's and 5% Dextrose Injection
Plasma-Lyte® M and 5% Dextrose

Intramuscular (IM) Solutions

The contents of an aztreonam vial should be constituted with at least 3 mL of an appropriate diluent per gram aztreonam. The following diluents may be used:

Sterile Water for Injection
Sterile Bacteriostatic Water for Injection (with benzyl alcohol or with methyl- and propylparabens)

Sodium Chloride Injection, 0.9%
Bacteriostatic Sodium Chloride Injection (with benzyl alcohol)

Stability Of IV And IM Solutions

Aztreonam solutions for IV infusion at concentrations not exceeding 2% w/v must be used within 48 hours following constitution if kept at 20° to 25°C (68° to 77°F) (see USP controlled room temperature) or within seven days if refrigerated 2° to 8°C (36° to 46°F).

(b) (4)

Aztreonam solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection or Sodium Chloride Injection, should be used promptly after preparation; the two excepted solutions must be used within 48 hours if stored at controlled room temperature or within seven days if refrigerated.

Yes

Thanks

In the 3/16/07 amendment, Bedford added Isolyte E and Isolyte E with 5% Dexrose to DOSAGE AND ADMINISTRATION. Bedford also submitted stability studies in support. A copy of the stability studies was submitted to chemistry.

PENDING USP ISSUE- USP will be official on December 1, 2008, also see item #8 in the FTR below.

From: Vu, Thuyanh (Ann)
Sent: Thursday, July 24, 2008 11:29 AM
To: Takiar, Neeru B
Subject: RE: Labeling comment for 65-286 (Bedford's aztreonam)

Neeru, until the USP becomes official, I could not comment to the firm. Could you also email me when you have "comment to the labeling reviewer"?
Thanks
Ann

From: Takiar, Neeru B
Sent: Thursday, July 24, 2008 11:06 AM
To: Vu, Thuyanh (Ann)
Subject: RE: Labeling comment for 65-286 (Bedford's aztreonam)

Ann,
(b) (4)
. USP monograph will be updated soon.
Neeru

From: Vu, Thuyanh (Ann)
Sent: Thursday, July 24, 2008 10:30 AM
To: Takiar, Neeru B
Subject: Labeling comment for 65-286 (Bedford's aztreonam)

Neeru,
I found this statement for 65-286 from your review #3

Comment to the Labeling reviewer:

(b) (4) Please contact the firm (b) (4) recommended
labeling (b) (4).
From your review, the proposed (b) (4)
(b) (4)
I do not understand the meaning of (b) (4)

Thanks
Ann

FOR THE RECORD: (portions taken from previous review)

1. Labeling model

   Azactam®, by Bristol-Myers Squibb Company
   NDA 50-580/S-040 approved 1/22/08

2. The listing of the active and inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the composition listed in the application. [Vol. 1.2, p. 96]
   NOTE: The USP indicates that Aztreonam for Injection is a dry mixture of sterile Aztreonam and Arginine. This is consistent with the RLD. (b) (4)

3. Physical Description

   Dry: White to off-white powder
   (b) (4) [per chemist review]
   Solution: clear, colorless to yellow solution
   [Vol 2.1, p. 86, 201]

4. Manufacturing Facility

   Ben Venue Laboratories, Inc.
   300 Northfield Road
   Bedford, OH 44146
   [Vol. 1.2, p. 217]

5. Patent/ Exclusivities

Patent Data – 50-521

No	Expiration	Use Code	Use	File
None				I

Exclusivity Data –

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

6. Package Sizes

   RLD- Single-dose 15 mL capacity vials:
   500 mg/vial – 10s
   1 g/vial – 10s
   2 g/vial - 10s

   ANDA - 1 g/vial; 10 mL capacity vial; carton of 10

   Bedford is developing a 2 gram dosage in a 15 mL vial and chose to use a 10 mL vial for the 1 gram dosage to differentiate between the two dosages and therefore prevent

medication errors. Bedford acknowledge that the RLD is in a 15 mL vial. Bedford will not change the 1 gram dosage to 10 mL vial [AF dated 5/31/06]. After speaking with Jackie Council on 9/21/06, I will ask Bedford to revise their vial size to be the same as the innovator's (15 mL). Note that the innovator's 1 gram and 2 gram sizes are marketed in a 15 mL capacity vial.

Refer to the chemist question above. Neeru will send out chemistry deficiencies-one will include to revise to 15 mL vial size. In the 3/16/07 AF, Bedford refused to change vial size.

In AM dated 7/27/07, Bedford provided a justification to the 10 mL vial for 1 gram. To recap, Beford has developed a 2 gram dosage in a 15 mL vial and has chosen to use a 10 mL vial for the 1 gram dosage to differentiate the two products. There is enough volume in the 10 mL vial to allow for the reconstitution using the maximum amount of diluent. The stability testing was conducted in a 10 mL vial and the results are within the allowable limits. Thus, the 10 mL vial should not present any problems in the market for reconstitution of the DP according to the PI labeling. From the labeling standpoint, the difference in vial sizes between the RLD and innovator is acceptable (please read the email between Lilly and Carol about the difference in vial sizes).

From: Holquist, Carol A
Sent: Thursday, July 26, 2007 5:10 PM
To: Golson, Lillie D
Cc: Toyer, Denise P
Subject: RE: Vial size differences

Lillie,

Denise is on leave this week. It appears from your e-mail that there is no direct correlation to the size of vial per strength. If there is no pre-existing correlation then I don't see much of a problem with this proposal. I would just hope they differentiate the strengths adequately.

Thanks,
Carol

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 3:57 PM
To: Holquist, Carol A
Cc: Toyer, Denise P
Subject: Vial size differences

Hi Guys,

Quick question. What are your thoughts on a firm proposing a different vial size for a powder for injection product. The RLD for an antibiotic packages its 500 mg, 1 g, and 2 g products in 15 mL size vials. A generic firm is proposing to package its products in 20 mL and 30 mL vials. Rationale, their product is lyophilized. Another generic firm is proposing a 10 mL vial. No rationale provided. In speaking with a couple of pharmacists, they see no problem with this since a syringe is used to draw up the diluent and would be measuring the amount added so vial size shouldn't matter. What are your thoughts on this?

Thanks much.

7. Container/Closure

The configuration of container/closure system used for packaging the drug product (is summarized in the table below:
[Vol. 1.2, p. 96]

Container/Closure	Description
10 mL vial	10 cc, 20 mm, Type I Flint Tubing Vials
Closure	20 mm Gray Lyo stoppers
Seal	Mist gray 20 mm, Flip-off Aluminum Seals
(b) (4)	(b) (4)

* The firm indicates that this (b) (4)

8. Storage, Packaging and/or Dispensing:

USP - Preserve in *Containers for Sterile Solids* as described under *Injections*

NDA - Store original packages at room temperature: avoid excessive heat

ANDA - Store original packages at 20° to 25° C (68° to 77° F). See USP controlled room temperature; avoid excessive heat.

9. This is the first generic.

10. Post approval revisions:
CONTAINER and CARTON: acceptable in final as of the 8/30/07 submission.
    1. CONTAINER: 1 gram
        i. Add an asterisk after the strength, "1 gram*/vial" and immediately prior to the "*Each vial contains…" statement.
        ii. Side panel
        Revise to read, "…solution stability".
    2. CARTON: 10s
        See comments under CONTAINER.

Date of Review: 3/13/08

Date of Submission: 9/5/08

Primary Reviewer: Jacqueline Council, Pharm.D. Date:

Team Leader: Captain Lillie Golson Date:

cc: ANDA: 65-286
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSAM\BEDFORD\LTRS&REV\65286na5.l.doc
Review

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

/s/

Jacqueline Council
3/31/2009 03:18:41 PM
LABELING REVIEWER

Lillie Golson
4/2/2009 05:28:57 PM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-286 Date of Submission: June 25, 2008

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

Labeling Deficiencies:

1. CONTAINER: 1 gram

   Acceptable in final print.

2. CARTON: 10 vials per carton

   Acceptable in final print.

3. INSERT

   a. ADVERSE REACTIONS

      First and second paragraphs, revise "percent" to "%".

   b. DOSAGE AND ADMINISTRATION

      i. Dosage in Adult Patients, Renal Impairment in Adult Patients, first paragraph, revise to read "...between 10 mL/min/1.73 m^2 and 30 mL/min/1.73m^2 ..."

      ii. Stability of IV and IM Solutions- delete second paragraph.

      iii. Intravenous Administration, second paragraph, revise to read "(see Preparation Of Parenteral Solutions- Intravenous (IV) Solutions: For Infusion)

4. SPL

   DOSAGE AND ADMINISTRATIONS

   Aztreonam for Injection Dosage Guidelines table, please clearly separate the rows for the adults. It is hard to read the dosage corresponding to the types of infection.

Submit labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -
http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No. see comments

Container Labels (1 vial): Yes, August 30, 2007 e-submission

Carton Labels (10s): Yes, August 30, 2007 e-submission

Professional Package Insert Labeling: No.

Revisions needed post-approval: None

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Azactam

NDA Number: NDA 50-580/S-040, approved 1/22/08, provided for CDAD class labeling language

NDA Drug Name: Azactam

NDA Firm:Bristol Myers Squibb

Date of Approval of NDA Insert and supplement #: NDA 50-580/S-040, approved 1/22/08

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

NOTES/QUESTIONS TO THE CHEMIST

Pl see below.

-----Original Message-----
From: Nguyen, Ryan
Sent: Wednesday, February 01, 2006 4:37 PM
To: Takiar, Neeru B
Cc: Zuk, Susan; Park, Sarah Soojung
Subject: FW: 65-286.

Hi Neeru,

Please respond to Jackie's questions below. Thanks.

Ryan

-----Original Message-----
From: Council, Jacqueline
Sent: Wednesday, February 01, 2006 4:36 PM
To: Nguyen, Ryan
Subject: 65-286.

Good afternoon Ryan,

I completed the review [with deficiencies]. Please see below.

Thanks,
Jacqueline

ANDA Number: 65-286

Dates of Submission: December 23, 2004

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

NOTES/QUESTIONS TO THE CHEMIST

1. The innovator's vial size is "15 mL" and the ANDA vial size is "10 mL" We plan to inform the ANDA that the vial size should be the same as the innovator's, "15 mL".

That is fine.

Neeru's email dated 4/19/07:

As per comment 6 (see below) in my review #2,10 mL size is not acceptable.

Please note that it is recommended in your labeling that for intravenous solutions (bolus injection), the contents of the aztreonam for injection 1 gram vial should be are constituted with 6 to 10 mL Sterile Water for Injection. Therefore, we recommend that you revise your vial size to same as the innovator "15 mL" because the proposed vial size "10 mL" may not be an adequate size for constituting IV solutions. Please revise your labels and labeling accordingly.

Neeru

2. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION SECTION, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]? See text from insert labeling below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam not exceeding 2% w/v prepared with Sodium Chloride Injection 0.9% or Dextrose Injection 5%, to which clindamycin phosphate, gentamicin sulfate, tobramycin sulfate, or cefazolin sodium have been added at concentrations usually used clinically, are stable for up to 48 hours at room temperature or seven days under refrigeration. Ampicillin sodium admixtures with aztreonam in Sodium Chloride Injection 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection 5% is two hours at room temperature and eight hours under refrigeration.

Aztreonam-cloxacillin sodium and aztreonam-vancomycin hydrochloride admixtures are stable in Dianeal® 137 (Peritoneal Dialysis Solution) with 4.25% Dextrose for up to 24 hours at room temperature.

Aztreonam is incompatible with nafcillin sodium, cephradine, and metronidazole.

Other admixtures are not recommended since compatibility data are not available.

Intravenous (IV) Solutions

For Bolus Injection: The contents of the aztreonam for injection 1 gram vial should be constituted with 6 to 10 mL Sterile Water for Injection.

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Ringer's Injection
Lactated Ringer's Injection

Dextrose Injection, 5% or 10%
Dextrose and Sodium Chloride Injection, 5%:0.9%, 5%:0.45% or 5%:0.2%
Sodium Lactate Injection (M/6 Sodium Lactate)
Ionosol® B and 5% Dextrose
lsolyte® M with 5% Dextrose
Normosol®-R
Normosol®-R and 5% Dextrose
Normosol®-M and 5% Dextrose
Mannitol Injection, 5% or 10%
Lactated Ringer's and 5% Dextrose Injection
Plasma-Lyte® M and 5% Dextrose

Intramuscular (IM) Solutions

The contents of an aztreonam vial should be constituted with at least 3 mL of an appropriate diluent per gram aztreonam. The following diluents may be used:

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Sterile Bacteriostatic Water for Injection (with benzyl alcohol or with methyl- and propylparabens)

Sodium Chloride Injection, 0.9%
Bacteriostatic Sodium Chloride Injection (with benzyl alcohol)

Stability Of IV And IM Solutions

Aztreonam solutions for IV infusion at concentrations not exceeding 2% w/v must be used within 48 hours following constitution if kept at 20° to 25°C (68° to 77°F) (see USP controlled room temperature) or within seven days if refrigerated 2° to 8°C (36° to 46°F).

(b) (4)

Aztreonam solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection or Sodium Chloride Injection, should be used promptly after preparation; the two excepted solutions must be used within 48 hours if stored at controlled room temperature or within seven days if refrigerated.

Yes

Thanks

In the 3/16/07 amendment, Bedford added Isolyte E and Isolyte E with 5% Dexrose to DOSAGE AND ADMINISTRATION. Bedford also submitted stability studies in support. A copy of the stability studies was submitted to chemistry.

PENDING USP ISSUE- USP will be official on December 1, 2008, also see item #8 in the FTR below.

From: Vu, Thuyanh (Ann)
Sent: Thursday, July 24, 2008 11:29 AM
To: Takiar, Neeru B
Subject: RE: Labeling comment for 65-286 (Bedford's aztreonam)

Neeru, until the USP becomes official, I could not comment to the firm. Could you also email me when you have "comment to the labeling reviewer"?

Thanks
Ann

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Sent: Thursday, July 24, 2008 11:06 AM
To: Vu, Thuyanh (Ann)
Subject: RE: Labeling comment for 65-286 (Bedford's aztreonam)

Ann,

(b) (4)
. USP monograph will be updated soon.

Neeru

From: Vu, Thuyanh (Ann)
Sent: Thursday, July 24, 2008 10:30 AM
To: Takiar, Neeru B
Subject: Labeling comment for 65-286 (Bedford's aztreonam)

Neeru,

I found this statement for 65-286 from your review #3

Comment to the Labeling reviewer:

(b) (4)
. Please contact the firm (b) (4)
recommended
labeling (b) (4)

From your review, the proposed [redacted] (b) (4)

I do not understand the meaning of [redacted] (b) (4)

Thanks
Ann

FOR THE RECORD: (portions taken from previous review)

1. Labeling model

   Azactam®, by Bristol-Myers Squibb Company
   NDA 50-580/S-040, approved 1/22/08, provided for CDAD class labeling language

2. The listing of the active and inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the composition listed in the application. [Vol. 1.2, p. 96]
   NOTE: The USP indicates that Aztreonam for Injection is a dry mixture of sterile Aztreonam and Arginine. This is consistent with the RLD. [redacted] (b) (4)

3. Physical Description

   Dry: White to off-white powder
   [redacted] (b) (4) [per chemist review]
   Solution: clear, colorless to yellow solution
   [Vol 2.1, p. 86, 201]

4. Manufacturing Facility

   Ben Venue Laboratories, Inc.
   300 Northfield Road
   Bedford, OH 44146
   [Vol. 1.2, p. 217]

5. Patent/ Exclusivities

Patent Data – 50-521

No	Expiration	Use Code	Use	File
None				I

Exclusivity Data –

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

6. Package Sizes

RLD- Single-dose 15 mL capacity vials:
500 mg/vial – 10s
1 g/vial – 10s
2 g/vial - 10s

ANDA - 1 g/vial; 10 mL capacity vial; carton of 10

Bedford is developing a 2 gram dosage in a 15 mL vial and chose to use a 10 mL vial for the 1 gram dosage to differentiate between the two dosages and therefore prevent medication errors. Bedford acknowledge that the RLD is in a 15 mL vial. Bedford will not change the 1 gram dosage to 10 mL vial [AF dated 5/31/06]. After speaking with Jackie Council on 9/21/06, I will ask Bedford to revise their vial size to be the same as the innovator's (15 mL). Note that the innovator's 1 gram and 2 gram sizes are marketed in a 15 mL capacity vial.

Refer to the chemist question above. Neeru will send out chemistry deficiencies-one will include to revise to 15 mL vial size. In the 3/16/07 AF, Bedford refused to change vial size. From Chemist review #3, the chemist also noted thta the 10 mL vial should not present any problems in the market for reconstitution of the DP according to the package insert labeling.

