CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 065439

Name: Aztreonam for Injection USP, 500 mg/vial, 1 g/vial, and 2 g/vial

Sponsor: APP Pharmaceuticals, LLC

Approval Date: June 18, 2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065439

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065439

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 065439

APP Pharmaceuticals, LLC
Attention: Georgia Hizon
Senior Regulatory Scientist
1501 East Woodfield Road, Suite 300E
Schaumburg, IL 60173

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated October 5, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Aztreonam for Injection USP, 500 mg/vial, 1 g/vial, and 2 g/vial.

Reference is also made to your amendments dated September 11, 2007; March 14, October 29, and December 5, 2008; February 2, March 13, April 10, September 11, November 3, December 14, and December 18, 2009; and January 19, 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, 500 mg/vial, 1 g/vial, and 2 g/vial, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Azactam® for Injection, 500 mg/vial, 1 g/vial, and 2 g/vial, respectively, 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.

We 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.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] 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. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as "***Miscellaneous Correspondence - SPL for Approved ANDA 065439***".

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-65439	ORIG-1	APP PHARMACEUTICALS LLC	AZTREONAM

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
06/18/2010
Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065439

LABELING

NDC 63323-397-20 309720

AZTREONAM

FOR INJECTION, USP

500 mg*/vial

Single Dose Vial

For IV or IM use after constitution

Rx only

Sterile, Nonpyrogenic

Lyophilized

*Each vial contains 500 mg aztreonam with approximately 390 mg arginine.

Sodium free.

Add diluent; shake immediately and vigorously. See insert for dosage, constitution, solution stability.

Store original package at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]; avoid excessive heat.

Vial stoppers do not contain natural rubber latex.

APP

APP Pharmaceuticals, LLC

Schaumburg, IL 60173

402330

LOT/EXP

3 63323-397-20 3

NDC 63323-401-20 400120

AZTREONAM

FOR INJECTION, USP

1 gram* /vial

Single Dose Vial

For IV or IM use after constitution

Rx only

Sterile, Nonpyrogenic

Lyophilized

*Each vial contains 1 g aztreonam with approximately 780 mg arginine.

Sodium free.

Add diluent; shake immediately and vigorously. See insert for dosage, constitution, solution stability.

Store original package at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]; avoid excessive heat.

Vial stoppers do not contain natural rubber latex.

APP

APP Pharmaceuticals, LLC
Schaumburg, IL 60173

402331A

LOT/EXP

3 63323-401-20 7

NDC 63323-402-20 400220

AZTREONAM
FOR INJECTION, USP

2 grams*/vial

Single Dose Vial

For IV or IM use after constitution

Rx only

Sterile, Nonpyrogenic

Lyophilized

*Each vial contains 2 g aztreonam with approximately 1.56 grams arginine.

Sodium free.

Add diluent; shake immediately and vigorously. See insert for dosage, constitution, solution stability.

Store original package at 20° to 25°C (68° to 77°F)[see USP Controlled Room Temperature]; avoid excessive heat.

Vial stoppers do not contain natural rubber latex.

APP

APP Pharmaceuticals, LLC

Schaumburg, IL 60173

402332A

LOT/EXP

3 63323-402-20 4

APP

451086B/Issued: February 2009

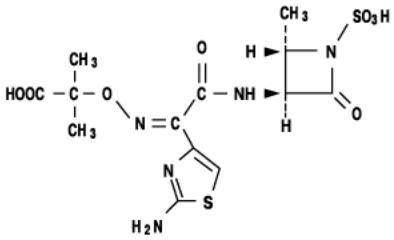
AZTREONAM
FOR INJECTION, USP Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of aztreonam for injection and other antibacterial drugs, aztreonam for injection should only be used 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)[[(2S,3S)-2-methyl- 4-oxo-1-sulfo-3 azetidinyl] carbamoyl]methylene]amino]oxy]-2-methylpropionic acid. Structural formula:



$C_{13}H_{17}N_5O_8S_2$ MW 435.44

Aztreonam for injection is a sterile, nonpyrogenic, sodium-free lyophilized, off-white to slightly yellow solid 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.

Each 500 mg contains 500 mg aztreonam with approximately 390 mg arginine.

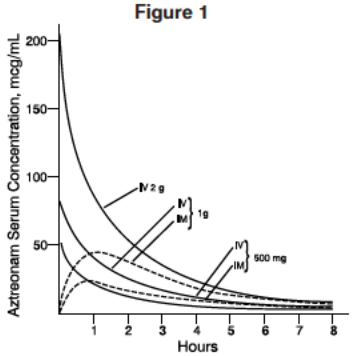
Each 1 gram vial contains 1 gram aztreonam with approximately 780 mg arginine.

Each 2 gram vial contains 2 grams aztreonam with approximately 1.56 grams arginine.

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 8 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 5 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 1 hour. After identical single intravenous or intramuscular doses of aztreonam for injection the serum concentrations of aztreonam are comparable at 1 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 for injection exceed the MIC_{90} for *Neisseria* sp., *Haemophilus influenzae* and most genera of the Enterobacteriaceae for 8 hours (for *Enterobacter* sp., the 8-hour serum levels exceed the MIC for 80% of strains). For *Pseudomonas aeruginosa*, a single 2 g intravenous dose produces serum levels that exceed the MIC_{90} for approximately 4 to 6 hours. All of the above doses of aztreonam for injection 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) 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 for injection 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 for injection (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 2 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 8 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 for injection 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-ß-glucosaminidase, alanine aminopeptidase and $ß_2$-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[1]

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 to 4.3	16	3
pericardial fluid	2	IV	1	6	33
pleural fluid	2	IV	1.1 to 3	3	51
synovial fluid	2	IV	0.8 to 1.9	11	83

EXTRAVASCULAR CONCENTRATIONS OF AZTREONAM AFTER A SINGLE PARENTERAL DOSE[1] (continued)

Fluid or Tissue	Dose (g)	Route	Hours Post-injection	Number of Patients	Mean Concentration (mcg/mL or mcg/g)
Tissues					
atrial appendage	2	IV	0.9 to 1.6	12	22
endometrium	2	IV	0.7 to 1.9	4	9
fallopian tube	2	IV	0.7 to 1.9	8	12
fat	2	IV	1.3 to 2	10	5
femur	2	IV	1 to 2.1	15	16
gallbladder	2	IV	0.8 to 1.3	4	23
kidney	2	IV	2.4 to 5.6	5	67
large intestine	2	IV	0.8 to 1.9	9	12
liver	2	IV	0.9 to 2	6	47
lung	2	IV	1.2 to 2.1	6	22
myometrium	2	IV	0.7 to 1.9	9	11
ovary	2	IV	0.7 to 1.9	7	13
prostate	1	IM	0.8 to 3	8	8
skeletal muscle	2	IV	0.3 to 0.7	6	16
skin	2	IV	0 to 1	8	25
sternum	2	IV	1	6	6

[1]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 1g 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 the **INDICATIONS AND USAGE** section.