In AM dated 7/27/07, Bedford provided a justification to the 10 mL vial for 1 gram. To recap, Beford has developed a 2 gram dosage in a 15 mL vial and has chosen to use a 10 mL vial for the 1 gram dosage to differentiate the two products. There is enough volume in the 10 mL vial to allow for the reconstitution using the maximum amount of diluent. The stability testing was conducted in a 10 mL vial and the results are within the allowable limits. Thus, the 10 mL vial should not present any problems in the market for reconstitution of the DP according to the PI labeling. From the labeling standpoint, the difference in vial sizes between the RLD and innovator is acceptable (please read the email between Lilly and Carol about the difference in vial sizes).

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 6:44 PM
To: Barlow, James T; Birch, Postelle; Council, Jacqueline; Dillahunt, Michelle; Golson, Lillie D; Grace, John F; Hoppes, Charles V; Lee, Koung U; Park, Chan H; Park, Sarah Soojung; Payne, Angela; Shin, Melaine M; Vezza, Adolph E; Vu, Thuyanh (Ann); Weitzman, Beverly; Wu, Ruby (Chi-Ann)
Subject: FW: Vial size differences

FYI

From: Holquist, Carol A
Sent: Thursday, July 26, 2007 6:42 PM
To: Golson, Lillie D
Subject: RE: Vial size differences

Yes thanks

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 6:09 PM
To: Holquist, Carol A
Subject: RE: Vial size differences

Just to verify, on the vial, rather than

Single Use Vial

AMPICILLIN FOR INJECTION
500 Gram
IM or IV Use

You'd prefer:

Single Use Vial

AMPICILLIN FOR INJECTION
500 Gram/Vial
IM or IV Use

From: Holquist, Carol A
Sent: Thursday, July 26, 2007 5:53 PM
To: Golson, Lillie D
Subject: RE: Vial size differences

Lillie,

Thanks. I know you probably do this already as well but can you please make sure the strength is expressed in mg/vial and directions for reconstitution. We have seen a bunch of errors with powders when it doesn't say mg/vial or the resultant concentration once the diluent is added.

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 5:12 PM
To: Holquist, Carol A
Subject: RE: Vial size differences

Thanks Carol. We do ask for differentiation, and they are powders. So we will move forward on these.

Take care.

From: Holquist, Carol A
Sent: Thursday, July 26, 2007 5:10 PM
To: Golson, Lillie D
Cc: Toyer, Denise P
Subject: RE: Vial size differences

Lillie,

Denise is on leave this week. It appears from your e-mail that there is no direct correlation to the size of vial per strength. If there is no pre-existing correlation then I don't see much of a problem with this proposal. I would just hope they differentiate the strengths adequately.

Thanks,
Carol

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 3:57 PM
To: Holquist, Carol A
Cc: Toyer, Denise P
Subject: Vial size differences

Hi Guys,

Quick question. What are your thoughts on a firm proposing a different vial size for a powder for injection product. The RLD for an antibiotic packages its 500 mg, 1 g, and 2 g products in 15 mL size vials. A generic firm is proposing to package its products in 20 mL and 30 mL vials. Rationale, their product is lyophilized. Another generic firm is proposing a 10 mL vial. No rationale provided. In speaking with a couple of pharmacists, they see no problem with this since a syringe is used to draw up the diluent and would be measuring the amount added so vial size shouldn't matter. What are your thoughts on this?

Thanks much.

7. Container/Closure

   The configuration of container/closure system used for packaging the drug product (is summarized in the table below:
   [Vol. 1.2, p. 96]

Container/Closure	Description
10 mL vial	10 cc, 20 mm, Type I Flint Tubing Vials
Closure	20 mm Gray Lyo stoppers
Seal	Mist gray 20 mm, Flip-off Aluminum Seals
(b) (4)	(b) (4)

   * The firm indicates that this (b) (4)

8. Storage, Packaging and/or Dispensing:

   USP - Preserve in *Containers for Sterile Solids* as described under *Injections*

   Note: (b) (4)

   (b) (4)

   NDA - Store original packages at room temperature: avoid excessive heat

   ANDA - Store original packages at 20° to 25° C (68° to 77° F). See USP controlled room temperature; avoid excessive heat.

9. This is the first generic.

Primary Reviewer: Thuyanh Vu Date:

Team Leader: John Grace Date:

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

/s/

Thuyanh Vu
7/25/2008 11:41:14 AM
LABELING REVIEWER

John Grace
7/31/2008 10:49:58 AM
LABELING REVIEWER

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-286 Date of Submission: August 30, 2007

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes, August 30, 2007 e-submission and May 31, 2006 e-submission.

Container Labels (1 vial): Yes, August 30, 2007 e-submission

Carton Labels (10s): Yes, August 30, 2007 e-submission

Professional Package Insert Labeling: May 31, 2006 e-submission

Revisions needed post-approval: None

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Azactam

NDA Number: NDA 50-580/S-033 approved 3/25/02, provided for Geriatric Use and S-037 approved 12/16/04 provided for the antibiotic class labeling.

NDA Drug Name: Azactam

NDA Firm:Bristol Myers Squibb

Date of Approval of NDA Insert and supplement #: NDA 50-580/S-033 approved 3/25/02

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

NOTES/QUESTIONS TO THE CHEMIST

Pl see below.

-----Original Message-----
From: Nguyen, Ryan
Sent: Wednesday, February 01, 2006 4:37 PM
To: Takiar, Neeru B
Cc: Zuk, Susan; Park, Sarah Soojung
Subject: FW: 65-286.

Hi Neeru,

Please respond to Jackie's questions below. Thanks.

Ryan

-----Original Message-----
From: Council, Jacqueline
Sent: Wednesday, February 01, 2006 4:36 PM
To: Nguyen, Ryan
Subject: 65-286.

Good afternoon Ryan,

I completed the review [with deficiencies]. Please see below.

Thanks,
Jacqueline

ANDA Number: 65-286

Dates of Submission: December 23, 2004

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

NOTES/QUESTIONS TO THE CHEMIST

1. The innovator's vial size is "15 mL" and the ANDA vial size is "10 mL" We plan to inform the ANDA that the vial size should be the same as the innovator's, "15 mL".

That is fine.

Neeru's email dated 4/19/07:

As per comment 6 (see below) in my review #2,10 mL size is not acceptable.

Please note that it is recommended in your labeling that for intravenous solutions (bolus injection), the contents of the aztreonam for injection 1 gram vial should be are constituted with 6 to 10 mL Sterile Water for Injection. Therefore, we

recommend that you revise your vial size to same as the innovator “15 mL” because the proposed vial size “10 mL” may not be an adequate size for constituting IV solutions. Please revise your labels and labeling accordingly.

Neeru

2. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION SECTION, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]? See text from insert labeling below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam not exceeding 2% w/v prepared with Sodium Chloride Injection 0.9% or Dextrose Injection 5%, to which clindamycin phosphate, gentamicin sulfate, tobramycin sulfate, or cefazolin sodium have been added at concentrations usually used clinically, are stable for up to 48 hours at room temperature or seven days under refrigeration. Ampicillin sodium admixtures with aztreonam in Sodium Chloride Injection 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection 5% is two hours at room temperature and eight hours under refrigeration.

Aztreonam-cloxacillin sodium and aztreonam-vancomycin hydrochloride admixtures are stable in Dianeal® 137 (Peritoneal Dialysis Solution) with 4.25% Dextrose for up to 24 hours at room temperature.

Aztreonam is incompatible with nafcillin sodium, cephradine, and metronidazole.

Other admixtures are not recommended since compatibility data are not available.

Intravenous (IV) Solutions

For Bolus Injection: The contents of the aztreonam for injection 1 gram vial should be constituted with 6 to 10 mL Sterile Water for Injection.

For Infusion (b) (4) Each gram of aztreonam should be initially constituted with at least 3 mL Sterile Water for Injection and transferred to an appropriate infusion solution. Further dilution may be obtained with one of the following intravenous infusion solutions:

Sodium Chloride Injection, 0.9%
Ringer's Injection
Lactated Ringer's Injection
Dextrose Injection, 5% or 10%
Dextrose and Sodium Chloride Injection, 5%:0.9%, 5%:0.45% or 5%:0.2%
Sodium Lactate Injection (M/6 Sodium Lactate)
Ionosol® B and 5% Dextrose
lsolyte® M with 5% Dextrose
Normosol®-R
Normosol®-R and 5% Dextrose
Normosol®-M and 5% Dextrose
Mannitol Injection, 5% or 10%
Lactated Ringer's and 5% Dextrose Injection
Plasma-Lyte® M and 5% Dextrose

Intramuscular (IM) Solutions

The contents of an aztreonam vial should be constituted with at least 3 mL of an appropriate diluent per gram aztreonam. The following diluents may be used:

Sterile Water for Injection
Sterile Bacteriostatic Water for Injection (with benzyl alcohol or with methyl- and propylparabens)

Sodium Chloride Injection, 0.9%
Bacteriostatic Sodium Chloride Injection (with benzyl alcohol)

Stability Of IV And IM Solutions

Aztreonam solutions for IV infusion at concentrations not exceeding 2% w/v must be used within 48 hours following constitution if kept at 20° to 25°C (68° to 77°F) (see USP controlled room temperature) or within seven days if refrigerated 2° to 8°C (36° to 46°F).

(b) (4)

Aztreonam solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection or Sodium Chloride Injection, should be used promptly after preparation; the two excepted solutions must be used within 48 hours if stored at controlled room temperature or within seven days if refrigerated.

Yes

Thanks

In the 3/16/07 amendment, Bedford added Isolyte E and Isolyte E with 5% Dexrose to DOSAGE AND ADMINISTRATION. Bedford also submitted stability studies in support. A copy of the stability studies was submitted to chemistry.

FOR THE RECORD: (portions taken from previous review)

1. Labeling model

   Azactam®, by Bristol-Myers Squibb Company
   NDA 50-580/S-033 approved 3/25/02

   Note: S-037 approved 12/16/04 contains the "Labeling Requirements for Systemic Antibacterial Drug Products Indented for Human Use". [This ANDA has included this text].

2. The listing of the active and inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the composition listed in the application. [Vol. 1.2, p. 96]
   NOTE: The USP indicates that Aztreonam for Injection is a dry mixture of sterile Aztreonam and Arginine. This is consistent with the RLD. (b) (4)

3. Physical Description

   Dry: White to off-white powder
   (b) (4) [per chemist review]
   Solution: clear, colorless to yellow solution
   [Vol 2.1, p. 86, 201]

4. Manufacturing Facility

   Ben Venue Laboratories, Inc.
   300 Northfield Road
   Bedford, OH 44146
   [Vol. 1.2, p. 217]

5. Patent/ Exclusivities

Patent Data – 50-521

No	Expiration	Use Code	Use	File

None				I

Exclusivity Data –

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

6. Package Sizes

RLD- Single-dose 15 mL capacity vials:
500 mg/vial – 10s
1 g/vial – 10s
2 g/vial - 10s

ANDA - 1 g/vial; 10 mL capacity vial; carton of 10

Bedford is developing a 2 gram dosage in a 15 mL vial and chose to use a 10 mL vial for the 1 gram dosage to differentiate between the two dosages and therefore prevent medication errors. Bedford acknowledge that the RLD is in a 15 mL vial. Bedford will not change the 1 gram dosage to 10 mL vial [AF dated 5/31/06]. After speaking with Jackie Council on 9/21/06, I will ask Bedford to revise their vial size to be the same as the innovator's (15 mL). Note that the innovator's 1 gram and 2 gram sizes are marketed in a 15 mL capacity vial.

Refer to the chemist question above. Neeru will send out chemistry deficiencies-one will include to revise to 15 mL vial size. In the 3/16/07 AF, Bedford refused to change vial size.

In AM dated 7/27/07, Bedford provided a justification to the 10 mL vial for 1 gram. To recap, Beford has developed a 2 gram dosage in a 15 mL vial and has chosen to use a 10 mL vial for the 1 gram dosage to differentiate the two products. There is enough volume in the 10 mL vial to allow for the reconstitution using the maximum amount of diluent. The stability testing was conducted in a 10 mL vial and the results are within the allowable limits. Thus, the 10 mL vial should not present any problems in the market for reconstitution of the DP according to the PI labeling. From the labeling standpoint, the difference in vial sizes between the RLD and innovator is acceptable (please read the email between Lilly and Carol about the difference in vial sizes).

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 6:44 PM
To: Barlow, James T; Birch, Postelle; Council, Jacqueline; Dillahunt, Michelle; Golson, Lillie D; Grace, John F; Hoppes, Charles V; Lee, Koung U; Park, Chan H; Park, Sarah Soojung; Payne, Angela; Shin, Melaine M; Vezza, Adolph E; Vu, Thuyanh (Ann); Weitzman, Beverly; Wu, Ruby (Chi-Ann)
Subject: FW: Vial size differences
FYI

From: Holquist, Carol A
Sent: Thursday, July 26, 2007 6:42 PM
To: Golson, Lillie D
Subject: RE: Vial size differences

Yes thanks

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 6:09 PM
To: Holquist, Carol A
Subject: RE: Vial size differences

Just to verify, on the vial, rather than

Single Use Vial

AMPICILLIN FOR INJECTION
500 Gram
IM or IV Use

You'd prefer:

Single Use Vial

AMPICILLIN FOR INJECTION
500 Gram/Vial
IM or IV Use

From: Holquist, Carol A
Sent: Thursday, July 26, 2007 5:53 PM
To: Golson, Lillie D
Subject: RE: Vial size differences

Lillie,

Thanks. I know you probably do this already as well but can you please make sure the strength is expressed in mg/vial and directions for reconstitution. We have seen a bunch of errors with powders when it doesn't say mg/vial or the resultant concentration once the diluent is added.

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 5:12 PM
To: Holquist, Carol A
Subject: RE: Vial size differences

Thanks Carol. We do ask for differentiation, and they are powders. So we will move forward on these.

Take care.

From: Holquist, Carol A
Sent: Thursday, July 26, 2007 5:10 PM
To: Golson, Lillie D
Cc: Toyer, Denise P
Subject: RE: Vial size differences

Lillie,

Denise is on leave this week. It appears from your e-mail that there is no direct correlation to the size of vial per strength. If there is no pre-existing correlation then I don't see much of a problem with this proposal. I would just hope they differentiate the strengths adequately.

Thanks,
Carol

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 3:57 PM
To: Holquist, Carol A
Cc: Toyer, Denise P
Subject: Vial size differences

Hi Guys,

Quick question. What are your thoughts on a firm proposing a different vial size for a powder for injection product. The RLD for an antibiotic packages its 500 mg, 1 g, and 2 g products in 15 mL size vials. A generic firm is proposing to package its products in 20 mL and 30 mL vials. Rationale, their product is lyophilized. Another generic firm is proposing a 10 mL vial. No rationale provided. In speaking with a couple of pharmacists, they see no problem with this since a syringe is used to draw up the diluent and would be measuring the amount added so vial size shouldn't matter. What are your thoughts on this?

Thanks much.

7. Container/Closure

The configuration of container/closure system used for packaging the drug product (is summarized in the table below:
[Vol. 1.2, p. 96]

Container/Closure	Description
10 mL vial	10 cc, 20 mm, Type I Flint Tubing Vials
Closure	20 mm Gray Lyo stoppers
Seal	Mist gray 20 mm, Flip-off Aluminum Seals
(b) (4)	(b) (4)

* The firm indicates that this (b) (4)

8. Storage, Packaging and/or Dispensing:

USP - Preserve in *Containers for Sterile Solids* as described under *Injections*

NDA - Store original packages at room temperature: avoid excessive heat

ANDA - Store original packages at 20° to 25° C (68° to 77° F). See USP controlled room temperature; avoid excessive heat.

9. This is the first generic. Bedford did not submit SPL.

Date of Review: September 17, 2007	Date of Submission: 8/30/07
Primary Reviewer: Thuyanh Vu	Date:
Team Leader: John Grace	Date:

Following this page, 4 pages withheld in full (b)(4)

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

/s/

Thuyanh Vu
9/17/2007 03:01:12 PM
LABELING REVIEWER

John Grace
9/18/2007 10:17:07 AM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-286 Date of Submission: July 27, 2007

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

Labeling Deficiencies:

1. CONTAINER: 1 gram

   Please revise your label to read:

   1 gram/Vial

2. CARTON: 10 vials per carton

   Please see CONTAINER comment.

3. INSERT

   Acceptable in final print.

Submit labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -
http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No see comments.
Container Labels (100's): No see comments
Professional Package Insert Labeling: No see comments
Revisions needed post-approval: None

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Azactam

NDA Number: NDA 50-580/S-033 approved 3/25/02, provided for Geriatric Use and S-037 approved 12/16/04 provided for the antibiotic class labeling.

NDA Drug Name: Azactam

NDA Firm:Bristol Myers Squibb

Date of Approval of NDA Insert and supplement #: NDA 50-580/S-033 approved 3/25/02

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Appears this way on original.

NOTES/QUESTIONS TO THE CHEMIST

Pl see below.

-----Original Message-----
From: Nguyen, Ryan
Sent: Wednesday, February 01, 2006 4:37 PM
To: Takiar, Neeru B
Cc: Zuk, Susan; Park, Sarah Soojung
Subject: FW: 65-286.

Hi Neeru,

Please respond to Jackie's questions below. Thanks.

Ryan

-----Original Message-----
From: Council, Jacqueline
Sent: Wednesday, February 01, 2006 4:36 PM
To: Nguyen, Ryan
Subject: 65-286.

Good afternoon Ryan,

I completed the review [with deficiencies]. Please see below.

Thanks,
Jacqueline

ANDA Number: 65-286

Dates of Submission: December 23, 2004

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

NOTES/QUESTIONS TO THE CHEMIST

1. The innovator's vial size is "15 mL" and the ANDA vial size is "10 mL" We plan to inform the ANDA that the vial size should be the same as the innovator's, "15 mL".

That is fine.

Neeru's email dated 4/19/07:

As per comment 6 (see below) in my review #2,10 mL size is not acceptable.

Please note that it is recommended in your labeling that for intravenous solutions (bolus injection), the contents of the aztreonam for injection 1 gram vial should be

are constituted with 6 to 10 mL Sterile Water for Injection. Therefore, we recommend that you revise your vial size to same as the innovator “15 mL” because the proposed vial size “10 mL” may not be an adequate size for constituting IV solutions. Please revise your labels and labeling accordingly.

Neeru

2. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION SECTION, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]? See text from insert labeling below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam not exceeding 2% w/v prepared with Sodium Chloride Injection 0.9% or Dextrose Injection 5%, to which clindamycin phosphate, gentamicin sulfate, tobramycin sulfate, or cefazolin sodium have been added at concentrations usually used clinically, are stable for up to 48 hours at room temperature or seven days under refrigeration. Ampicillin sodium admixtures with aztreonam in Sodium Chloride Injection 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection 5% is two hours at room temperature and eight hours under refrigeration.

Aztreonam-cloxacillin sodium and aztreonam-vancomycin hydrochloride admixtures are stable in Dianeal® 137 (Peritoneal Dialysis Solution) with 4.25% Dextrose for up to 24 hours at room temperature.

Aztreonam is incompatible with nafcillin sodium, cephradine, and metronidazole.

Other admixtures are not recommended since compatibility data are not available.

Intravenous (IV) Solutions

For Bolus Injection: The contents of the aztreonam for injection 1 gram vial should be constituted with 6 to 10 mL Sterile Water for Injection.

For Infusion (b) (4) Each gram of aztreonam should be initially constituted with at least 3 mL Sterile Water for Injection and transferred to an appropriate infusion solution. Further dilution may be obtained with one of the following intravenous infusion solutions:

Sodium Chloride Injection, 0.9%
Ringer's Injection
Lactated Ringer's Injection
Dextrose Injection, 5% or 10%
Dextrose and Sodium Chloride Injection, 5%:0.9%, 5%:0.45% or 5%:0.2%
Sodium Lactate Injection (M/6 Sodium Lactate)
Ionosol® B and 5% Dextrose
lsolyte® M with 5% Dextrose
Normosol®-R
Normosol®-R and 5% Dextrose
Normosol®-M and 5% Dextrose
Mannitol Injection, 5% or 10%
Lactated Ringer's and 5% Dextrose Injection
Plasma-Lyte® M and 5% Dextrose

Intramuscular (IM) Solutions

The contents of an aztreonam vial should be constituted with at least 3 mL of an appropriate diluent per gram aztreonam. The following diluents may be used:

Sterile Water for Injection
Sterile Bacteriostatic Water for Injection (with benzyl alcohol or with methyl- and propylparabens)

Sodium Chloride Injection, 0.9%
Bacteriostatic Sodium Chloride Injection (with benzyl alcohol)

Stability Of IV And IM Solutions

Aztreonam solutions for IV infusion at concentrations not exceeding 2% w/v must be used within 48 hours following constitution if kept at 20° to 25°C (68° to 77°F) (see USP controlled room temperature) or within seven days if refrigerated 2° to 8°C (36° to 46°F).

(b) (4)

(b) (4)

Aztreonam solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection or Sodium Chloride Injection, should be used promptly after preparation; the two excepted solutions must be used within 48 hours if stored at controlled room temperature or within seven days if refrigerated.

Yes

Thanks

In the 3/16/07 amendment, Bedford added Isolyte E and Isolyte E with 5% Dexrose to DOSAGE AND ADMINISTRATION. Bedford also submitted stability studies in support. A copy of the stability studies was submitted to chemistry.

FOR THE RECORD: (portions taken from previous review)

1. Labeling model

   Azactam®, by Bristol-Myers Squibb Company
   NDA 50-580/S-033 approved 3/25/02

   Note: S-037 approved 12/16/04 contains the "Labeling Requirements for Systemic Antibacterial Drug Products Indented for Human Use". [This ANDA has included this text].

2. The listing of the active and inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the composition listed in the application. [Vol. 1.2, p. 96]
   NOTE: The USP indicates that Aztreonam for Injection is a dry mixture of sterile Aztreonam and Arginine. This is consistent with the RLD. (b) (4)

3. Physical Description

   Dry: White to off-white powder
   (b) (4) [per chemist review]
   Solution: clear, colorless to yellow solution
   [Vol 2.1, p. 86, 201]

4. Manufacturing Facility

   Ben Venue Laboratories, Inc.
   300 Northfield Road
   Bedford, OH 44146
   [Vol. 1.2, p. 217]

5. Patent/ Exclusivities

Patent Data – 50-521

No	Expiration	Use Code	Use	File
None				I

Exclusivity Data –

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

6. Package Sizes

RLD- Single-dose 15 mL capacity vials:
500 mg/vial – 10s
1 g/vial – 10s
2 g/vial - 10s

ANDA - 1 g/vial; 10 mL capacity vial; carton of 10

Bedford is developing a 2 gram dosage in a 15 mL vial and chose to use a 10 mL vial for the 1 gram dosage to differentiate between the two dosages and therefore prevent medication errors. Bedford acknowledge that the RLD is in a 15 mL vial. Bedford will not change the 1 gram dosage to 10 mL vial [AF dated 5/31/06]. After speaking with Jackie Council on 9/21/06, I will ask Bedford to revise their vial size to be the same as the innovator's (15 mL). Note that the innovator's 1 gram and 2 gram sizes are marketed in a 15 mL capacity vial.

Refer to the chemist question above. Neeru will send out chemistry deficiencies-one will include to revise to 15 mL vial size. In the 3/16/07 AF, Bedford refused to change vial size.

In AM dated 7/27/07, Bedford provided a justification to the 10 mL vial for 1 gram. To recap, Beford has developed a 2 gram dosage in a 15 mL vial and has chosen to use a 10 mL vial for the 1 gram dosage to differentiate the two products. There is enough volume in the 10 mL vial to allow for the reconstitution using the maximum amount of diluent. The stability testing was conducted in a 10 mL vial and the results are within the allowable limits. Thus, the 10 mL vial should not present any problems in the market for reconstitution of the DP according to the PI labeling. From the labeling standpoint, the difference in vial sizes between the RLD and innovator is acceptable (please read the email between Lilly and Carol about the difference in vial sizes).

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 6:44 PM
To: Barlow, James T; Birch, Postelle; Council, Jacqueline; Dillahunt, Michelle; Golson, Lillie D; Grace, John F; Hoppes, Charles V; Lee, Koung U; Park, Chan H; Park, Sarah Soojung; Payne, Angela; Shin, Melaine M; Vezza, Adolph E; Vu, Thuyanh (Ann); Weitzman, Beverly; Wu, Ruby (Chi-Ann)
Subject: FW: Vial size differences
FYI

_____

From: Holquist, Carol A
Sent: Thursday, July 26, 2007 6:42 PM
To: Golson, Lillie D
Subject: RE: Vial size differences

Yes thanks

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 6:09 PM
To: Holquist, Carol A
Subject: RE: Vial size differences

Just to verify, on the vial, rather than

Single Use Vial

AMPICILLIN FOR INJECTION
500 Gram
IM or IV Use

You'd prefer:

Single Use Vial

AMPICILLIN FOR INJECTION
500 Gram/Vial
IM or IV Use

From: Holquist, Carol A
Sent: Thursday, July 26, 2007 5:53 PM
To: Golson, Lillie D
Subject: RE: Vial size differences

Lillie,

Thanks. I know you probably do this already as well but can you please make sure the strength is expressed in mg/vial and directions for reconstitution. We have seen a bunch of errors with powders when it doesn't say mg/vial or the resultant concentration once the diluent is added.

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 5:12 PM
To: Holquist, Carol A
Subject: RE: Vial size differences

Thanks Carol. We do ask for differentiation, and they are powders. So we will move forward on these.

Take care.

From: Holquist, Carol A
Sent: Thursday, July 26, 2007 5:10 PM
To: Golson, Lillie D

Cc: Toyer, Denise P
Subject: RE: Vial size differences

Lillie,

Denise is on leave this week. It appears from your e-mail that there is no direct correlation to the size of vial per strength. If there is no pre-existing correlation then I don't see much of a problem with this proposal. I would just hope they differentiate the strengths adequately.

Thanks,
Carol

From: Golson, Lillie D
Sent: Thursday, July 26, 2007 3:57 PM
To: Holquist, Carol A
Cc: Toyer, Denise P
Subject: Vial size differences

Hi Guys,

Quick question. What are your thoughts on a firm proposing a different vial size for a powder for injection product. The RLD for an antibiotic packages its 500 mg, 1 g, and 2 g products in 15 mL size vials. A generic firm is proposing to package its products in 20 mL and 30 mL vials. Rationale, their product is lyophilized. Another generic firm is proposing a 10 mL vial. No rationale provided. In speaking with a couple of pharmacists, they see no problem with this since a syringe is used to draw up the diluent and would be measuring the amount added so vial size shouldn't matter. What are your thoughts on this?

Thanks much.

7. Container/Closure

The configuration of container/closure system used for packaging the drug product (is summarized in the table below:
[Vol. 1.2, p. 96]

Container/Closure	Description
10 mL vial	10 cc, 20 mm, Type I Flint Tubing Vials
Closure	20 mm Gray Lyo stoppers
Seal	Mist gray 20 mm, Flip-off Aluminum Seals
(b) (4)	(b) (4)

* The firm indicates that this (b) (4)

8. Storage, Packaging and/or Dispensing:

USP - Preserve in *Containers for Sterile Solids* as described under *Injections*

NDA - Store original packages at room temperature: avoid excessive heat

ANDA - Store original packages at 20° to 25° C (68° to 77° F). See USP controlled room temperature; avoid excessive heat.

9. This is the first generic.

Date of Review: August 9, 2007 Date of Submission: 7/27/07

Primary Reviewer: Thuyanh Vu Date:

Team Leader: John Grace Date:

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

/s/

Thuyanh Vu
8/9/2007 03:38:46 PM
LABELING REVIEWER

John Grace
8/14/2007 11:34:55 AM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-286 Date of Submission: March 16, 2007

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

Labeling Deficiencies:

1. CONTAINER: 1 gram

   Please revise your vial size to 15 mL. Your vial size should be the same size as the innovator "15 mL". Revise your labeling accordingly.

2. CARTON: 10 vials per carton

   Acceptable in final print.

3. INSERT

   Refer to CONTAINER comment.

Submit labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -
http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Appears this way on original.

NOTES/QUESTIONS TO THE CHEMIST

Pl see below.

-----Original Message-----
From: Nguyen, Ryan
Sent: Wednesday, February 01, 2006 4:37 PM
To: Takiar, Neeru B
Cc: Zuk, Susan; Park, Sarah Soojung
Subject: FW: 65-286.

Hi Neeru,

Please respond to Jackie's questions below. Thanks.

Ryan

-----Original Message-----
From: Council, Jacqueline
Sent: Wednesday, February 01, 2006 4:36 PM
To: Nguyen, Ryan
Subject: 65-286.

Good afternoon Ryan,

I completed the review [with deficiencies]. Please see below.

Thanks,
Jacqueline

ANDA Number: 65-286

Dates of Submission: December 23, 2004

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

NOTES/QUESTIONS TO THE CHEMIST

1. The innovator's vial size is "15 mL" and the ANDA vial size is "10 mL" We plan to inform the ANDA that the vial size should be the same as the innovator's, "15 mL".

That is fine.

Neeru's email dated 4/19/07:

> As per comment 6 (see below) in my review #2,10 mL size is not acceptable.
>
> Please note that it is recommended in your labeling that for intravenous solutions (bolus injection), the contents of the aztreonam for injection 1 gram vial should be are constituted with 6 to 10 mL Sterile Water for Injection. Therefore, we recommend that you revise your vial size to same as the innovator "15 mL" because the proposed vial size "10 mL" may not be an adequate size for constituting IV solutions. Please revise your labels and labeling accordingly.
>
> Neeru

2. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION SECTION, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]? See text from insert labeling below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam not exceeding 2% w/v prepared with Sodium Chloride Injection 0.9% or Dextrose Injection 5%, to which clindamycin phosphate, gentamicin sulfate, tobramycin sulfate, or cefazolin sodium have been added at concentrations usually used clinically, are stable for up to 48 hours at room temperature or seven days under refrigeration. Ampicillin sodium admixtures with aztreonam in Sodium Chloride Injection 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection 5% is two hours at room temperature and eight hours under refrigeration.

Aztreonam-cloxacillin sodium and aztreonam-vancomycin hydrochloride admixtures are stable in Dianeal® 137 (Peritoneal Dialysis Solution) with 4.25% Dextrose for up to 24 hours at room temperature.

Aztreonam is incompatible with nafcillin sodium, cephradine, and metronidazole.

Other admixtures are not recommended since compatibility data are not available.

Intravenous (IV) Solutions

For Bolus Injection: The contents of the aztreonam for injection 1 gram vial should be constituted with 6 to 10 mL Sterile Water for Injection.

For Infusion (b) (4) Each gram of aztreonam should be initially constituted with at least 3 mL Sterile Water for Injection and transferred to an appropriate infusion solution. Further dilution may be obtained with one of the following intravenous infusion solutions:

Sodium Chloride Injection, 0.9%
Ringer's Injection
Lactated Ringer's Injection
Dextrose Injection, 5% or 10%
Dextrose and Sodium Chloride Injection, 5%:0.9%, 5%:0.45% or 5%:0.2%
Sodium Lactate Injection (M/6 Sodium Lactate)
Ionosol® B and 5% Dextrose
lsolyte® M with 5% Dextrose
Normosol®-R
Normosol®-R and 5% Dextrose
Normosol®-M and 5% Dextrose
Mannitol Injection, 5% or 10%
Lactated Ringer's and 5% Dextrose Injection
Plasma-Lyte® M and 5% Dextrose

Intramuscular (IM) Solutions

The contents of an aztreonam vial should be constituted with at least 3 mL of an appropriate diluent per gram aztreonam. The following diluents may be used:

Sterile Water for Injection
Sterile Bacteriostatic Water for Injection (with benzyl alcohol or with methyl- and propylparabens)

Sodium Chloride Injection, 0.9%

Bacteriostatic Sodium Chloride Injection (with benzyl alcohol)

Stability Of IV And IM Solutions

Aztreonam solutions for IV infusion at concentrations not exceeding 2% w/v must be used within 48 hours following constitution if kept at 20° to 25°C (68° to 77°F) (see USP controlled room temperature) or within seven days if refrigerated 2° to 8°C (36° to 46°F).

(b) (4)

Aztreonam solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection or Sodium Chloride Injection, should be used promptly after preparation; the two excepted solutions must be used within 48 hours if stored at controlled room temperature or within seven days if refrigerated.

Yes

Thanks

In the 3/16/07 amendment, Bedford added Isolyte E and Isolyte E with 5% Dexrose to DOSAGE AND ADMINISTRATION. Bedford also submitted stability studies in support. A copy of the stability studies was submitted to chemistry.

FOR THE RECORD: (portions taken from previous review)

1. Labeling model

   Azactam®, by Bristol-Myers Squibb Company
   NDA 50-580/S-033 approved 3/25/02

   Note: S-037 approved 12/16/04 contains the “Labeling Requirements for Systemic Antibacterial Drug Products Indented for Human Use”. [This ANDA has included this text].