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 (MICs) 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 (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs 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 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 con- sidered 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 to 0.25
Haemophilus influenzae[a] ATCC 49247	0.12 to 0.5
Pseudomonas aeruginosa ATCC 27853	2 to 8

[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 to 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 to 36 mm
Haemophilus influenzae[a] ATCC 49247	30 to 38 mm
Pseudomonas aeruginosa ATCC 27853	23 to 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 for injection and other antibacterial drugs, aztreonam for injection should only be used 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**, *Pseu-*

domonas 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**.

Aztreonam for injection 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 for injection is effective against most of the commonly encountered gram-negative aerobic pathogens seen in general surgery.

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

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 for injection (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. Following identification 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 for injection 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 for injection, 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 antimicrobial 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 for injection 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 for injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When aztreonam for injection 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 for injection 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 2 or more months after having taken the last dose of the 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 for injection in these age groups is supported by evidence from adequate and well-controlled studies of aztreonam for injection 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 for injection may be warranted (see **CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION**, and **CLINICAL STUDIES**).

Geriatric Use

Clinical studies of aztreonam for injection 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 for injection 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 for injection 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 3 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/mm^3) 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 q6h. 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 for injection 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 for injection 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 for injection should be halved in patients with estimated creatinine clearances between 10 mL/min/1.73 m^2 and 30 mL/min/1.73 m^2 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 m^2), 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 for injection 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, USP, 0.9% or Dextrose Injection, USP, 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, USP, 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection, USP, 5% is 2 hours at room temperature and 8 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

Aztreonam for Injection for IV bolus administration should be reconstituted as follows:

CONSTITUTION FOR IV BOLUS		
Strength	**Vial size**	**Amount of Diluent to be added (mL)**
500 mg/vial (IV bolus)	20 mL	6 to 10
1 g/vial (IV bolus)	20 mL	6 to 10
2 g/vial (IV bolus)	30 mL	6 to 10

The contents of aztreonam for injection vial should be constituted with 6 to 10 mL Sterile Water for Injection, USP.

For Infusion

Aztreonam for Injection for IV infusion should be reconstituted as follows:

CONSTITUTION FOR IV INFUSION		
Strength	**Vial size**	**Initial Amount of Diluent to be added (mL)***
500 mg/vial (IV Infusion)	20 mL	1.5
1 g/vial (IV Infusion)	20 mL	3
2 g/vial (IV Infusion)	30 mL	6

*Further dilution required, see list of infusion solutions below.

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, USP. Further dilution may be obtained with one of the following intravenous infusion solutions:

- Sodium Chloride Injection, USP, 0.9%
- Ringer's Injection, USP
- Lactated Ringer's Injection, USP
- Dextrose Injection, USP, 5% or 10%
- Dextrose and Sodium Chloride Injection, USP, 5%:0.9%, 5%:0.45% or 5%:0.2%
- Sodium Lactate Injection, USP (M/6 Sodium Lactate)
- Ionosol® B and 5% Dextrose
- Isolyte® E
- Isolyte® E with 5% Dextrose
- Isolyte® M with 5% Dextrose
- Normosol®-R
- Normosol®-R and 5% Dextrose
- Normosol®-M and 5% Dextrose
- Mannitol Injection, USP, 5% or 10%
- Lactated Ringer's and 5% Dextrose Injection
- Plasma-Lyte® M and 5% Dextrose
- 10% Travert Injection
- 10% Travert and Electrolyte No. 1 Injection
- 10% Travert and Electrolyte No. 2 Injection
- 10% Travert and Electrolyte No. 3 Injection

Intramuscular (IM) Solutions

Aztreonam for Injection for IM solution administration should be reconstituted as follows:

Strength	Vial size	Amount of Diluent to be added (mL)
500 mg/vial (IM)	20 mL	1. 5
1 g/vial (IM)	20 mL	3
2 g/vial (IM)	30 mL	6

The contents of aztreonam for injection 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, USP
- Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and propylparabens)
- Sodium Chloride Injection, USP, 0.9%
- Bacteriostatic Sodium Chloride Injection, USP (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 controlled room temperature (20° to 25°C/68° to 77°F, see USP) or within 7 days if refrigerated (2° to 8°C/ 36° to 46°F).

Aztreonam for Injection, USP, solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection, USP or Sodium Chloride Injection, USP, should be used promptly after preparation; the 2 excepted solutions must be used within 48 hours if stored at controlled room temperature or within 7 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 for injection (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

Product No.	NDC No.	Strength	
309720	63323-397-20	500 mg/vial	20 mL single dose vial, supplied in packages of ten.
400120	63323-401-20	1 g/vial	20 mL single dose vial, supplied in packages of ten.
400220	63323-402-20	2 g/vial	30 mL single dose vial, supplied in packages of ten.

Storage

Store original packages at 20° to 25°C (68° to 77°F)[see USP Controlled Room Temperature]; avoid excessive heat.

REFERENCES:

1. Naber KG, Dette GA, Kees F, Knothe 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.
2. Creasey WA, Platt TB, Frantz M, Sugerman AA. Pharmacokinetics of aztreonam in elderly male volunteers. *Br J Clin Pharmacol* 1985; 19:233-237.
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.
5. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*—Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January 2000.
6. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests*—Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Wayne, PA, January 2000.
7. Deger F, Douchamps J, Freschi E, *et al*: Aztreonam in the treatment of serious gram-negative infections in the elderly. *Int J Clin Pharmacol Ther and Toxicol* 1988; 26: 22-26.
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.
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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.

APP

APP Pharmaceuticals, LLC
Schaumburg, IL 60173

451086B
Issued: February 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065439

LABELING REVIEWS

APPROVAL SUMMARY – Note/Questions to Chemist updated on 9/9/09

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

ANDA Number: 65-439

Dates of Submission: March 13, 2009

Applicant's Name: Abraxis Pharmaceutical Products

Established Name: Aztreonam for Injection USP, 500 mg, 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

CONTAINER: 500 mg, 1 gram and 2 grams
Satisfactory as of the December 5, 2008 submission

TRAY label: 500 mg, 1 gram and 2 grams
Satisfactory as of the March 14, 2008 submission

INSERT: Satisfactory as of the March 13, 2009 submission.

Revisions needed post-approval:
Container: Increase the size of the asterisk on the side panel.

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

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

Has this been verified by the MIS system for the NDA? Checked Drugs@FDA

Was this approval based upon an OGD labeling guidance? No

NOTES/QUESTIONS TO THE CHEMIST

From: Cohran, Carolyn
Sent: Wednesday, September 09, 2009 8:22 AM
To: Council, Jacqueline
Cc: Zuk, Susan
Subject: RE: ANDA 65-439, Aztreonam FIJ, APP

Hi Jackie,
I think I have answered these questions before.

For question 1, the question of being nonpyrogenic is not a chemistry issue. There is no evidence of sodium being present. The rest of the description matches information that is provided by the firm.

For question 2, the difference is acceptable.

Thanks.
Carolyn

Carolyn Cohran, Ph.D.
Tel. 240-276-8462
carolyn.cohran@fda.hhs.gov

From: Council, Jacqueline
Sent: Friday, September 04, 2009 3:55 PM
To: Cohran, Carolyn
Cc: Szydlo, Roberta; Zuk, Susan
Subject: FW: ANDA 65-439, Aztreonam FIJ, APP

Good afternoon Carolyn,

I think you can omit question #3 due to Q1 and Q2. If not, please inform me.

Thanks,
Jacqueline

NOTES/QUESTIONS TO THE CHEMIST

1. The firm revised the description of the drug product again. It now reads, “Aztreonam for injection is a sterile, nonpyrogenic, sodium-free, lyophilized, off-white to slightly yellow solid containing approximately 780 mg arginine per gram of aztreonam.” Is this now accurate?
2. The firm informed us that their “formulation” differs from the innovator, “powder fill” vs. “lyophilized”. Is this difference acceptable?

3. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION section of the insert labeling, Please see text below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 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 USP 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection USP 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.

Intramuscular (IM) Solutions

The contents of aztreonam for injection 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 USP, Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and propylparabens), Sodium Chloride Injection USP, 0.9%, Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol).

[The chemist has to review the firm's response to chemist before all of the questions are answered].

1. The firm revised the description of the drug product to read, "Aztreonam for injection is a sterile, nonpyrogenic, sodium-free, lyophilized, (b) (4) containing approximately 780 mg arginine per gram of aztreonam." Is this now accurate?
2. The innovator's vial size is "15 mL" and the ANDA's vial sizes are "20 mL" and "30 mL". Is this acceptable?
3. The firm has the statements, "Sodium free-nonpyrogenic" and "Vial stoppers do not contain natural rubber latex". Do you concur?
4. The firm informed us that their "formulation" differs from the innovator, "powder fill" vs. "lyophilized".
   Is it acceptable for the ANDA to have a lyophilized drug product which differs from the innovator's formulation?
5. The firm indicates that the "vial sizes" differs from the innovator's because of the difference in formulation. (b) (4)

6. Intramuscular use
   a. Has the firm submitted data to support the recommended volume for reconstitution for IM use, "i.e., 3 mL"?
   b. Does the lyophilized product and the powder filled product usually require the different volumes for diluent?
7. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION section of the insert labeling, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]? See text below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 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 USP 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration;

stability in Dextrose Injection USP 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 aztreonam for injection should be constituted with 6 to 10 mL Sterile Water for Injection USP.

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 USP. Further dilution may be obtained with one of the following intravenous infusion solutions: Sodium Chloride Injection USP, 0.9%, Ringer's Injection USP
Lactated Ringer's Injection USP, Dextrose Injection USP, 5% or 10%,
Dextrose and Sodium Chloride Injection USP, 5%:0.9%,5%:0.45% or 5%:0.2%
Sodium Lactate Injection USP (M/6 Sodium Lactate),Ionosol® B and 5% Dextrose
Isolyte® E, Isolyte® E with 5% Dextrose, Isolyte® M with 5% Dextrose, Normosol®-R
Normosol®-R and 5% Dextrose, Normosol®-M and 5% Dextrose, Mannitol Injection USP, 5% or 10%, Lactated Ringer's and 5% Dextrose Injection, Plasma-Lyte® M and 5% Dextrose, 10% Travert® Injection, 10% Travert® and Electrolyte No. 1 Injection
10% Travert® and Electrolyte No. 2 Injection, 10% Travert® and Electrolyte No. 3 Injection

Intramuscular (IM) Solutions

The contents of aztreonam for injection 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 USP, Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and propylparabens), Sodium Chloride Injection USP, 0.9%, Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol)

Stability of IV and IM Solutions

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

(b) (4)

[redacted]

Aztreonam for injection, USP solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection USP or Sodium Chloride Injection USP, 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.