2. The listing of the active and inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the composition listed in the application. [Vol. 1.2, p. 96]

NOTE: The USP indicates that Aztreonam for Injection is a dry mixture of sterile Aztreonam and Arginine. This is consistent with the RLD. (b) (4)

3. Physical Description

Dry: White to off-white powder
(b) (4) [per chemist review]
Solution: clear, colorless to yellow solution
[Vol 2.1, p. 86, 201]

4. Manufacturing Facility

Ben Venue Laboratories, Inc.
300 Northfield Road
Bedford, OH 44146
[Vol. 1.2, p. 217]

5. Patent/ Exclusivities

Patent Data – 50-521

No	Expiration	Use Code	Use	File
None				I

Exclusivity Data –

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

6. Package Sizes

RLD- Single-dose 15 mL capacity vials:
500 mg/vial – 10s
1 g/vial – 10s
2 g/vial - 10s

ANDA - 1 g/vial; 10 mL capacity vial; carton of 10

Bedford is developing a 2 gram dosage in a 15 mL vial and chose to use a 10 mL vial for the 1 gram dosage to differentiate between the two dosages and therefore prevent medication errors. Bedford acknowledge that the RLD is in a 15 mL vial. Bedford will not change the 1 gram dosage to 10 mL vial [AF dated 5/31/06]. After speaking with Jackie Council on 9/21/06, I will ask Bedford to revise their vial size to be the same as the innovator's (15 mL). Note that the innovator's 1 gram and 2 gram sizes are marketed in a 15 mL capacity vial.

Refer to the chemist question above. Neeru will send out chemistry deficiencies-one will include to revise to 15 mL vial size. In the 3/16/07 AF, Bedford refused to change vial size.

7. Container/Closure

The configuration of container/closure system used for packaging the drug product (is summarized in the table below:
[Vol. 1.2, p. 96]

Container/Closure	Description
10 mL vial	10 cc, 20 mm, Type I Flint Tubing Vials
Closure	20 mm Gray Lyo stoppers
Seal	Mist gray 20 mm, Flip-off Aluminum Seals
(b) (4)	(b) (4)

* The firm indicates that this (b) (4)

8. Storage, Packaging and/or Dispensing:

USP - Preserve in *Containers for Sterile Solids* as described under *Injections*

NDA - Store original packages at room temperature: avoid excessive heat

ANDA - Store original packages at 20° to 25° C (68° to 77° F). See USP controlled room temperature; avoid excessive heat.

9. This is the first generic.

Date of Review: April 23, 2007 Date of Submission: 3/16/07

Primary Reviewer: Thuyanh Vu Date:

Team Leader: John Grace Date:

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

/s/

Thuyanh Vu
4/23/2007 10:45:18 AM
MEDICAL OFFICER

John Grace
4/24/2007 08:03:14 AM
MEDICAL OFFICER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-286 Date of Submission: May 31, 2006

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

Labeling Deficiencies:

1. CONTAINER: 1 gram

   We note that you have proposed a 10 mL vial. Your vial size should be the same size as the innovator "15 mL". Revise your labels and labeling accordingly and submit any necessary supporting documentation.

2. INSERT

   a. CLINICAL PHARMACOLOGY

      i. Figure 1, revise to read "Aztreonam Serum Concentrations, mcg/mL".

      ii. Microbiology, Susceptibility Testing, Dilution Techniques, footnote a, please change reference "[5]" to "[1]".

   b. DOSAGE AND ADMINISTRATION

      Intravenous (IV) Solutions, For Infusion: We note that you did not include Isolyte E and Isolyte E with 5% Dextrose solutions for secondary further dilution. Your labeling should be the same as the innovator. Please revise accordingly and forward all necessary supporting information.

Submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -
http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling?
Container Labels (1 gram): See above comments.
Carton Labeling (1 g/vial, 10's): Satisfactory with May 31, 2006 submission
Professional Package Insert Labeling:
Revisions needed post-approval:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Azactam

NDA Number: 50-580

NDA Drug Name: Azactam (Aztreonam for Injection USP)

NDA Firm: Bristol Myers Squibb Company

Date of Approval of NDA Insert and supplement #: 50-580/S-037, approved 12/16/2004

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

NOTES/QUESTIONS TO THE CHEMIST

Please see below. Note from Ann Vu: …spoke with Jackie, she stated that Bedford should be the same as RLD's. Bedford's rationale is weak.

-----Original Message-----
From: Nguyen, Ryan
Sent: Wednesday, February 01, 2006 4:37 PM
To: Takiar, Neeru B
Cc: Zuk, Susan; Park, Sarah Soojung
Subject: FW: 65-286.

Hi Neeru,

Please respond to Jackie's questions below. Thanks.

Ryan

-----Original Message-----
From: Council, Jacqueline
Sent: Wednesday, February 01, 2006 4:36 PM
To: Nguyen, Ryan
Subject: 65-286.

Good afternoon Ryan,

I completed the review [with deficiencies]. Please see below.

Thanks,
Jacqueline

ANDA Number: 65-286

Dates of Submission: December 23, 2004

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

NOTES/QUESTIONS TO THE CHEMIST

1. The innovator's vial size is "15 mL" and the ANDA vial size is "10 mL" We plan to inform the ANDA that the vial size should be the same as the innovator's, "15 mL".

That is fine.

2. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION SECTION, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]?

Yes

Appears this way on original.

FOR THE RECORD – First Generic: (portions taken from previous review)

1. Labeling model

   Azactam®, by Bristol-Myers Squibb Company
   NDA 50-580/S-033 approved 3/25/02

   Note: S-037 approved 12/16/04 contains the "Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use". [This ANDA has included this text].

2. The listing of the active and inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the composition listed in the application. [Vol. 1.2, p. 96]
   NOTE: The USP indicates that Aztreonam for Injection is a dry mixture of sterile Aztreonam and Arginine. This is consistent with the RLD. (b) (4)

3. Physical Description

   Dry: White to off-white powder
   (b) (4) [per chemist review]
   Solution: clear, colorless to yellow solution
   [Vol 2.1, p. 86, 201]

4. Manufacturing Facility

   Ben Venue Laboratories, Inc.
   300 Northfield Road
   Bedford, OH 44146
   [Vol. 1.2, p. 217]

5. Patent/ Exclusivities

Patent Data – 50-521

No	Expiration	Use Code	Use	File
None				I

Exclusivity Data –

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

6. Package Sizes

   RLD- Single-dose 15 mL capacity vials:
   500 mg/vial – 10s
   1 g/vial – 10s
   2 g/vial - 10s

   ANDA - 1 g/vial; 10 mL capacity vial; carton of 10

   Note from Ann Vu: Bedford is developing a 2 gram dosage in a 15 mL vial and chose to use a 10 mL vial for the 1 gram dosage to differentiate between the two dosages and therefore prevent medication errors. Bedford acknowledge that the RLD is in a 15 mL vial. Bedford will not change the 1 gram dosage to 10 mL vial [AF dated 5/31/06]. After

speaking with Jackie Council on 9/21/06, I will ask Bedford to revise their vial size to be the same as the innovator's (15 mL). Note that the innovator's 1 gram and 2 gram sizes are marketed in a 15 mL capacity vial.

7. Container/Closure

The configuration of container/closure system used for packaging the drug product (is summarized in the table below:
[Vol. 1.2, p. 96]

Container/Closure	Description
10 mL vial	10 cc, 20 mm, Type I Flint Tubing Vials
Closure	20 mm Gray Lyo stoppers
Seal	Mist gray 20 mm, Flip-off Aluminum Seals
(b) (4)	(b) (4)

* The firm indicates that this (b) (4)

8. Storage, Packaging and/or Dispensing:

USP - Preserve in *Containers for Sterile Solids* as described under *Injections*

NDA - Store original packages at room temperature: avoid excessive heat

ANDA - Store original packages at 20° to 25° C (68° to 77° F). See USP controlled room temperature; avoid excessive heat.

Date of Review: 12/1/06 Date of Submission: 5/31/06

Primary Reviewer: Charlie Hoppes Date:

Team Leader: John Grace Date:

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

/s/

Charles Hoppes
12/1/2006 11:25:01 AM
MEDICAL OFFICER

John Grace
12/3/2006 11:26:44 AM
MEDICAL OFFICER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-286

Dates of Submission: December 23, 2004

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

Labeling Deficiencies:

1. CONTAINER: 1 gram

   a. General Comment

      We note that your vial size is 10 mL. Your vial size should be the same size as the innovator "15 mL". Revise your labels and labeling accordingly.

   b. Front panel

      Add a comma prior to "USP".

   c. Side panel

      Revise to read, "... vigorously. See insert for dosage, constitution, and stability".

      To provide space for the above statement you may relocate the text "Sterile, Sodium free, Single Dose Vial" to the bottom of the front panel.

2. CARTON: 10 vials per carton

   a. See comment 1(b) under CONTAINER.

   b. Revise "10 x Sterile Single Dose Vials" to read " 10 Sterile Single Dose Vials". [Two locations].

   c. Back panel

      Revise to read, "... vigorously. See insert for dosage, constitution, and stability".

3. INSERT

a. GENERAL COMMENT

We note that some of the reference subscripts differ from the innovator. We refer you to Azactam®, by Bristol-Myers Squibb Company/NDA 50-580/S-033 approved March 25, 2002. Please revise accordingly.

b. CLINICAL PHARMACOLOGY

i. Revise the sixth paragraph to read as follows:

In the elderly patients, the mean serum half-life of aztreonam increased and the renal clearance decreased, consistent with the age-related decrease in creatinine clearance. [1-4] The dosage of aztreonam should be adjusted accordingly (see DOSAGE AND ADMINISTRATION: Renal Impairment in Adult Patients).

ii. Microbiology

Revise the second sentence to read, "...in the INDICATIONS AND USAGE section".

c. DOSAGE AND ADMINISTRATION

i. Renal Impairment in Adult Patients

Second paragraph

In the equation, center the text "Males: Clcr =", so that it does not appear on the same line as the dominator.

ii. Dosage in Pediatric Patients

In the table title revise "AZTREONAM" to read "AZTREONAM FOR INJECTION".

iii. Preparation Of Parenteral Solutions/General

Add the following as the last sentence of the last paragraph:

... not affected). Parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit.

iv. Intravenous (IV) Solutions

A) For Bolus Injection

Once your vial size has been changed to 15 mL, revise the first sentence to be consistent with the innovator.

B) For Infusion

Once your vial size has been changed to 15 mL, revise the text to be consistent with the innovator.

C) We note that you did not include all of the intravenous infusion solutions for secondary further dilution. Your labeling should be the same as the innovator. Please revise accordingly.

v. Intramuscular (IM) Solution

Once your vial size has been changed to 15 mL, revise the text to be consistent with the innovator.

Please revise your labels and labeling as described above and submit electronically in final print. The immediate container labels and carton labeling may be submitted either electronically or in hard copy.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2alG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 29			
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? *RLD packaged in cartons.	X*		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation – see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	

Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. *Same as the RLD.	*		
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST

1. The innovator's vial size is "15 mL" and the ANDA vial size is "10 mL" We plan to inform the ANDA that the vial size should be the same as the innovator's, "15 mL".

2. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION SECTION, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]? See text from insert labeling below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam not exceeding 2% w/v prepared with Sodium Chloride Injection 0.9% or Dextrose Injection 5%, to which clindamycin phosphate, gentamicin sulfate, tobramycin sulfate, or cefazolin sodium have been added at concentrations usually used clinically, are stable for up to 48 hours at room temperature or seven days under refrigeration. Ampicillin sodium admixtures with aztreonam in Sodium Chloride Injection 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection 5% is two hours at room temperature and eight hours under refrigeration.

Aztreonam-cloxacillin sodium and aztreonam-vancomycin hydrochloride admixtures are stable in Dianeal® 137 (Peritoneal Dialysis Solution) with 4.25% Dextrose for up to 24 hours at room temperature.

Aztreonam is incompatible with nafcillin sodium, cephradine, and metronidazole.

Other admixtures are not recommended since compatibility data are not available.

Intravenous (IV) Solutions

For Bolus Injection: The contents of the aztreonam for injection 1 gram vial should be constituted with 6 to 10 mL Sterile Water for Injection.

For Infusion (b) (4) Each gram of aztreonam should be initially constituted with at least 3 mL Sterile Water for Injection and transferred to an appropriate infusion solution. Further dilution may be obtained with one of the following intravenous infusion solutions:

Sodium Chloride Injection, 0.9%
Ringer's Injection
Lactated Ringer's Injection

Dextrose Injection, 5% or 10%
Dextrose and Sodium Chloride Injection, 5%:0.9%, 5%:0.45% or 5%:0.2%
Sodium Lactate Injection (M/6 Sodium Lactate)
Ionosol® B and 5% Dextrose
Isolyte® M with 5% Dextrose
Normosol®-R
Normosol®-R and 5% Dextrose
Normosol®-M and 5% Dextrose
Mannitol Injection, 5% or 10%
Lactated Ringer's and 5% Dextrose Injection
Plasma-Lyte® M and 5% Dextrose

Intramuscular (IM) Solutions

The contents of an aztreonam vial should be constituted with at least 3 mL of an appropriate diluent per gram aztreonam. The following diluents may be used:

Sterile Water for Injection
Sterile Bacteriostatic Water for Injection (with benzyl alcohol or with methyl- and propylparabens)

Sodium Chloride Injection, 0.9%
Bacteriostatic Sodium Chloride Injection (with benzyl alcohol)

Stability Of IV And IM Solutions

Aztreonam solutions for IV infusion at concentrations not exceeding 2% w/v must be used within 48 hours following constitution if kept at 20° to 25°C (68° to 77°F) (see USP controlled room temperature) or within seven days if refrigerated 2° to 8°C (36° to 46°F).

(b) (4)

Aztreonam solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection or Sodium Chloride Injection, should be used promptly after preparation; the two excepted solutions must be used within 48 hours if stored at controlled room temperature or within seven days if refrigerated.

FOR THE RECORD:

1. Labeling model

   Azactam®, by Bristol-Myers Squibb Company
   NDA 50-580/S-033 approved 3/25/02

   Note: S-037 approved 12/16/04 contains the "Labeling Requirements for Systemic Antibacterial Drug Products Indented for Human Use". [This ANDA has included this text].

2. The listing of the active and inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the composition listed in the application. [Vol. 1.2, p. 96]
   NOTE: The USP indicates that Aztreonam for Injection is a dry mixture of sterile Aztreonam and Arginine. This is consistent with the RLD. (b) (4)

3. Physical Description

   Dry: White to off-white powder
   (b) (4) [per chemist review]
   Solution: clear, colorless to yellow solution
   [Vol 2.1, p. 86, 201]

4. Manufacturing Facility

   Ben Venue Laboratories, Inc.
   300 Northfield Road
   Bedford, OH 44146
   [Vol. 1.2, p. 217]

5. Patent/ Exclusivities

Patent Data – 50-521

No	Expiration	Use Code	Use	File
None				I

Exclusivity Data –

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

6. Package Sizes

   RLD- Single-dose 15 mL capacity vials:
   500 mg/vial – 10s
   1 g/vial – 10s
   2 g/vial - 10s

   ANDA - 1 g/vial; 10 mL capacity vial; carton of 10
   [See comment to the firm].

7. Container/Closure

The configuration of container/closure system used for packaging the drug product (is summarized in the table below:
[Vol. 1.2, p. 96]

Container/Closure	Description
10 mL vial	10 cc, 20 mm, Type I Flint Tubing Vials
Closure	20 mm Gray Lyo stoppers
Seal	Mist gray 20 mm, Flip-off Aluminum Seals
(b) (4)	(b) (4)

* The firm indicates that this (b) (4)

8. Storage, Packaging and/or Dispensing:

USP - Preserve in *Containers for Sterile Solids* as described under *Injections* 〉

NDA - Store original packages at room temperature: avoid excessive heat

ANDA - Store original packages at 20° to 25° C (68° to 77° F). See USP controlled room temperature; avoid excessive heat.

8. Data element:

STRENGTH	1 gram
DOSAGE FORM	Lyophilized powder for injection
ROUTE OF ADMINISTRATION	Intravenous or Intramuscular
DEA SCHEDULE	n/a
ACTIVE INGREDIENT(S)	Arginine
INACTIVE INGREDIENT(S)	n/a
COLOR	Dry form: (b) (4) Solution: clear, colorless to yellow solution pale yellow
SHAPE	n/a
IMPRINT	n/a

SIZE	n/a
SCORE	n/a
SYMBOL	n/a
COATING	n/a

9. This is the first generic.

Date of Review: 1/13/06

Date of Submission: 12/23/04

Primary Reviewer:
Jacqueline Council, Pharm.D. Date: 2.2.06

Team Leader:
Captain Lillie Golson Date: 2/3/06

cc: ANDA: 65-286
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSAM\BEDFORD\LTRS&REV\65286na1.l.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065286

CHEMISTRY REVIEWS

ANDA 065286

Aztreonam for Injection USP, 1 g and 2 g per vial

Bedford Laboratories (a Division of Ben Venue Laboratories, Inc.)