Preparation of Parenteral Solutions/General

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

From: Cohran, Carolyn
Sent: Thursday, July 26, 2007 10:29 AM
To: Zuk, Susan
Subject: RE: 65-439

ANDA Number: 65-439

Applicant's Name: Abraxis Pharmaceutical Products

Established Name: Aztreonam for Injection USP, 500 mg, 1 gram and 2 grams

NOTES/QUESTIONS TO THE CHEMIST

1. The innovator's vial size is "15 mL" and the ANDA's vial sizes are "20 mL" and "30 mL". We plan to inform the ANDA that the vial sizes should be the same as the innovator's, "15 mL". Do you concur with this plan**? - We don't look at the vial size.**

2. The firm has the statements, "Sodium free-nonpyrogenic" and "Vial stoppers do not contain natural rubber latex". Do you concur?
The vials are Type I glass, and the stoppers are made from (b) (4) **rubber. Check the container/closure section.**

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

This is from my review:

Representative diluents, in terms of electrolytes and sugar, were tested for admixture compatibility. Diluents used in the study are as follows: Dextrose Injection USP, 10%, Dextrose and Sodium chloride Injection USP (5%:0.9%), Sodium Lactate Injection USP (M/6 Sodium Lactate), Ionosol® B and 5% Dextrose, Lactated Ringer's and 5% Dextrose Injection, and Plasma-Lyte® M and 5% Dextrose.
For the LVP Admixture Compatibility Study, the vials parameters studied were visual inspection, pH, and assay.
For the LVP Admixture stability study, the samples passed the visual inspection except for (b) (4) found in a sample. No other (b) (4) or precipitate was found. The pH values did not change significantly from the zero time point, and the aztreonam assay concentrations met the limit.

No studies with other antibiotics were submitted.
We don't test for deliverable volume, we do look at fill weight and assay values.
(b) (4)

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 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 USP 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection USP 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 aztreonam for injection should be constituted with 6 to 10 mL Sterile Water for Injection USP.

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 USP.

Further dilution may be obtained with one of the following intravenous infusion solutions: Sodium Chloride Injection USP, 0.9%, Ringer's Injection USP
Lactated Ringer's Injection USP, Dextrose Injection USP, 5% or 10%,
Dextrose and Sodium Chloride Injection USP, 5%:0.9%,5%:0.45% or 5%:0.2%
Sodium Lactate Injection USP (M/6 Sodium Lactate),Ionosol® B and 5% Dextrose
Isolyte® E, Isolyte® E with 5% Dextrose, Isolyte® M with 5% Dextrose, Normosol®-R
Normosol®-R and 5% Dextrose, Normosol®-M and 5% Dextrose, Mannitol Injection USP, 5% or 10%, Lactated Ringer's and 5% Dextrose Injection, Plasma-Lyte® M and 5% Dextrose, 10% Travert® Injection, 10% Travert® and Electrolyte No. 1 Injection
10% Travert® and Electrolyte No. 2 Injection, 10% Travert® and Electrolyte No. 3 Injection

Intramuscular (IM) Solutions

The contents of aztreonam for injection 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 USP, Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and propylparabens), Sodium Chloride Injection USP, 0.9%, Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol)

Stability of IV and IM Solutions

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

(b) (4)

Aztreonam for injection, USP solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection USP or Sodium Chloride Injection USP, 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.

The firm recently informed us of the following:

4. The firm proposes to revise the description of the drug product from "Aztreonam for injection is a sterile, nonpyrogenic, sodium-free, (b) (4) containing approximately 780 mg arginine per gram of aztreonam" to "Aztreonam for injection is a sterile, nonpyrogenic, sodium-free, lyophilized, (b) (4) containing approximately 780 mg arginine per gram of aztreonam." (added words underlined).
Is this new description accurate?
- There is not a test for (b) (4) in the drug product specifications. The firm describes their product as "off white to slightly yellow solid..". If they want to add " (b) (4) they need to include a (b) (4) test in the specifications.

5. The firm informed us that their formulation differs from the innovator, "powder fill" vs. "lyophilized".

Is it acceptable for the ANDA to have a lyophilized drug product which differs from the innovator's formulation? **– Yes, this is acceptable.**

6. The firm indicates that the vial sizes differs from the innovator's because of the difference in formulation. (b) (4)

(b) (4) ?

This is copied from my review.

Product configuration for Aztreonam for Injection

Strength	Vial size	Fill volume
500 mg Aztreonam/vial	20 ml	(b) (4)
1 g Aztreonam/vial	20 ml	
2 g Aztreonam/vial	30 ml	

(b) (4)

From: Cohran, Carolyn
Sent: Thursday, July 26, 2007 1:23 PM
To: Council, Jacqueline
Subject: RE: 65-439

1. If the firm removes the text " (b) (4) would the following statement be accurate? "Aztreonam for injection is a sterile, nonpyrogenic, sodium-free, lyophilized, (b) (4) containing approximately 780 mg arginine per gram of aztreonam.
- This should be accurate

2. Has the firm submitted stability data to support the following claims?

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

(b) (4)

Aztreonam for injection, USP solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection USP or Sodium Chloride Injection USP, 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.
- I don't have any mention of the (b) (4) solution studies in my review. We will call the firm on Monday. I will get back to you.

3. Will the firm be requested to submit capability and stabilities studies to support the claims in the "admixtures with other antibiotics" subsection in the Dosage and Administration section of the package insert labeling?
-Looking at an old guidance, I don't believe this is necessary since it is Q1 and and Q2.

From: Cohran, Carolyn
Sent: Monday, July 30, 2007 10:37 AM
To: Council, Jacqueline

Subject: 65-439 Aztreonam for Injection

We called the firm today about the (b) (4) infusion solution study you had asked about. They said they did have the data, and they would submit it in their response to our deficiency letter.

Carolyn

Carolyn Cohran, Ph.D.
Regulatory Review Chemist
FDA/CDER/OPS/OGD/DCIII
7500 Standish Place, Room E148
MPN 2, HFD-643
Rockville, MD 20855
Tel. 301-827-5745
carolyn.cohran@fda.hhs.gov

From: Cohran, Carolyn
Sent: Monday, November 03, 2008 1:30 PM
To: Council, Jacqueline
Cc: Zuk, Susan
Subject: RE: Update 65-439

See responses below.

Carolyn Cohran, Ph.D.
Tel. 240-276-8462
carolyn.cohran@fda.hhs.gov

NOTES/QUESTIONS TO THE CHEMIST

1. The firm has the statements, “Sodium free-nonpyrogenic” and “Vial stoppers do not contain natural rubber latex”. Do you concur?

Answer: Sodium does not appear to be present in either ingredient. With regard to being nonpyrogenic, that is not something that we look it. Stoppers are (b) (4) rubber. Check the container closure section for more detail.

2. Intramuscular use
   a. Has the firm submitted data to support the recommended volume for reconstitution for IM use, “i.e., 3 mL”?

Answer: This is not a test that we require. We look at the assay values after being reconstituted according to the label to see that the values are correct.

   b. Does the lyophilized product and the powder filled product usually require different volumes for diluent?

Answer: No

3. For this question, I tried only to include the solutions not listed in your previous response. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION section of the insert labeling, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]? See text below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 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 USP 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection USP 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 aztreonam for injection should be constituted with 6 to 10 mL Sterile Water for Injection USP.

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 USP. Further dilution may be obtained with one of the following intravenous infusion solutions: Normosol®-M and 5% Dextrose, Mannitol Injection USP, 5% or 10%, Lactated Ringer's and 5% Dextrose Injection, Plasma-Lyte® M and 5% Dextrose, 10% Travert® Injection, 10% Travert® and Electrolyte No. 1 Injection
10% Travert® and Electrolyte No. 2 Injection, 10% Travert® and Electrolyte No. 3 Injection

Intramuscular (IM) Solutions

The contents of aztreonam for injection 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 USP, Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and propylparabens), Sodium Chloride Injection USP, 0.9%, Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol)

Stability of IV and IM Solutions

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

(b) (4)

[redacted]

Aztreonam for injection, USP solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection USP or Sodium Chloride Injection USP, 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.

Preparation of Parenteral Solutions/General

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

Answer: I have not looked at all the responses from the firm.

From: Council, Jacqueline
Sent: Wednesday, February 11, 2009 10:34 AM
To: Cohran, Carolyn
Subject: 65-439

Good morning Carolyn,

I am working on the labeling review of 65-439. Your answer regarding the firm's stability data in your last e-mail was, "Answer: I have not looked at all the responses from the firm". Have you had an opportunity to review it yet? If so, is text regarding the (b) (4) product and the rest of stability text acceptable?

Thanks,
Jacqueline

From: Cohran, Carolyn
Sent: Wednesday, April 01, 2009 3:44 PM
To: Council, Jacqueline
Subject: RE: 65-439

Hi Jackie
I am attaching a copy of my final review of this ANDA. There is a labeling section in the executive summary. I tried to cover all the questions you had asked about this drug product. Let me know if you have any more questions.

Thanks.
Carolyn

Carolyn Cohran, Ph.D.
Tel. 240-276-8462
carolyn.cohran@fda.hhs.gov

Information for Labeling reviewer:

The drug product is Aztreonam for Injection, USP, 500 mg/vial, 1 g/vial, and 2 g/vial. This antibiotic is a sterile, lyophilized powder that will be reconstituted and administered by intravenous (IV) or intramuscular (IM) injection. Aztreonam for Injection is packaged as strengths of 500 mg/vial, 1 g/vial, and 2 g/vial in glass vials with (b) (4) rubber stopper. The stopper is stated to not contain natural rubber (latex).

Aztreonam solutions exceeding 2% w/v concentration were prepared for IV bolus injection or IM injection. Finished products of 500 mg/vial and 2 g/vial were reconstituted with 1.5 ml and 6 ml diluents, respectively. The reconstituted solution stability of the RLD (2 g/vial) and APP's Aztreonam for Injection (500 mg/vial) using SWFI and Sodium chloride Injection (NS) as diluents were tested. The study design is provided. The duration of storage was zero time control, 48 hours at 25 ± 2°C and 7 days at 5 ± 3°C. For the reconstituted solution stability study, four parameters were studied: Visual inspection, pH, Assay, and Impurities. For the Reconstituted solution stability study, all samples passed the visual inspection test, the pH did not change significantly and was comparable with the RLD, the assay values met the label claim limits, and while slightly higher than the RLD, impurity levels were comparable. The data was acceptable.

Abraxis also tested the LVP admixture stability of the drug product for the 500 mg/vial strength. Representative diluents, in terms of electrolytes and sugar, were tested for admixture compatibility. Diluents used in the study are as follows: Dextrose Injection USP, 10%, Dextrose and Sodium Chloride Injection USP (5%:0.9%), Sodium Lactate Injection USP (M/6 Sodium Lactate), Ionosol® B and 5% Dextrose, Lactated Ringer's and 5% Dextrose Injection, and Plasma-Lyte® M and 5% Dextrose. These same diluents were used for the (b) (4) infusion studies. LVP admixture solutions were prepared with 1.5 ml SWFI followed by dilution with secondary diluents at a final concentration of 20 mg/ml. The LVP preparations were tested at zero time point, after storage for 48 hours at 25 ± 2°C and 7 days at 5 ± 3°C. Samples were also (b) (4) and test performed after storage for 24 hours at 48 hours at 25 ± 2°C and 72 hours at 5 ± 3°C. For the LVP Admixture Compatibility Study, the vials parameters studied were visual inspection, pH, and assay. For the LVP Admixture stability study, the samples passed the visual inspection except for (b) (4) found in a sample. No other (b) (4) or precipitate was found. The pH values did not change significantly from the zero time point, and the aztreonam assay concentrations met the limit. For the (b) (4) samples, samples also passed visual inspection, pH values were comparable to the zero time point, and passed the assay specifications. The data was acceptable.

Appears this way on original.

Appears this way on original.

FOR THE RECORD:

1. Labeling model

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

- The ANDA vial sizes differ from the innovator's. The RLD vial capacity is 15 mL for all three strengths, 500 mg, 1 gram and 2 grams. The ANDA vial sizes are 20 mL for the 500 mg and 1 gram strengths and 30 mL for 2 gram strength.
The RLD includes the "15 mL vial capacity" in the following portion of the labeling.
(b) (4)

DOSAGE AND ADMINISTRATION
i Intravenous (IV) Solutions
A) For Bolus Injection –first paragraph.
B) For Infusion – second paragraph.

Generic firms should be requested to include the vial sizes (b) (4) on the labels and in the PI, since they differ from the RLD.
Note: In the 12/5/09 submission the firm indicates that their product uses the same volume for constitution.