Neeru B. Takiar
Office of Generic Drugs/Division of Chemistry III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 065286

2. REVIEW #: 4

3. REVIEW DATE: 8/2/2010, 9/15/2010, 10/25/2010, 11/10/2010, and 11/22/2010

4. REVIEWER: Neeru B. Takiar

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	23-DEC-2004
Minor Amendment	23-June-2006
Gratuitous Amendment	16-March-2007
Minor Amendment	27-July-2007
Gratuitous Amendment	08-Feb-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment (CMC) and Gratuitous Amendment (Addition of 2 g strength)	16-June-2010/17-June-2010 EDR
Telephone amendment	25-August-2010
Telephone Amendment	24-September-2010
Telephone Amendment	04-November-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Bedford Laboratories (a Division of Ben Venue Laboratories, Inc.)
Address:	300 Northfield Road Bedford, OH 44146
Representative:	Amy Schutte, Manager, Regulatory Affairs
Telephone:	(440) 201-3251
Fax:	(440) 439-6080

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Aztreonam for Injection, USP

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug (RLD): Azactam® (Aztreonam for Injection, USP, 1 g and 2 g per vial) is approved for Bristol Myers Squibb (NDA 50-580).

Patent Certification: No unexpired U.S. patents (vol.1.1, p7-8)
Exclusivity: None (vol.1.1, p7-8)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Lyophilized Injectable

12. STRENGTH/POTENCY: 1 g per vial and 2 g per vial

13. ROUTE OF ADMINISTRATION: Intravenous or Intramuscular
The Maximum recommended daily dose for adults is 8 g/day (2 g every 6 to 8 hrs), p87

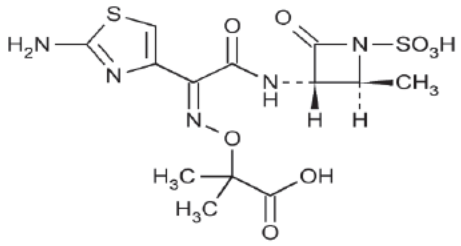
14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Aztreonam: Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl) amino]-2-oxoethylidene] amino] oxy]-2-methyl-, [2*S*-[2a, 3b (*Z*)]]-; [*78110-38-0*]; $C_{13}H_{17}N_5O_8S_2$; 435.43



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		**1**	**Adequate**	**11/22/2010**	Reviewed by N. Takiar
2315	V	Ben Venue Labs.	Manufacturing facility	3,4			
(b) (4)	III	(b) (4)		3,4			
	III			3,4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Azactam	50-580	Reference Listed Drug (RLD)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	11/15/2007	Jesse Wells
EES	Acceptable	10/7/2010	A. Inyard
Methods Validation	Not Required	-	
Labeling	Acceptable	9/9/2009	Jacqueline
Bioequivalence	Acceptable	12/23/2004	
EA	Not Applicable (category exclusion)	-	
Radiopharmaceutical	Not Applicable	-	

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
Yes ____ No If no, explain reason(s) below:

Expedited – Requested by OGD

Minor including gratuitous amendment (addition of 2 g strength) and three (3) telephone amendments.

The Chemistry Review for ANDA 065286

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC Approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:
The proposed drug product, Aztreonam for Injection USP is a Compendial product. The drug product is proposed for the treatment of infections caused by susceptible gram-negative microorganisms.

Azteronam for injection is a sterile, nonpyrogenic, sodium free, white powder containing approximately 780 mg arginine per gram of aztreonam. After constitution, the product is used for IM/IV. Aqueous solutions of the product have a pH between 4.5 to 7.5.

The drug product formulation contains Aztreonam, Arginine and (b) (4) (b) (4) (Comparison between RLD and Generic). The product is packaged into single dose vials, 1 g/vial; 10 mL capacity with gray stoppers and misty grey aluminum flip-off seals ((b) (4)). There is no indication for light protection. Only excessive heat to be avoided.

2 g/vial dosage form was added in Gratuitous Amendment (June 16, 2010). 15 mL vial with gray stopper and blue flip-off seal.

New exhibit batch for1 g/vial was manufactured in addition to the manufacture of proposed 2 g/vial (Gratuitous amendment 6/16/2010). Therefore, all updated information for 1 g and 2 g is included in this amendment below, as most of the previously submitted information for 1 g is obsolete. The CMC section of revised review (part II) was updated as applicable.

Drug Substance:
The active agent for this product is Aztreonam, a monobactam. It is a synthetic bactericidal antibiotic. The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other beta-lactam antibiotics. For example, penicillins, cephalosporins, cephamycins. It is effective against infections caused by bacteria. The sulfonic acid substituent at C-1 position of the ring activates the beta-lactam moiety; aminothiazolyl oxime side chain at the C-3 position and a methyl group at C-4 position gives the specific antibacterial spectrum and beta-lactamase stability. Manufacturing (b) (4)

(b) (4)
for Aztreonam, a monobactam.

Aztreonam is a white to off-white powder. Its chemical name is Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl) amino]-2-oxoethylidene] amino] oxy]-2-methyl-, [2*S*-[2a, 3b (*Z*)]]-. It is soluble in DMF and DMSO. The DMF (b) (4) referenced for the drug substance is currently adequate. The proposed drug substance is (b) (4) (b) (4) of Azetreonam.

The data provided for 1 g and 2 g exhibit batches in 6/16/2010 gratuitous amendment (lots # 2530-13- 1931735 and 2530-14-1931717) were manufactured at commercial scale of (b) (4) (1 g dosage) and (b) (4) (2 g dosage).

The test methods and specifications for active ingredient are according to the current USP monograph for Aztreonam and per validated in-house methods for impurities and (b) (4) (b) (4) The proposed drug is aztreonam (b) (4). The validation of the in-house methods by the FDA District Laboratory will not be needed based on the OGD memo dated 10/2/03 (Not a low dose drug and no new emerging analytical technologies).

The proposed expiration date for this product is (b) (4) months.

B. Description of How the Drug Product is Intended to be Used

The product will be marketed for prescription use only.

Aztreonam for Injection is indicated for the treatment of bacterial infections caused by susceptible organisms; urinary tract infections, lower respiratory tract infections, Septicemia, Skin and skin structure, Intra-abdominal, and Gynecological infections etc. In summary, Aztreonam, a monobactam is a sterile, synthetic, bactericidal antibiotic for intravenous or intramuscular administration.

MDD for adults is 8 g/day (2 g every 6 to 8 hrs).

C. Basis for Approvability or Not-Approval Recommendation

This ANDA was found approvable at the Team level. The review may need an addendum per current OGD policy after review by Division or First Generic Audit Team or after finalization of other discipline reviews or EES.

Following this page, 47 pages withheld in full - (b)(4). It was noted the page numbering is not correct. The review actually contains 57 pages in total, from cover page to signature page.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert Acceptable 9/9/2009 Jacqueline

Aztreonam for Injection USP, Single-Dose Vials is supplied as follows:
NDC 55390-177-10; 1 g/vial; 10 mL capacity; carton of 10.

Storage: At 20ºC to 25°C (68º to 77°F). See USP controlled room temperature; avoid excessive heat.

B. Environmental Assessment or Claim of Categorical Exclusion

Satisfactory as per review #1

III. List Of Deficiencies To Be Communicated (None)

HFD-630/NTakiar/8/2/2010; 9/15/2010; 10/25/2010, 11/10/2010 and 11/22/2010
HFD-630/LNagavelli/
HFD-617/LBradford/
V:\Chemistry Division III\Team 34\Final Version For DARRTS Folder\ANDA\65286R04.doc
F/T by:

TYPE OF LETTER: APPROVABLE

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

/s/

NEERU B TAKIAR
12/01/2010

LAXMA R NAGAVELLI
12/01/2010

LEIGH A BRADFORD
12/01/2010

ANDA 65-286

Aztreonam for Injection USP, 1 g per vial

Bedford Laboratories (a Division of Ben Venue Laboratories, Inc.)

Neeru B. Takiar
Office of Generic Drugs/Division of Chemistry III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 65-286

2. REVIEW #: 3

3. REVIEW DATE: 3/31/2008 Revised: 5/19/2008

4. REVIEWER: Neeru B. Takiar

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	23-DEC-2004
Minor Amendment	23-June-2006
Gratuitous Amendment	16-March-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	27-July-2007
Gratuitous Amendment	08-Feb-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Bedford Laboratories (a Division of Ben Venue Laboratories, Inc.)
Address:	300 Northfield Road Bedford, OH 44146
Representative:	Molly Rapp, Manager, Regulatory Affairs
Telephone:	(440) 201-3576
Fax:	(440) 439-6080

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Aztreonam for Injection, USP

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug (RLD): Azactam® (Aztreonam for Injection, USP, 1 gm/vial) is approved for Bristol Myers Squibb (NDA 50-580).

Chemistry Review Data Sheet

Patent Certification: No unexpired U.S. patents (vol.1.1, p7-8)
Exclusivity: None (vol.1.1, p7-8)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Lyophilized powder

12. STRENGTH/POTENCY: 1 g per vial

13. ROUTE OF ADMINISTRATION: Intravenous or Intramuscular
The Maximum recommended daily dose for adults is 8 g/day (2 g every 6 to 8 hrs), p87

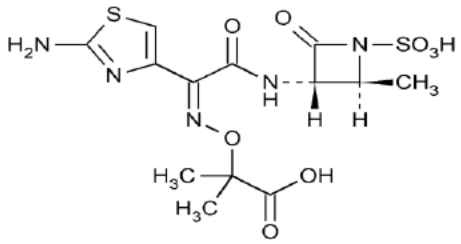
14. Rx/OTC DISPENSED: __X__ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Aztreonam: Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl) amino]-2-oxoethylidene] amino] oxy]-2-methyl-, [2*S*-[2a, 3b (*Z*)]]-; [*78110-38-0*]; $C_{13}H_{17}N_5O_8S_2$; 435.43



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	**Inadequate**	5/19/08	Reviewed by N. Takiar
2315	V	Ben Venue Labs.	Manufacturing facility	3	Adequate	19-JUL-2004	Sterilization
(b) (4)	III		(b) (4)	4			
	III			3	Adequate	26-JUL-2001	

Chemistry Review Data Sheet

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Azactam	50-580	Reference Listed Drug (RLD)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	11/15/2007	Jesse Wells
EES	Pending FUR		
Methods Validation	Not Required	-	
Labeling	Acceptable	9/18/2007	T. Vu
Bioequivalence	Acceptable	12/23/2004	
EA	Not Applicable (category exclusion)	-	
Radiopharmaceutical	Not Applicable	-	

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 65-286

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable [Minor]

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:
The proposed drug product, Aztreonam for Injection USP, 1 g per vial is a Compendial product. The drug product is proposed for the treatment of infections caused by susceptible gram-negative microorganisms.

Azteronam for injection is a sterile, nonpyrogenic, sodium free, white powder containing approximately 780 mg arginine per gram of aztreonam. After constitution, the product is used for IM/IV. Aqueous solutions of the product have a pH between 4.5 to 7.5.

The drug product formulation contains Aztreonam, Arginine and (b) (4) (b) (4) (Comparison between RLD and Generic). The product is packaged into single dose vials, 1 g/vial; 10 mL capacity with gray stoppers and misty grey aluminum flip-off seals ((b) (4) (b) (4)). There is no indication for light protection. Only excessive heat to be avoided.

Note: As per July 27, 2007 minor amendment response, the firm intends to supplement 2 g dosage form following the approval of the subject 1 g product.

Drug Substance:
The active agent for this product is Aztreonam, a monobactam. It is a synthetic bactericidal antibiotic. The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other beta-lactam antibiotics. For example, penicillins, cephalosporins, cephamycins. It is effective against infections caused by bacteria. The sulfonic acid substituent at C-1 position of the ring activates the beta-lactam moiety; aminothiazolyl oxime side chain at the C-3 position and a methyl group at C-4 position gives the specific antibacterial spectrum and beta-lactamase stability. Manufacturing (b) (4)

(b) (4) for Aztreonam, a monobactam.

Aztreonam is a white to off-white powder. Its chemical name is Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl) amino]-2-oxoethylidene] amino] oxy]-2-methyl-, [2*S*-[2a, 3b (*Z*)]]-. It is soluble in DMF and DMSO. The DMF (b) (4) referenced for the drug substance is currently inadequate. The proposed drug substance is (b) (4) (b) (4) of Azetreonam.

The maximum commercial batch size Aztreonam for Injection, 1 g per vial is (b) (4) The size of ANDA batch is (b) (4).

The test methods and specifications for active ingredient conforms to the current USP monograph for Aztreonam except for (b) (4) specification. The proposed drug is aztreonam (b) (4) (b) (4) The validation of the in-house methods by the FDA District Laboratory will not be needed based on the OGD memo dated 10/2/03 (Not a low dose drug and no new emerging analytical technologies).

The proposed expiration date for this product is (b) (4) months.

B. Description of How the Drug Product is Intended to be Used

The product will be marketed for prescription use only.

Aztreonam for Injection is indicated for the treatment of bacterial infections caused by susceptible organisms; urinary tract infections, lower respiratory tract infections, Septicemia, Skin and skin structure, Intra-abdominal, and Gynecological infections etc. In summary, Aztreonam, a monobactam is a sterile, synthetic, bactericidal antibiotic for intravenous or intramuscular administration. The maximum daily dose The Maximum recommended daily dose for adults is 8 g/day (2 g every 6 to 8 hrs).

C. Basis for Approvability or Not-Approval Recommendation

The application is not-approvable (CMC including DMF (b) (4) is deficient).

Following this page, 15 pages withheld in full - (b)(4). It was noted the page numbering is not correct. The review actually contains 26 pages in total, from cover page to signature page.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-286 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Aztreonam for Injection USP, 1 g per vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. DMF (b) (4) has been found inadequate. The DMF holder, (b) (4) has been informed. Please do not respond to this minor amendment until the DMF holder has responded to the deficiencies.

2. (b) (4)

3.

4.

5.

6.

7.

(b) (4)

8.

9.

10.

11.

12.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please be informed that until revised monograph for Aztreonam drug substance becomes official, your request for compendial status for the drug product is not acceptable. Accordingly, the relevant specifications for Aztreonam should be revised.

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Endorsements (Draft and Final with Dates):

HFD-630/NTakiar/3/31/2008; 5/19/2008
HFD-630/RISer/5/20/2008; 5/21/2008
HFD-617/JSkanchy/5/29/2008
V:\Chemistry Division III\Team 12\Final Version For DFS Folder\Drafts for ANDAs\65286R03.doc
F/T by:

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

Neeru Takiar
5/29/2008 04:39:01 PM
CHEMIST

Jeanne Skanchy
5/30/2008 11:04:28 AM
CSO

Robert Iser
6/2/2008 07:52:55 AM
CHEMIST

ANDA 65-286

Aztreonam for Injection USP, 1 g per vial

Bedford Laboratories (a Division of Ben Venue Laboratories, Inc.)

Neeru B. Takiar
Office of Generic Drugs/Division of Chemistry III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 65-286

2. REVIEW #: 2

3. REVIEW DATE: 4/4/07

4. REVIEWER: Neeru B. Takiar

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	23-DEC-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	23-June-2006
Gratuitous Amendment	16-March-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Bedford Laboratories (a Division of Ben Venue Laboratories, Inc.)
Address:	300 Northfield Road Bedford, OH 44146
Representative:	Molly Rapp, Manager, Regulatory Affairs
Telephone:	(440) 201-3576
Fax:	(440) 439-6080

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Aztreonam for Injection, USP

9. LEGAL BASIS FOR SUBMISSION:

This ANDA is the first generic application for Aztreonam.

Reference Listed Drug (RLD): Azactam® (Aztreonam for Injection, USP, 1 gm/vial) is approved for Bristol Myers Squibb (NDA 50-580).