- From Team Leader, Captain Lillie Golson:
I contacted DMETs with your proposal and they have no problem as long as the strengths are clearly differentiated. So your proposal to use 20 mL and 30 mL size vials with this product is acceptable.

2. The listing of the active and inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the composition statement listed in the application.
[Vol. 1.1, p. 86]

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)

NOTE: The firm indicates that the drug product is lyophilized.

[Vol. 1.1, p. 86]

3. Physical Description

Dry: Slightly yellow solids
Solution: Light yellow
[Chemistry review]

4. Manufacturing Facility of the Drug Product

Abraxis Pharmaceutical Products
Grand Island, New York
[Vol. 1.1, p. 99]

5. Patent/ Exclusivities

Patent Data – ---

No	Expiration	Use Code	Use	File
None				

Exclusivity Data – ---

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

6. Package Sizes

RLD- Single-dose 15 mL capacity vials:
[Note: The RLD previously marketed a 500 mg/vial – 10s]
1 g/vial – 10s
2 g/vial - 10s

ANDA - Single-dose 20 mL and 30 mL capacity vials:
500 mg/vial – 10s [20 mL]
1 g/vial – 10s [20 mL]
2 g/vial - 10s [30 mL]

7. Container/Closure

The configuration of container/closure system used for packaging the drug product (is summarized below:
[Vol. 1.1, p. 275 to 278]

Container/Closure	Description
20 mL and 30 mL vial	Type I USP glass
Closure	Gray rubber stoppers
Seal	Flip-off Aluminum Seals
Color	Mist gray, green and blue

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. Solution pH

USP – between 4.5 and 7.5, in a solution containing 100 mg of aztreonam per mL.
NDA – 4.5 to 7.5
ANDA – 4.5 to 7.5 [insert labeling] (b) (4) [chemistry review]
[Vol. 1.1, p. 285]

10. The firm provided the supporting documents that verify the statement, "Vial stoppers do not contain natural rubber latex" in the 3/13/09 submission.

Appears this way on original.

Date of Review: 3/30/09 – Note the chemist updated on 9/9/09

Date of Submission: 3/13/09

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

Team Leader:
Captain Lillie Golson Date:

cc: ANDA: 65-439
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSAM\ABRAXIS PHARMACEUTICAL PRODUCTS\LTRS&REV\65439ap.ll.l.doc
Review

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-65439	ORIG-1	APP PHARMACEUTICALS LLC	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
10/15/2009

LILLIE D GOLSON
10/21/2009

APPROVAL SUMMARY

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

ANDA Number: 65-439

Dates of Submission: March 13, 2009

Applicant's Name: Abraxis Pharmaceutical Products

Established Name: Aztreonam for Injection USP, 500 mg, 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

CONTAINER: 500 mg, 1 gram and 2 grams
Satisfactory as of the December 5, 2008 submission

TRAY label: 500 mg, 1 gram and 2 grams
Satisfactory as of the March 14, 2008 submission

INSERT: Satisfactory as of the March 13, 2009 submission.

Revisions needed post-approval:
Container: Increase the size of the asterisk on the side panel.

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

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

Has this been verified by the MIS system for the NDA? Checked Drugs@FDA

Was this approval based upon an OGD labeling guidance? No

NOTES/QUESTIONS TO THE CHEMIST [The chemist has to review the firm's response to chemist before all of the questions are answered].

1. The firm revised the description of the drug product to read, "Aztreonam for injection is a sterile, nonpyrogenic, sodium-free, lyophilized, (b) (4) containing approximately 780 mg arginine per gram of aztreonam." Is this now accurate?
2. The innovator's vial size is "15 mL" and the ANDA's vial sizes are "20 mL" and "30 mL". Is this acceptable?
3. The firm has the statements, "Sodium free-nonpyrogenic" and "Vial stoppers do not contain natural rubber latex". Do you concur?
4. The firm informed us that their "formulation" differs from the innovator, "powder fill" vs. "lyophilized".
   Is it acceptable for the ANDA to have a lyophilized drug product which differs from the innovator's formulation?
5. The firm indicates that the "vial sizes" differs from the innovator's because of the difference in formulation. (b) (4)

6. Intramuscular use
   a. Has the firm submitted data to support the recommended volume for reconstitution for IM use, "i.e., 3 mL"?
   b. Does the lyophilized product and the powder filled product usually require the different volumes for diluent?
7. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION section of the insert labeling, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]? See text below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 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 USP 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection USP 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 aztreonam for injection should be constituted with 6 to 10 mL Sterile Water for Injection USP.

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 USP. Further dilution may be obtained with one of the following intravenous infusion solutions: Sodium Chloride Injection USP, 0.9%, Ringer's Injection USP
Lactated Ringer's Injection USP, Dextrose Injection USP, 5% or 10%,
Dextrose and Sodium Chloride Injection USP, 5%:0.9%,5%:0.45% or 5%:0.2%

Sodium Lactate Injection USP (M/6 Sodium Lactate),Ionosol® B and 5% Dextrose
Isolyte® E, Isolyte® E with 5% Dextrose, Isolyte® M with 5% Dextrose, Normosol®-R
Normosol®-R and 5% Dextrose, Normosol®-M and 5% Dextrose, Mannitol Injection USP, 5% or
10%, Lactated Ringer's and 5% Dextrose Injection, Plasma-Lyte® M and 5% Dextrose, 10%
Travert® Injection, 10% Travert® and Electrolyte No. 1 Injection
10% Travert® and Electrolyte No. 2 Injection, 10% Travert® and Electrolyte No. 3 Injection

Intramuscular (IM) Solutions

The contents of aztreonam for injection 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 USP, Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and propylparabens), Sodium Chloride Injection USP, 0.9%, Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol)

Stability of IV and IM Solutions

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

(b) (4)

Aztreonam for injection, USP solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection USP or Sodium Chloride Injection USP, 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.

Preparation of Parenteral Solutions/General

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

From: Cohran, Carolyn
Sent: Thursday, July 26, 2007 10:29 AM
To: Zuk, Susan
Subject: RE: 65-439

ANDA Number: 65-439

Applicant's Name: Abraxis Pharmaceutical Products

Established Name: Aztreonam for Injection USP, 500 mg, 1 gram and 2 grams

NOTES/QUESTIONS TO THE CHEMIST

1. The innovator's vial size is "15 mL" and the ANDA's vial sizes are "20 mL" and "30 mL". We plan to inform the ANDA that the vial sizes should be the same as the innovator's, "15 mL". Do you concur with this plan? **- We don't look at the vial size.**

2. The firm has the statements, "Sodium free-nonpyrogenic" and "Vial stoppers do not contain natural rubber latex". Do you concur?
The vials are Type I glass, and the stoppers are made from (b) (4) **rubber. Check the container/closure section.**

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

This is from my review:

Representative diluents, in terms of electrolytes and sugar, were tested for admixture compatibility. Diluents used in the study are as follows: Dextrose Injection USP, 10%, Dextrose and Sodium chloride Injection USP (5%:0.9%), Sodium Lactate Injection USP (M/6 Sodium Lactate), Ionosol® B and 5% Dextrose, Lactated Ringer's and 5% Dextrose Injection, and Plasma-Lyte® M and 5% Dextrose.
For the LVP Admixture Compatibility Study, the vials parameters studied were visual inspection, pH, and assay.
For the LVP Admixture stability study, the samples passed the visual inspection except for (b) (4) found in a sample. No other (b) (4) or precipitate was found. The pH values did not change significantly from the zero time point, and the aztreonam assay concentrations met the limit.

No studies with other antibiotics were submitted.
We don't test for deliverable volume, we do look at fill weight and assay values.
(b) (4)

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 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 USP 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection USP 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 aztreonam for injection should be constituted with 6 to 10 mL Sterile Water for Injection USP.

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 USP. Further dilution may be obtained with one of the following intravenous infusion solutions: Sodium Chloride Injection USP, 0.9%, Ringer's Injection USP
Lactated Ringer's Injection USP, Dextrose Injection USP, 5% or 10%,
Dextrose and Sodium Chloride Injection USP, 5%:0.9%,5%:0.45% or 5%:0.2%
Sodium Lactate Injection USP (M/6 Sodium Lactate),Ionosol® B and 5% Dextrose
Isolyte® E, Isolyte® E with 5% Dextrose, Isolyte® M with 5% Dextrose, Normosol®-R
Normosol®-R and 5% Dextrose, Normosol®-M and 5% Dextrose, Mannitol Injection USP, 5% or 10%, Lactated Ringer's and 5% Dextrose Injection, Plasma-Lyte® M and 5% Dextrose, 10% Travert® Injection, 10% Travert® and Electrolyte No. 1 Injection
10% Travert® and Electrolyte No. 2 Injection, 10% Travert® and Electrolyte No. 3 Injection

Intramuscular (IM) Solutions

The contents of aztreonam for injection 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 USP, Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and propylparabens), Sodium Chloride Injection USP, 0.9%, Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol)

Stability of IV and IM Solutions

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

(b) (4)

Aztreonam for injection, USP solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection USP or Sodium Chloride Injection USP, 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.

The firm recently informed us of the following:

4. The firm proposes to revise the description of the drug product from "Aztreonam for injection is a sterile, nonpyrogenic, sodium-free (b) (4) containing approximately 780 mg arginine per gram of aztreonam" to "Aztreonam for injection is a sterile, nonpyrogenic, sodium-free, lyophilized (b) (4) containing approximately 780 mg arginine per gram of aztreonam." (added words underlined).

Is this new description accurate?

- There is not a test for (b) (4) in the drug product specifications. The firm describes their product as "off white to slightly yellow solid..". If they want to add (b) (4) they need to include a (b) (4) test in the specifications.

5. The firm informed us that their formulation differs from the innovator, "powder fill" vs. "lyophilized".

Is it acceptable for the ANDA to have a lyophilized drug product which differs from the innovator's formulation? – **Yes, this is acceptable.**

6. The firm indicates that the vial sizes differs from the innovator's because of the difference in formulation, (b) (4)

(b) (4)

This is copied from my review.

Product configuration for Aztreonam for Injection

Strength	Vial size	Fill volume
500 mg Aztreonam/vial	20 ml	(b) (4)
1 g Aztreonam/vial	20 ml	
2 g Aztreonam/vial	30 ml	

(b) (4)

.

From: Cohran, Carolyn
Sent: Thursday, July 26, 2007 1:23 PM
To: Council, Jacqueline
Subject: RE: 65-439

1. If the firm removes the text [redacted] (b) (4) would the following statement be accurate? "Aztreonam for injection is a sterile, nonpyrogenic, sodium-free, lyophilized, [redacted] (b) (4) containing approximately 780 mg arginine per gram of aztreonam.
- This should be accurate

2. Has the firm submitted stability data to support the following claims?

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

[redacted] (b) (4)

Aztreonam for injection, USP solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection USP or Sodium Chloride Injection USP, 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.
- I don't have any mention of the [redacted] (b) (4) solution studies in my review. We will call the firm on Monday. I will get back to you.

3. Will the firm be requested to submit capability and stabilities studies to support the claims in the "admixtures with other antibiotics" subsection in the Dosage and Administration section of the package insert labeling?
-Looking at an old guidance, I don't believe this is necessary since it is Q1 and and Q2.

From: Cohran, Carolyn
Sent: Monday, July 30, 2007 10:37 AM
To: Council, Jacqueline
Subject: 65-439 Aztreonam for Injection

We called the firm today about the [redacted] (b) (4) infusion solution study you had asked about. They said they did have the data, and they would submit it in their response to our deficiency letter.

Carolyn

Carolyn Cohran, Ph.D.
Regulatory Review Chemist
FDA/CDER/OPS/OGD/DCIII
7500 Standish Place, Room E148
MPN 2, HFD-643
Rockville, MD 20855

Tel. 301-827-5745
carolyn.cohran@fda.hhs.gov

From: Cohran, Carolyn
Sent: Monday, November 03, 2008 1:30 PM
To: Council, Jacqueline
Cc: Zuk, Susan
Subject: RE: Update 65-439

See responses below.