Chemistry Review Data Sheet

Patent Certification: No unexpired U.S. patents (vol.1.1, p7-8)
Exclusivity: None (vol.1.1, p7-8)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Lyophilized powder

12. STRENGTH/POTENCY: 1 g per vial

13. ROUTE OF ADMINISTRATION: Intravenous or Intramuscular
The Maximum recommended daily dose for adults is 8 g/day (2 g every 6 to 8 hrs), p87

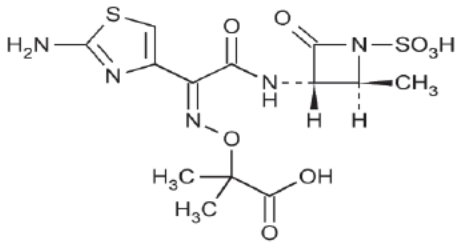
14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Aztreonam: Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl) amino]-2-oxoethylidene] amino] oxy]-2-methyl-, [2*S*-[2a, 3b (*Z*)]]-; [*78110-38-0*]; $C_{13}H_{17}N_5O_8S_2$; 435.43



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Inadequate	4/4/07	Reviewed by N. Takiar
2315	V	Ben Venue Labs.	Manufacturing facility	3	Adequate	19-JUL-2004	Sterilization
(b) (4)	III	(b) (4)		4			
	III			3	Adequate	26-JUL-2001	

Chemistry Review Data Sheet

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Azactam	50-580	Reference Listed Drug (RLD)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Not Required		
Labeling	Pending		
Bioequivalence	Acceptable	12/23/2004	
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 65-286

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable [Minor]

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:
The proposed drug product, Aztreonam for Injection USP, 1 g per vial; 200 mg/mL is a Compendial product. The drug product is proposed for the treatment of infections caused by susceptible gram-negative microorganisms.

Azteronam for injection is a sterile, nonpyrogenic, sodium free, white powder containing approximately 780 mg arginine per gram of aztreonam. After constitution, the product is used for IM/IV. Aqueous solutions of the product have a pH between 4.5 to 7.5.

The drug product formulation contains Aztreonam, Arginine and (b) (4) (b) (4) (Comparison between RLD and Generic). The product is packaged into single dose vials, 1 g/vial; 10 mL capacity with gray stoppers and misty grey aluminum flip-off seals ((b) (4) (b) (4)). There is no indication for light protection. Only excessive heat to be avoided.

Drug Substance:
The active agent for this product is Aztreonam, a monobactam. It is a synthetic bactericidal antibiotic. The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other beta-lactam antibiotics. For example, penicillins, cephalosporins, cephamycins. It is effective against infections caused by bacteria. The sulfonic acid substituent at C-1 position of the ring activates the beta-lactam moiety; aminothiazolyl oxime side chain at the C-3 position and a methyl group at C-4 position gives the specific antibacterial spectrum and beta-lactamase stability. Manufacturing (b) (4) (b) (4) for Aztreonam, a monobactam.

Aztreonam is a white to off-white powder. Its chemical name is Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl) amino]-2-oxoethylidene] amino] oxy]-2-methyl-, [2*S*-[2a, 3b (*Z*)]]-. It is soluble in DMF and DMSO. The DMF (b) (4) referenced for the drug substance is currently inadequate.

The maximum commercial batch size Aztreonam for Injection, 1 g per vial is (b) (4) The size of ANDA batch is (b) (4)

The test methods and specifications for active ingredient conforms to the current USP monograph for Aztreonam except for (b) (4) specification. The proposed drug is aztreonam (b) (4) (b) (4) The validation of the in-house methods by the FDA District Laboratory will not be needed based on the OGD memo dated 10/2/03 (Not a low dose drug and no new emerging analytical technologies).

The proposed expiration date for this product is (b) (4) months.

B. Description of How the Drug Product is Intended to be Used

The product will be marketed for prescription use only.

Aztreonam for Injection is indicated for the treatment of bacterial infections caused by susceptible organisms; urinary tract infections, lower respiratory tract infections, Septicemia, Skin and skin structure, Intra-abdominal, and Gynecological infections etc. In summary, Aztreonam, a monobactam is a sterile, synthetic, bactericidal antibiotic for intravenous or intramuscular administration. The maximum daily dose The Maximum recommended daily dose for adults is 8 g/day (2 g every 6 to 8 hrs).

C. Basis for Approvability or Not-Approval Recommendation

The application is not-approvable (CMC including DMF (b) (4) is deficient).

Following this page, 17 pages withheld in full - (b)(4). It was noted the page numbering is not correct. The review actually contains 29 pages in total, from cover page to signature page.

B. Environmental Assessment or Claim of Categorical Exclusion
Satisfactory as per review #1

III. List Of Deficiencies To Be Communicated

See Letter (Section 36).

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-286 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Aztreonam for Injection USP, 1 g per vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. DMF (b) (4) has been found inadequate. The DMF holder (b) (4) has been informed. Please do not respond to this minor amendment until the DMF holder has responded to the deficiencies.

2. (b) (4)

3.

4.

5. in most cases. Please explain.

6. Please note that it is recommended in your labeling that for intravenous solutions (bolus injection), the contents of the Aztreonam for Injection, 1 gram vial should be constituted with 6 to 10 mL Sterile Water for Injection. Therefore, we recommend that you revise your vial size to be the same as the innovator "15 mL" because the proposed vial size "10 mL" may not be an adequate size for constituting IV solutions. Please revise your labels and labeling accordingly.

7. Regarding the finished drug product, we have the following comments:

   a. (b) (4)

   b.

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 65-286
ANDA DUP
DIV FILE

Endorsements (Draft and Final with Dates):

HFD-630/NTakiar/4/4/2007
HFD-630/HKhorshidi/4/11/2007
HFD-617/JSkanchy/4/13/2007
V:\FIRMSAM\BEDFORD\LTRS&REV\65286R02.doc
F/T by:

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

Neeru Takiar
4/26/2007 09:31:35 AM
CHEMIST

Jeanne Skanchy
4/26/2007 09:40:52 AM
CSO

Hossein Khorshidi
5/1/2007 12:33:57 PM
CHEMIST

ANDA 65-286

Aztreonam for Injection, USP
1 g per vial

Bedford Laboratories
(a Division of Ben Venue Laboratories, Inc.)

Neeru B. Takiar
Office of Generic Drugs/Division of Chemistry III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 65-286

2. REVIEW #: 1

3. REVIEW DATE: June 16, 2005

4. REVIEWER: Neeru B. Takiar

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	23-DEC-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Bedford Laboratories (a Division of Ben Venue Laboratories, Inc.)
Address:	300 Northfield Road Bedford, OH 44146
Representative:	Molly Rapp, Manager, Regulatory Affairs
Telephone:	(440) 201-3576
Fax:	(440) 439-6080

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Aztreonam for Injection, USP

9. LEGAL BASIS FOR SUBMISSION:

This ANDA is the first generic application for Aztreonam.

Reference Listed Drug (RLD): Azactam® (Aztreonam for Injection, USP, 1 gm/vial) is approved for Bristol Myers Squibb (NDA 50-580).

Patent Certification: No unexpired U.S. patents (vol.1.1, p7-8)

Exclusivity: None (vol.1.1, p7-8)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Lyophilized powder

12. STRENGTH/POTENCY: 1 g per vial

13. ROUTE OF ADMINISTRATION: Intravenous or Intramuscular
The Maximum recommended daily dose for adults is 8 g/day (2 g every 6 to 8 hrs), p87

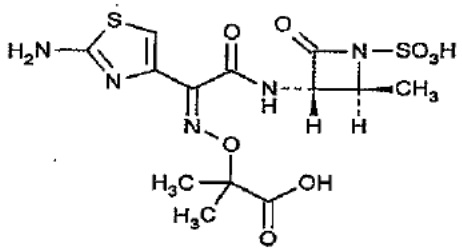
14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Aztreonam: Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl) amino]-2-oxoethylidene] amino] oxy]-2-methyl-, [2*S*-[2a, 3b (*Z*)]]-; [*78110-38-0*]; $C_{13}H_{17}N_5O_8S_2$; 435.43



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Inadequate	16-JUN-2005	
2315	V	Ben Venue Labs.	Manufacturing facility	3	Adequate	19-JUL-2004	Sterilization
(b) (4)	III		(b) (4)	4			
	III			3	Adequate	26-JUL-2001	

[1] Action codes for DMF Table:

Chemistry Review Data Sheet

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Azactam	50-580	Reference Listed Drug (RLD)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Not Required		
Labeling	Pending		
Bioequivalence	Pending		
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 65-286

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approval, MINOR [DMF Deficient]

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

The proposed drug product, Aztreonam for Injection USP, 1 g per vial; 200 mg/mL is a Compendial product. The drug product is proposed for the treatment of infections caused by susceptible gram-negative microorganisms.

Azteronam for injection is a sterile, nonpyrogenic, sodium free, white powder containing approximately 780 mg arginine per gram of aztreonam. After constitution, the product is used for IM/IV. Aqueous solutions of the product have a pH between 4.5 to 7.5.

The drug product formulation contains Aztreonam, Arginine and (b) (4) (b) (4) (Comparison between RLD and Generic). The product is packaged into single dose vials, 1 g/vial; 10 mL capacity with gray stoppers and misty grey aluminum flip-off seals ((b) (4) (b) (4)). There is no indication for light protection. Only excessive heat to be avoided.

Drug Substance:

The active agent for this product is Aztreonam, a monobactam. It is a synthetic bactericidal antibiotic. The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other beta-lactam antibiotics. For example, penicillins, cephalosporins, cephamycins. It is effective against infections caused by bacteria. The sulfonic acid substituent at C-1 position of the ring activates the beta-lactam moiety; aminothiazolyl oxime side chain at the C-3 position and a methyl group at C-4 position gives the specific antibacterial spectrum and beta-lactamase stability. Manufacturing (b) (4) (b) (4) for Aztreonam, a monobactam.

Aztreonam is a white to off-white powder. Its chemical name is Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl) amino]-2-oxoethylidene] amino] oxy]-2-methyl-, [2*S*-[2a, 3b (*Z*)]]-. It is soluble in DMF and DMSO. The DMF (b) (4) referenced for the drug substance is currently Inadequate.

The maximum commercial batch size Aztreonam for Injection, 1 g per vial is (b) (4) The size of ANDA batch is (b) (4)

The test methods and specifications for active ingredient conforms to the current USP monograph for Aztreonam except for (b) (4) specification. The proposed drug is aztreonam (b) (4) (b) (4) The validation of the in-house methods by the FDA District Laboratory will not be needed based on the OGD memo dated 10/2/03 (Not a low dose drug and no new emerging analytical technologies).

The proposed expiration date for this product is (b) (4) months.

B. Description of How the Drug Product is Intended to be Used

The product will be marketed for prescription use only.

Aztreonam for Injection is indicated for the treatment of bacterial infections caused by susceptible organisms; urinary tract infections, lower respiratory tract infections, Septicemia, Skin and skin structure, Intra-abdominal, and Gynecological infections etc. In summary, Aztreonam, a monobactam is a sterile, synthetic, bactericidal antibiotic for intravenous or intramuscular administration. The maximum daily dose The Maximum recommended daily dose for adults is 8 g/day (2 g every 6 to 8 hrs).

C. Basis for Approvability or Not-Approval Recommendation

The application is not-approvable (CMC including DMF (b) (4), Bio, labeling, and EES are pending).

III. Administrative

A. Reviewer's Signature

Nevine Takiar

B. Endorsement Block

HFD-643/NTakiar/ 6/21/05

HFD-643/SFurness/ M Scott Furness 6/27/05

V:\Firmam\Bedford\Ltrs&rev\65286.rev1.na.doc

F/T by: EW 6/21/05

C. CC Block

Following this page, 24 pages withheld in full - (b)(4). It was noted the page numbering is not correct. The review actually contains 37 pages in total, from cover page to signature page.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:65-286 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Aztreonam for Injection USP, 1 g per vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please note that DMF [redacted] (b) (4) has been reviewed and found inadequate. The DMF holder [redacted] (b) (4) (b) (4) has been informed. Please be aware that a satisfactory resolution of the DMF deficiencies is required prior to the approval of this ANDA.

2. We have the following comments regarding the drug substance:

a. [redacted] (b) (4)

b.

c.

d.

e.

f.

Following this page, 2 pages withheld in full (b)(4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please note that Aztreonam for Injection USP, 2 g per vial is not the subject of this application. All references pertaining to the 2 g drug product should be removed from this application.

2. The Labeling and Bioequivalence portions of your application are pending review. Deficiencies, if any, will be conveyed to you under separate covers.

3. Please provide all available room temperature stability data for the drug product accrued to date for evaluation.

Sincerely yours,

M. Scott Jensen for

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 65-286
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/NTakiar/6/16/05/ N-Takiar 6/21/05

HFD-643/SFurness/6/19/05/ S. Furness 6/27/05

HFD-617/RNguyen/6/21/05/ R. Nguyen 6/28/05

F/T by: EW 6/21/05

V:\Firmam\Bedford\Ltrs&rev\65286.rev1.na.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065286

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	65-286
Drug Product Name	Aztreonam Injection, USP
Strength	1 g vial
Applicant Name	Bedford Laboratories, Inc.
Address	Bedford, OH
Submission Date(s)	December 23, 2004
Amendment Date(s)	
Reviewer	Steven Mazzella
First Generic	Yes
File Location	V:\firmsam\bedford\ltrs&rev\65286W1204

I. Submission Summary

A. Drug Product Information

Test Product	Aztreonam Injection, USP, 1 g vial
Reference Product	Azactam® Aztreonam Injection, USP, 1 g vial
RLD Manufacturer	Bristol Myers Squibb
NDA No.	050580
RLD Approval Date	December 31, 1986 (per Orange Book)
Indication	Treatment of infections caused by susceptible gram negative microorganisms.

B. Formulation

Ingredient	Test (mg/mL)	Reference (mg/mL)
Aztreonam	1000	1000
Arginine	780	780

Recommendations

The Division of Bioequivalence agrees that the information submitted by Bedford Laboratories, Inc. demonstrates that its test product, Aztreonam Injection, USP, 1 g vial, fall under the criteria set forth in 21 CFR 320.22(b)(1) of the Bioavailability/ Bioequivalence Regulations. The waiver is granted.

6/22/05

Steven Mazzella, R.Ph.
Project Manager, Branch III
Division of Bioequivalence

6/22/05

Lizzie Sanchez, Pharm.D.
Special Assistant to the Director
Division of Bioequivalence

6/22/05

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-286 APPLICANT: Bedford Laboratories, Inc.

DRUG PRODUCT: Aztreonam Injection, USP, 1 g vial

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 65-286
ANDA DUPLICATE
DIVISION FILE

Printed in final on

Endorsements: (Final with Dates)
HFD-655/ Steven Mazzella 6/22/05
HFD-655/ L. Sanchez 6/22/05
HFD-650/ D. Conner 6/22/05

BIOEQUIVALENCE - ACCEPTABLE Submission date: December 23, 2004

1. **WAIVER** (WAI)

Strengths:
1 g vial
Outcome:AC

Outcome: AC- Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 65-286 SPONSOR: Bedford Laboratories, Inc.

DRUG AND DOSAGE FORM: Aztreonam Injection, USP

STRENGTH(S): 1 g vial

TYPES OF STUDIES: N/A

STUDY SUMMARY: The test drug product is a parenteral solution intended solely for administration by injection and contains the same active and inactive ingredients in the same concentration as the approved reference listed product. A waiver of the in-vivo bioavailability/bioequivalence study requirements is granted [21 CFR 320.22(b)(1)].

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic __Yes_ New facility _____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

Steven Mazzella, R.Ph.
Project Manager, Branch III, Division of Bioquivalence

INITIAL : _____ DATE : 6/22/05

Lizzie Sanchez, Pharm.D.
Special Assistant to the Director, Division of Bioequivalence

INITIAL : _____ DATE : 6/22/05

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.

INITIAL : _____ DATE : 6/22/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065286

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

03 JAN 2010

ANDA: 065286

Drug Product Name
Proprietary: N/A
Non-proprietary: Aztreonam for Injection USP

Review Number: 3

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
12/21/2010	12/21/2010	N/A	12/29/2010
6/17/2010	6/17/2010	N/A	12/29/2010

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
12/23/2004	1	7/23/2007
8/7/2007	2	8/16/2007
10/18/2007	2	11/8/20047

Applicant/Sponsor
Name: Bedford Laboratories
Address: 300 Northfield Road, Bedford, OH 44146
Representative: Molly Rapp
Telephone: (440) 201-3576

Name of Reviewer: Jesse Wells, Ph.D.

Conclusion: The submission is **recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUBMISSION:** gratuitous amendment

2. **SUBMISSION PROVIDES FOR:** New strength and change to [redacted] (b) (4)

3. **MANUFACTURING SITE:** Ben Venue Laboratories, 300 Northfield Rd., Bedford, OH 44146

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Lyophilized powder; Intravenous or intramuscular injection; 1g and 2 g per 10 cc vial; single-dose

5. **METHOD(S) OF STERILIZATION:** [redacted] (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Indicated for the treatment of infections caused by gram-negative microorganisms and for adjunctive therapy to surgery in the management of infections caused by susceptible organisms.

B. **SUPPORTING/RELATED DOCUMENTS:**
DMF 2315 and associated microbiology review 2315mic35.doc, dated 5/29/2009 by M. Stevens-Riley

C. **REMARKS:** The amendment was filed electronically. The ANDA was previously recommended for approval. The 6/17/2010 submission contained responses to chemistry deficiencies and also added a new strength to the drug product. The 12/21/2010 submission provides for changes to the [redacted] (b) (4) for the drug product.

filename: 065286a2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – The submission is recommended for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

B. Brief Description of Microbiology Deficiencies – None identified

C. Assessment of Risk Due to Microbiology Deficiencies – None; sufficient sterility assurance information is provided.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist/ Jesse Wells, Ph.D.
Microbiology Team Leader/ CDR Paul Dexter, M.S.

C. CC Block

cc: Field Copy

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – The applicant wishes to add a 2 g/ vial strength of the drug product along with the previously proposed 1 g/ vial strength.

- Drug product composition – Unchanged; the fill volume is doubled for the new strength.

- Description of container closure system –

Strength	Component	Manufacturer	Description
1 g/ vial	Vial	(b) (4)	
	Closure		
	Seal		
2 g/ vial	Vial *		
	Closure		
	Seal		

* new component

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity – The applicant provides Report PV-S14004m-ad1, which contains a comparison of the vial dimensional specifications of the 10 cc and 15 cc vials used for the drug product, as well as those for the vials used in the initial container closure integrity testing studies. The inner neck diameters of all the vials are identical ((b) (4) inches).

Acceptable

P.3 Manufacture

P.3.1 Manufacturers

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

Following this page, 3 pages withheld in full (b)(4)

and (b) (4) months. Exhibit batches 2530-13-1931735 (1 g) and 2530-14-1931717 (2 g) met the test requirement at the initial timepoint.

- Stability Commitment - Unchanged

Acceptable

P.8.3 Stability Data-See section P.8.2

R REGIONAL INFORMATION

R.1 Executed Batch Record – Executed batch records are provided for exhibit batches 2530-13-1931735 (1 g, (b) (4) vials) and 2530-14-1931717 (2 g, (b) (4) vials). The new exhibit batches were manufactured using the new manufacturing ((b) (4)) practices proposed for the drug product. Containers, closures, and equipment were sterilized according to the proposed production parameters. (b) (4)

Acceptable

R.2 Comparability Protocol – N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT- Unchanged except for addition of 2 g/vial strength.

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

/s/

JESSE WELLS
01/20/2011

ELIZABETH T MCNEAL
01/20/2011
Checked file and submission links. All correct.

NEAL J SWEENEY
01/20/2011

PAUL L DEXTER
01/21/2011

Product Quality Microbiology Review
Review for HFD-630

09 Nov 2007

ANDA 65-286

Drug Product Name
Proprietary: N/A
Non-proprietary: Aztreonam for Injection USP
Drug Product Priority Classification: N/A

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
8/7/2007	8/8/2007	N/A	8/16/2007
10/18/2007	10/19/2007	N/A	11/8/2007

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
12/23/2004	1	7/23/2007

Applicant/Sponsor
Name: Bedford Laboratories
Address: 300 Northfield Road, Bedford, OH 44146
Representative: Molly Rapp
Telephone: (440) 201-3576

Name of Reviewer: Jesse Wells, Ph.D.

Conclusion: The submission is **recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUBMISSION:** Amendment

2. **SUBMISSION PROVIDES FOR:** Response to Microbiology deficiencies

3. **MANUFACTURING SITE:** Ben Venue Laboratories, 300 Northfield Rd., Bedford, OH 44146

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Lyophilized powder; Intravenous or intramuscular injection; 1g per 10 cc vial; single-dose

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Indicated for the treatment of infections caused by gram-negative microorganisms and for adjunctive therapy to surgery in the management of infections caused by susceptible organisms.

B. **SUPPORTING/RELATED DOCUMENTS:**
DMF 2315 Benvenue laboratories: Manufacturing facility

C. **REMARKS:**
None

filename: 65-286a1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – The submission is **recommended** for approval on the basis of sterility assurance. Specific comments are provided in section H "List of Microbiology Deficiencies and Comments".

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - (b) (4)

B. Brief Description of Microbiology Deficiencies – None, sufficient sterility assurance information is provided.

C. Assessment of Risk Due to Microbiology Deficiencies – No deficiencies

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist / Jesse Wells, Ph.D.
Microbiology Team Leader/ Neal J. Sweeney, Ph.D.

C. CC Block

cc: Field Copy

Product Quality Microbiology Assessment

The following are responses to deficiencies sent regarding the original ANDA. The deficiency letter is dated 8/3/2007.

A. Microbiology Deficiencies:

1. Please provide a list of (b) (4) *to be used in the manufacture of the drug product.*

Applicant response:

The applicant provides a list of (b) (4) as follows:

(b) (4)

(b) (4)

P.3.5 Process Validation and/or Evaluation

(b) (4)

Acceptable

2. Please provide data that demonstrate that the drug product (b) (4)

Applicant response:

The applicant responds that they have (b) (4)

Following this page, 1 page withheld in full (b)(4)

(b) (4)

Acceptable

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/s/

Jesse Wells
11/15/2007 07:41:11 AM
CHEMIST

Bonnie McNeal
11/15/2007 02:54:10 PM
MICROBIOLOGIST
Checked for submission link only.

Neal Sweeney
11/16/2007 02:25:03 PM
MICROBIOLOGIST

Product Quality Microbiology Review
Review for HFD-630

23 JUL 2007

ANDA 65-286

Drug Product Name
Proprietary: N/A
Non-proprietary: Aztreonam for Injection USP
Drug Product Priority Classification: N/A

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
12/23/2004	12/27/2004	N/A	7/6/07

Submission History (for amendments only): None

Applicant/Sponsor
Name: Bedford Laboratories
Address: 300 Northfield Road, Bedford, OH 44146
Representative: Molly Rapp
Telephone: (440) 201-3576

Name of Reviewer: Jesse Wells, Ph.D.

Conclusion: The submission is **not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUBMISSION:** Original ANDA

2. **SUBMISSION PROVIDES FOR:** Initial marketing of sterile drug product

3. **MANUFACTURING SITE:** Ben Venue Laboratories, 300 Northfield Rd., Bedford, OH 44146

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Lyophilized powder; Intravenous or intramuscular injection; 1g per 10 cc vial; single-dose

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Indicated for the treatment of infections caused by gram-negative microorganisms and for adjunctive therapy to surgery in the management of infections caused by susceptible organisms.

B. **SUPPORTING/RELATED DOCUMENTS:**
DMF (b) (4)
DMF 2315 Benvenue laboratories: Manufacturing facility
DMF (b) (4)
DMF
DMF Micro reviews 2315mic22, 2315mic22a, 2315mic24, 2315mic28

C. **REMARKS:** None

filename: 65-286.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

B. Brief Description of Microbiology Deficiencies – (b) (4)

C. Assessment of Risk Due to Microbiology Deficiencies – The safety risk associated with the microbiology deficiencies is considered **low.**

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist / Jesse Wells Ph.D.
Microbiology Team Leader/ Lynne A. Ensor

C. CC Block
cc: Field Copy

Following this page, 9 pages withheld in full - (b)(4)

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 65-286 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Aztreonam for injection USP

A. Microbiology Deficiencies:

1. Please provide a list of (b) (4) to be used in the manufacture of the drug product.

2. Please provide data that demonstrate that the drug product (b) (4)

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Lynne A. Ensor, Ph.D.
Microbiology Team Leader
Office of Generic Drugs

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

/s/

Jesse Wells
8/1/2007 01:49:05 PM
CHEMIST

Bonnie McNeal
8/2/2007 01:01:25 PM
MICROBIOLOGIST
checked for submission link only.

Lynne Ensor
8/3/2007 06:43:06 AM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065286

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: III	Team: 34	PM: Leigh Ann Bradford

Electronic ANDA: Yes ☒ No ☐

ANDA #:065286
Firm Name:Bedford Laboratories (a Division of Ben Venue Laboratories, Inc.)
ANDA Name:Aztreonam for Injection USP, 1 g and 2 g per vial
RLD Name:Azactam for Injection USP, 1 g and 2 g per vial (NDA 50-580)

Electronic AP Routing Summary Located:

V:\Chemistry Division III\Team 34\Electronic AP Summary\65286_TA-AP APRV-ROUT_SUMRY.DOC

AP/TA Letter Located:

V:\Chemistry Division III\Team 34\Final Version For DARRTS Folder\APPROVAL LETTERS\ 65286_AP.DOC

Project Manager Evaluation: **Date: 12/06/2010 Initials:** LB

☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date 12/27/2004	Date of Application 12/23/2004	Date Acceptable for Filing 12/27/2004
Patent Certification (type) PI	Date Patent/Excl. expires n/a	Citizens' Petition/Legal Case? Yes☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐ **DMF#:** _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☒ Acceptable ☐ OAI *EES Date Acceptable: 10/07/2010* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 12/01/2010 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 12/23/2004 Bio reviews in DARRTS: Yes ☐ No ☐ (Volume location:)
Date of Acceptable Labeling 2/22/2011 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) 1/21/2011

Methods Val. Samples Pending: Yes ☐ No ☒; Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 2/23/2011 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☐ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

☐ Division

☒ 1st Generic Review

☒ Bob West / Peter Rickman
☐ Keith Webber

☒Filed AP Routing Summary in DARRTs	☒Notified Firm and Faxed Copy of Approval Letter	☒ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 23 Dec 2010**
Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD =Azactam NDA#50-580 Date Checked N/A Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☐ No ☐ Was applicant sued w/in 45 days:Yes ☐ No ☐ Has case been settled: Yes ☐ No ☐ Date settled: Is applicant eligible for 180 day	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒	
Type of Letter: ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:	
Comments:ANDA submitted on 12/27/2004, BOS=Azactam NDA 50-580, PI cert provided. ANDA ack for filing on 12/27/2004 for the 1 g/vial presentation (LO dated 2/28/2005). 2 g/vial presentation added in an amendment submitted on 6/16/2010. There are no remaining unexpired patents or exclusivities which protect the RLD. This ANDA is eligible for immediate Full Approval.	

2. ***Labeling Endorsement***

Reviewer, J. Counsel:
Date2/23/2011
InitialsL.S. for J.C.

Labeling Team Leader, Acting, M. Shin:
Date2/23/2011
InitialsL.S. for M.S.

REMS required? ☐Yes ☒No

REMS acceptable? ☐Yes ☐No ☒n/a

Comments:
From: Shin, Melaine M
Sent: Wednesday, February 23, 2011 2:30 PM
To: Council, Jacqueline; Sears, Leigh Ann; Golson, Lillie D
Subject: RE: Labeling sign-off for ANDA 065286 (Aztreonam for Injection USP, 1 g and 2 g per vial by Bedford Labs)
Hi Leigh Ann,

Please endorse the labeling for us.

Thanks,
Melaine

LCDR Melaine Shin, R.Ph.
CDER, FDA, OGD, DLPS
Labeling Reviewer
7520 Standish Place
Rockville, MD 20855
240-276-8976

From: Council, Jacqueline
Sent: Wednesday, February 23, 2011 2:10 PM

To: Sears, Leigh Ann; Shin, Melaine M; Golson, Lillie D
Subject: RE: Labeling sign-off for ANDA 065286 (Aztreonam for Injection USP, 1 g and 2 g per vial by Bedford Labs)
Good afternoon Leigh Ann and Melaine,

The approval summary is still current, [no new RLD labeling].

Jacqueline

From: Sears, Leigh Ann
Sent: Wednesday, February 23, 2011 12:23 PM
To: Council, Jacqueline; Shin, Melaine M; Golson, Lillie D
Subject: Labeling sign-off for ANDA 065286 (Aztreonam for Injection USP, 1 g and 2 g per vial by Bedford Labs)
Hello Jacqueline, Melaine, and Lillie,

Please perform labeling sign-off for this ANDA. It is ready for approval.

Thanks,
Leigh Ann

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 3/23/11**
OGD Regulatory Counsel **Initials rlw/for**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:N/A. There are no paragraph IV certifications associated with this ANDA.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 3/23/11**
Chemistry Div. **III (Sayeed)** **Initials rlw/for**
Comments: This approval package has been endorsed by V.Sayeed, Ph.D., Director, Division of Chemistry III on March 15, 2011. The endorsement was made on the approval routing summary accompanying the approval package.

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date 3/23/11**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
N/A. APP's ANDA 65-439 for this drug product was approved on June 18, 2010.

OGD Office Management Evaluation

6. Peter Rickman **Date 3/23/11**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: Bioequivalence waiver granted under 21 CFR 320.22(b)(1). drug product is "Q&Q" to the RLD. Office-level bio endorsed 6/22/05 (Archival jacket 1.1).

Microbiology/Sterility Assurance found acceptable for approval (Microbiology Review #3) 1/20/11.

Final-printed labeling (FPL) found acceptable for approval 2/22/11. No REMS required.

CMC found acceptable for approval (Chemistry Review #4) 12/1/10.

AND/OR

7. Robert L. West
Deputy Director, OGD
Date 3/23/11
Initials RLWest

Para.IV Patent Cert: Yes☐ No☒
Pending Legal Action: Yes☐ No☒
Petition: Yes☐ No☒
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 10/7/10 (Verified 3/23/11). No "OAI" Alerts noted.

There are no patents or exclusivity currently listed in the "Orange Book" for this drug product.

This ANDA is recommended for approval.

8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS

Comments: RLWest for Keith Webber, Ph.D. 3/23/11.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

9. Project Manager
Date 3/23/2011
Initials LS

Check Communication and Routing Summary into DARRTS

Orange Book Report:

Appears this way on original.

-

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Reference ID: 2922288

Patent and Exclusivity Search Results from query on Appl No 050580 Product 003 in the OB_Rx list.

<>

There are no unexpired patents for this product in the Orange Book Database.

<>

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through February, 2011
Patent and Generic Drug Product Data Last Updated: March 21, 2011

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- **Home**
- **About FDA**

Reference ID: 2922288

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/s/

LEIGH A SEARS
03/23/2011

Telephone Fax

ANDA 065286
OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7620 Standish Place
Rockville, MD 20855-2773

Dr. Council
240 276 8989

TO: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

TEL: 440/232-3320

ATTN: Molly Rapp

FAX: 440/439-6080

FROM: Labeling Review Branch

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Aztreonam for Injection USP, 1 gram and 2 grams

Pages (including cover): 2

SPECIAL INSTRUCTIONS:

Submit revised labeling as a labeling supplement, post-approval.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 065286

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram and 2 grams

---

Labeling Comments - Revisions required post-approval in a labeling supplement:

1. CONTAINER: 1 gram and 2 grams
    a. Front Panel
        Print “for Injection” using the same font size as “Aztreonam”.
    b. Side panel
        i. Revise to read, “…solution stability”.
        ii. Include the temperature range in the storage statement.
2. CARTON: 10s
    See comments under CONTAINER.
3. INSERT
    a. General Comments:
        i. Increase the size of the asterisks and superscripts.
        ii. Decrease the prominence of the company logo appearing prior to the TITLE.
    b. DESCRIPTION
        i. Revise the last paragraph to read, “…of aztreonam. Each 1 gram vial contains 1 gram aztreonam with approximately ... arginine. Each 2 gram vial contains….”.
    c. CLINICAL PHARMACOLOGY
        i. Following the second paragraph, increase the size of Figure 1.
        ii. If you are not able to print the entire table on the same page, then reprint the title at the top of the second portion of the table with the entire heading following by “(continued)” at the end of title.
    d. DOSAGE AND ADMINISTRATION
        Intravenous (IV) Solutions
        Upon further review, retain the IV solutions, “Isolyte® E” and “Isolyte® E with 5% Dextrose”. In addition, Plasma-Lyte M and 5% Dextrose should also be retained.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your previous submission with all differences annotated and explained.

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/s/

JACQUELINE D COUNCIL
03/07/2011

Memorandum to File

ANDA: 065286
Applicant: Bedford laboratories
Product: Aztreonam for Injection USP, 1 g and 2 g per vial

Call was made to the firm (9/20/2010) with regard to proposed expiration date in telephone amendment dated August 25, 2010 and control for (b) (4) in the drug product. It was recommend that the firm provide justification to change expiration date from (b) (4) months to 18 months and commit to evaluate (b) (4) specification after full long-term stability data for drug product is obtained.

The firm agreed to provide justification regarding revised expiration date and to reevaluate (b) (4) (b) (4) criteria and will respond as a telephone amendment.

N. Takiar 9/20/2010

V:\Chemistry Division III\Team 12\Final Version For DFS Folder\Telephone Deficiencies\65286_Tcon.doc

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/s/

NEERU B TAKIAR
09/20/2010

Telephone Fax

ANDA 65-286
OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240 276 8989

TO: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

TEL: 440/232-3320

ATTN: Molly Rapp

FAX: 440/439-6080

FROM: Labeling Review Branch

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Aztreonam for Injection USP, 1 gram

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling Comments for the 9/5/08 submission.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-286

Date of Submission: September 5, 2008

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

---

1 INSERT

a. General Comments

i. Delete the terminal zero, “1 instead of “1.0”.

ii. Increase the size of the asterisks.

b. DOSAGE AND ADMINISTRATION

i. Admixture with other Antibiotics

Add an asterisk following the trade name “Dianeal®137* (Peritoneal Dialysis Solution)”. Also, reference the manufacturer of the product in a footnote at the end of your insert.

ii. Preparation of Parenteral Solutions

Relocate the paragraph, “Parenteral drug products should…permit” to appear as the last paragraph of this subsection.

iii. Intravenous (IV) Solutions

A) For Bolus Injection

Revise to read, “… Injection vial should …”

B) For Infusion (b) (4)
Revise to read, “If the contents of the vial are to be transferred to an appropriate infusion solution, each gram…Injection, (b) (4) Further …”.

C) We note that you omitted some of the intravenous infusion solutions”. Your insert is required to be the same as the innovator. Is your drug product incompatible with the solutions you omitted? Please comment and/or revise accordingly. .

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling reference listed drug's labeling with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Lillie Golson
4/2/2009 05:29:30 PM
Lillie Golson for Wm. Peter Rickman

Telephone Fax

ANDA 65-286

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8986
Thuyanh.vu@fda.hhs.gov

TO: Bedford Laboratories, Inc.

TEL: 440-201-3576

ATTN: Molly Rapp

FAX: 440-439-6080

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Aztreonam for Injection USP, 1 gram

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-286 Date of Submission: June 25, 2008

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

Labeling Deficiencies:

1. CONTAINER: 1 gram

   Acceptable in final print.

2. CARTON: 10 vials per carton

   Acceptable in final print.

3. INSERT

   a. ADVERSE REACTIONS

      First and second paragraphs, revise "percent" to "%".

   b. DOSAGE AND ADMINISTRATION

      i. Dosage in Adult Patients, Renal Impairment in Adult Patients, first paragraph, revise to read "...between 10 mL/min/1.73 m^2 and 30 mL/min/1.73m^2 ..."

      ii. Stability of IV and IM Solutions- delete second paragraph.

      iii. Intravenous Administration, second paragraph, revise to read "(see Preparation Of Parenteral Solutions- Intravenous (IV) Solutions: For Infusion)

4. SPL

   DOSAGE AND ADMINISTRATIONS

   Aztreonam for Injection Dosage Guidelines table, please clearly separate the rows for the adults. It is hard to read the dosage corresponding to the types of infection.

Submit labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –
http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

John Grace
7/31/2008 10:49:41 AM
for Wm Peter Rickman

MINOR AMENDMENT

ANDA 65-286

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Bedford Labs TEL: 440-201-3576

ATTN: Molly L. Rapp FAX: 440-439-6080

FROM: Jeanne Skanchy FDA CONTACT PHONE: (240) 276-8467

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 23, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Aztreonam for Injection USP, 1 g per vial.

Reference is also made to your amendments dated July 27, 2007 and February 8, 2008.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (**3** pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-286 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Aztreonam for Injection USP, 1 g per vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. DMF (b) (4) has been found inadequate. The DMF holder, (b) (4) has been informed. Please do not respond to this minor amendment until the DMF holder has responded to the deficiencies.

2. (b) (4)

3.

4.

5.

6.

7.

8. (b) (4)

9.

10.

11.

12.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please be informed that until revised monograph for Aztreonam drug substance becomes official, your request for compendial status for the drug product is not acceptable. Accordingly, the relevant specifications for Aztreonam should be revised.

Sincerely yours,

(See appended electronic signature page)

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Robert Iser
6/2/2008 07:53:49 AM
signed for V. Sayeed

Telephone Fax

ANDA 65-286

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8986

TO: Bedford Laboratories, Inc.

TEL: 440-201-3576

ATTN: Molly Rapp

FAX: 440-439-6080

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Aztreonam for Injection USP, 1 gram

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-286 Date of Submission: July 27, 2007

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

Labeling Deficiencies:

1. CONTAINER: 1 gram

   Please revise your label to read:

   1 gram/Vial

2. CARTON: 10 vials per carton

   Please see CONTAINER comment.

3. INSERT

   Acceptable in final print.

Submit labels electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -
http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

John Grace
8/14/2007 11:34:15 AM
for Wm Peter Rickman

FAX – Microbiology Deficiencies Enclosed

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773 (301-594-0320)

TO: Molly L. Rapp		**FROM:** Bonnie McNeal
Bedford Labs		Microbiology Project Manager
PHONE: 440-201-3576		**PHONE:** (301) 827-0530
FAX: 440-439-6080		**FAX:** (301) 827-5911

Total number of pages, excluding this cover sheet: **2**

Date: August 3, 2007

Microbiology Deficiencies:

Enclosed are the microbiology deficiencies for ANDA 65-286 for Aztreonam. The submission reviewed was submitted on December 23, 2004. Please respond to this communication as quickly as possible. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review. The response to this communication will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT-RESPONSE TO MICROBIOLOGY DEFICIENCIES should appear prominently in your cover letter.

Should you also have other outstanding deficiencies, for review purposes, please attempt to consolidate your responses into a single submission for this application.

If you have questions, feel free to call Bonnie McNeal or Mark Anderson.

LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 65-286 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Aztreonam for Injection USP

Microbiology Deficiencies:

1. Please provide a list of (b) (4) to be used in the manufacture of the drug product.

2. Please provide data that demonstrate that the drug product (b) (4)

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Lynne A. Ensor, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
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/

Lynne Ensor
8/3/2007 06:42:36 AM

MINOR AMENDMENT

ANDA 65-286

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Bedford Labs

TEL: 440-201-3576

ATTN: Molly L. Rapp

FAX: 440-439-6080

FROM: Jeanne Skanchy

PROJECT MANAGER: (301) 827-5719

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 23, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Aztreonam for Injection USP, 1 g per vial.

Reference is also made to your amendments dated June 23, 2006 and March 16, 2007.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-286 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Aztreonam for Injection USP, 1 g per vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. DMF (b) (4) has been found inadequate. The DMF holder (b) (4) (b) (4) has been informed. Please do not respond to this minor amendment until the DMF holder has responded to the deficiencies.

2. (b) (4)

3.

4.

5.

in most cases. Please explain.

6. Please note that it is recommended in your labeling that for intravenous solutions (bolus injection), the contents of the Aztreonam for Injection, 1 gram vial should be are constituted with 6 to 10 mL Sterile Water for Injection. Therefore, we recommend that you revise your vial size to be the same as the innovator "15 mL" because the proposed vial size "10 mL" may not be an adequate size for constituting IV solutions. Please revise your labels and labeling accordingly.

7. Regarding the finished drug product, we have the following comments:

a. (b) (4)

b.

Sincerely yours,

(See appended electronic signature page)

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Hossein Khorshidi

5/1/2007 12:31:17 PM

Telephone Fax

ANDA 65-286

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301-827-7342

TO: Ben Venue Laboratories, Inc.

TEL: 440-201-3576

ATTN: Molly Rapp

FAX: 440-439-6080

FROM: Ann Vu

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Aztreonam for Injection USP, 1 gram

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-286 Date of Submission: March 16, 2007

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

Labeling Deficiencies:

1. CONTAINER: 1 gram

   Please revise your vial size to 15 mL. Your vial size should be the same size as the innovator "15 mL". Revise your labeling accordingly.

2. CARTON: 10 vials per carton

   Acceptable in final print.

3. INSERT

   Refer to CONTAINER comment.

Submit labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -
http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

John Grace
4/24/2007 08:02:28 AM
for Wm Peter Rickman

Telephone Fax

ANDA 65-286

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (301-827-7341)

TO: Ben Venue Laboratories, Inc.

TEL: 440-201-3576

ATTN: Molly Rapp

FAX: 440-439-6080

FROM: Charlie Hoppes

:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Aztreonam for Injection USP.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-286 Date of Submission: May 31, 2006

Applicant's Name: Bedford Laboratories (a division of Ben Venue Laboratories, Inc.)

Established Name: Aztreonam for Injection USP, 1 gram

Labeling Deficiencies:

1. CONTAINER: 1 gram

   We note that you have proposed a 10 mL vial. Your vial size should be the same size as the innovator "15 mL". Revise your labels and labeling accordingly and submit any necessary supporting documentation.

2. INSERT

   a. CLINICAL PHARMACOLOGY

      i. Figure 1, revise to read "Aztreonam Serum Concentrations, mcg/mL".

      ii. Microbiology, Susceptibility Testing, Dilution Techniques, footnote a, please change reference "[5]" to "[1]".

   b. DOSAGE AND ADMINISTRATION

      Intravenous (IV) Solutions, For Infusion: We note that you did not include Isolyte E and Isolyte E with 5% Dextrose solutions for secondary further dilution. Your labeling should be the same as the innovator. Please revise accordingly and forward all necessary supporting information.

Submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -
http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

John Grace
12/3/2006 11:27:33 AM
for Wm Peter Rickman

ANDA 65-286

Bedford Laboratories
(a division of Ben Venue Laboratories, Inc.)
Attention: Molly Rapp
300 Northfield Road
Bedford, OH 44146

FEB 28 2005

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Aztreonam for Injection USP, 1 g/vial

DATE OF APPLICATION: December 23, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 27, 2004

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Ryan Nguyen
Project Manager
(301) 827-9275

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 65-286
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-92

Endorsement:
HFD-615/M. Shimer, Chief, RSB _____ date 22 Feb 2005
HFD-615/C. Bina, CSO _____ date 2/18/05
Word File
V:/FIRMSAM\BEDFORD\LTRS&REV\65286.ACK
F/T CMB 2/18/2004
ANDA Acknowledgment Letter!

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	ANDA 65286/000	Action Goal:	
Stamp:	27-DEC-2004	District Goal:	27-NOV-2005
Regulatory Due:		Brand Name:	
Applicant:	BEDFORD LABS	Estab. Name:	AZTREONAM
	300 NORTHFIELD RD	Generic Name:	
	BEDFORD, OH 44146		
Priority:		Dosage Form:	(INJECTION)
Org Code:	600	Strength:	1 G PER VIAL

Application Comment:

FDA Contacts:	R. NGUYEN	(HFD-617)	301-827-5739	, Project Manager
	M. FURNESS	(HFD-640)	301-827-5849	, Team Leader

Overall Recommendation:

Establishment: CFN 1519257 FEI 1519257
BEN VENUE LABORATORIES INC
300 NORTHFIELD RD
BEDFORD, OH 441464650

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: SVL OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	25-FEB-2005				BINAC

Establishment: CFN FEI

(b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	25-FEB-2005				BINAC

CTD
First Generic
Scanned 2/18/0

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 65-286 **FIRM NAME**: BEDFORD LABORATORIES

RELATED APPLICATION(S): NA

First Generic Product Received? YES

DRUG NAME: AZTREONAM

DOSAGE FORM: FOR INJECTION USP, 1 G PER VIAL

Bio Assignments:		☒ **Micro Review**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☐ **BDI**	

Random Queue: 6

Chem Team Leader: Furness, Scott PM: Ryan Nguyen Labeling Reviewer: Jacqueline Council

Letter Date: DECEMBER 23, 2004	**Received Date**: DECEMBER 27, 2004
Comments: EC - 1 YES **On Cards:** YES **Therapeutic Code:** 4010900 OTHER ANTIBIOTICS - SYSTEMIC	
Archival Format: PAPER **Sections I** **(356H Sections per EDR Email)** **Review copy**: YES E-Media Disposition: YES SENT TO EDR Not applicable to electronic sections Field Copy Certification (Original Signature) YES	
Methods Validation Package (3 copies PAPER archive) **NO** (Required for Non-USP drugs)	
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

Reviewing **CSO/CST Christine Bina** **Date 2/14/2005**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: [signature]	**Date:** 18 Feb 2005
ADDITIONAL COMMENTS REGARDING THE ANDA: **Contact: Molly Rapp (440) 201-3576** **1) Note: Proposing 10 mL vial size (RLD uses 15 mL vial)** **2) Need COA for API from (b) (4)-p. 88-OK** **3) Need Reprocessing Statement-p. 323-OK**	
Top 200 Drug Product:	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES	☒
Sec. II	**Basis for Submission** **NDA# : 50-580** Ref Listed Drug: AZACTAM Firm: BRISTOL MYERS SQUIBB ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒
Sec. III	**Patent Certification** 1. Paragraph: I p. 7 2. Expiration of Patent: NA A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** YES	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Y 2. Active ingredients Y 3. Route of administration Y 4. Dosage Form Y 5. Strength Y	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL Electonic Submitted 2. 1 RLD label and 1 RLD container label Y 3. 1 side by side labeling comparison with all differences annotated and explained Y 4. Was a proprietary name request submitted? No (If yes, send email to Labeling Rvwr indicating such.)	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) NA **2. Request for Waiver of In-Vivo Study(ies): YES -based on 320.22** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) **4. Lot Numbers of Products used in BE Study(ies):** **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) NA a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: NO	☐

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. <u>Solutions</u> (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. <u>Suspensions</u> (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation Q1 and Q2 to RLD per Labeling and COMIS 2. Inactive ingredients as appropriate	☒

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers Y b. Type II DMF authorization letters or synthesis Y-DMF# (b) (4) letter p. 16 c. COA(s) specifications and test results from drug substance mfgr(s) Need COA from (b) (4) d. Applicant certificate of analysis Y e. Testing specifications and data from drug product manufacturer(s) Y f. Spectra and chromatograms for reference standards and test samples Y g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified Y-p. 427 b. Testing specifications (including identification and characterization) Y c. Suppliers' COA (specifications and test results) d. Applicant certificate of analysis Y	☐
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) Y-Ben Venue Labs 2. CGMP Certification: YES p. 216 3. CFN numbers	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address None used 2. Functions 3. CGMP Certification/GLP 4. CFN numbers	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Scale up OK-Proposed (b) (4) for Master 3.If sterile product: (b) (4) 4 (b) (4) 5. Reprocessing Statement Need (states Appendiz III)	☐
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation Lot# 2202-12-711828 PY= (b) (4) AY= (b) (4) PKY= Complete packaged (b) (4) 2. In-process Controls - Specifications and data	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data (Type III DMF References) Y 3. Packaging Configuration and Sizes Y 4. Container/Closure Testing Y 5. Source of supply and suppliers address Y-p. 521	☒

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data Y 2. Certificate of Analysis for Finished Dosage Form Y-p. 499	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted Y 2. Post Approval Commitments Y-p. 600 3. Expiration Dating Period (b)(4) months 4. Stability Data Submitted a. 3 month accelerated stability data Y-p. 604 b. Batch numbers on stability records the same as the test batch	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance Y 2. Finished Dosage Form Y 3. Same lot numbers Y	☒
Sec. XVII	**Environmental Impact Analysis Statement** Y-p. 11	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other:** 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) No US Agent 2. Debarment Certification (original signature): YES p. 13 3. List of Convictions statement (original signature) Y	☒

OGD Template Revised 04/01/2004 /T.Hinchliffe

ANDA 65-286 Final Check List for Branch Chief

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.

✓ 3) Check for gross errors in letter.

✓ 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 5) Check address and contact person on letter vs. 356h.

✓ 6) Check for any t-cons and verify date and correspondence date.

✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 8) Check for any comments or problems raised by reviewer on Check List.

✓ 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD. Azactam

N/A 12) Check for MOU patents

✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.

✓ 14) Review Basis for Submission. Azactam 50-580

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

✓ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature. a.1 | a.2

✓ 18) Pull USP information. (USP ✓ yes ____ no)

✓ 19) Final Grammar review on letter.

✓ 20) Verify information in OGD Patent Tracking System.

✓ 21) EES slip.

✓ 22) Document in record book.

Signature Martin H. Johnson date 18 Feb 2005

Telephone Conference

Date: **2/14/2005**

ANDA: **65-286**

Firm: **Bedford Laboratories**

Industry: **Molly Rapp**

Phone: **(440) 201-3576**

FDA: **Christine Bina**

Topic:

I contacted Molly Rapp's voice mail regarding ANDA 65-286. I asked Molly to provide:

1) Need COA for API from (b) (4)
2) Need Reprocessing Statement

p. 88 - OK
p323 OK