Carolyn Cohran, Ph.D.
Tel. 240-276-8462
carolyn.cohran@fda.hhs.gov

NOTES/QUESTIONS TO THE CHEMIST

1. The firm has the statements, "Sodium free-nonpyrogenic" and "Vial stoppers do not contain natural rubber latex". Do you concur?

Answer: Sodium does not appear to be present in either ingredient. With regard to being nonpyrogenic, that is not something that we look it. Stoppers are (b) (4) rubber. Check the container closure section for more detail.

2. Intramuscular use
   a. Has the firm submitted data to support the recommended volume for reconstitution for IM use, "i.e., 3 mL"?

Answer: This is not a test that we require. We look at the assay values after being reconstituted according to the label to see that the values are correct.

   b. Does the lyophilized product and the powder filled product usually require different volumes for diluent?

Answer: No

3. For this question, I tried only to include the solutions not listed in your previous response. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION section of the insert labeling, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]? See text below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 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 USP 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection USP 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 aztreonam for injection should be constituted with 6 to 10 mL Sterile Water for Injection USP.

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 USP. Further dilution may be obtained with one of the following intravenous infusion solutions: Normosol®-M and 5% Dextrose, Mannitol Injection USP, 5% or 10%, Lactated Ringer's and 5% Dextrose Injection, Plasma-Lyte® M and 5% Dextrose, 10% Travert® Injection, 10% Travert® and Electrolyte No. 1 Injection
10% Travert® and Electrolyte No. 2 Injection, 10% Travert® and Electrolyte No. 3 Injection

Intramuscular (IM) Solutions

The contents of aztreonam for injection 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 USP, Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and propylparabens), Sodium Chloride Injection USP, 0.9%, Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol)

Stability of IV and IM Solutions

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

(b) (4)

Aztreonam for injection, USP solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection USP or Sodium Chloride Injection USP, 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.

Preparation of Parenteral Solutions/General

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

Answer: I have not looked at all the responses from the firm.

From: Council, Jacqueline
Sent: Wednesday, February 11, 2009 10:34 AM
To: Cohran, Carolyn
Subject: 65-439

Good morning Carolyn,

I am working on the labeling review of 65-439. Your answer regarding the firm's stability data in your last e-mail was, "Answer: I have not looked at all the responses from the firm". Have you had an opportunity to review it yet? If so, is text regarding the (b) (4) product and the rest of stability text acceptable?

Thanks,
Jacqueline

From: Cohran, Carolyn
Sent: Wednesday, April 01, 2009 3:44 PM
To: Council, Jacqueline
Subject: RE: 65-439

Hi Jackie
I am attaching a copy of my final review of this ANDA. There is a labeling section in the executive summary. I tried to cover all the questions you had asked about this drug product. Let me know if you have any more questions.

Thanks.
Carolyn

Carolyn Cohran, Ph.D.
Tel. 240-276-8462
carolyn.cohran@fda.hhs.gov

Information for Labeling reviewer:

The drug product is Aztreonam for Injection, USP, 500 mg/vial, 1 g/vial, and 2 g/vial. This antibiotic is a sterile, lyophilized powder that will be reconstituted and administered by intravenous (IV) or intramuscular (IM) injection. Aztreonam for Injection is packaged as strengths of 500 mg/vial, 1 g/vial, and 2 g/vial in glass vials with (b) (4) rubber stopper. The stopper is stated to not contain natural rubber (latex).

Aztreonam solutions exceeding 2% w/v concentration were prepared for IV bolus injection or IM injection. Finished products of 500 mg/vial and 2 g/vial were reconstituted with 1.5 ml and 6 ml diluents, respectively. The reconstituted solution stability of the RLD (2 g/vial) and APP's Aztreonam for Injection (500 mg/vial) using SWFI and Sodium chloride Injection (NS) as diluents were tested. The study design is provided. The duration of storage was zero time control, 48 hours at 25 ± 2°C and 7 days at 5 ± 3°C. For the reconstituted solution stability study, four parameters were studied: Visual inspection, pH, Assay, and Impurities. For the Reconstituted solution stability study, all samples passed the visual inspection test, the pH did not change significantly and was comparable with the RLD, the assay values met the label claim limits, and while slightly higher than the RLD, impurity levels were comparable. The data was acceptable.

Abraxis also tested the LVP admixture stability of the drug product for the 500 mg/vial strength. Representative diluents, in terms of electrolytes and sugar, were tested for admixture compatibility. Diluents used in the study are as follows: Dextrose Injection USP, 10%, Dextrose and Sodium Chloride Injection USP (5%:0.9%), Sodium Lactate Injection USP (M/6 Sodium Lactate), Ionosol® B and 5% Dextrose, Lactated Ringer's and 5% Dextrose Injection, and Plasma-Lyte® M and 5% Dextrose. These same diluents were used for the (b) (4) infusion studies. LVP admixture solutions were prepared with 1.5 ml SWFI followed by dilution with secondary diluents at a final concentration of 20 mg/ml. The LVP preparations were tested at zero time point, after storage for 48 hours at 25 ± 2°C and 7 days at 5 ± 3°C. Samples were also (b) (4) and test performed after storage for 24

hours at 48 hours at 25 ± 2°C and 72 hours at 5 ± 3°C. For the LVP Admixture Compatibility Study, the vials parameters studied were visual inspection, pH, and assay. For the LVP Admixture stability study, the samples passed the visual inspection except for (b) (4) found in a sample. No other (b) (4) or precipitate was found. The pH values did not change significantly from the zero time point, and the aztreonam assay concentrations met the limit. For the (b) (4) samples, samples also passed visual inspection, pH values were comparable to the zero time point, and passed the assay specifications. The data was acceptable.

Appears this way on original.

FOR THE RECORD:

1. Labeling model

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

- The ANDA vial sizes differ from the innovator's. The RLD vial capacity is 15 mL for all three strengths, 500 mg, 1 gram and 2 grams. The ANDA vial sizes are 20 mL for the 500 mg and 1 gram strengths and 30 mL for 2 gram strength.
The RLD includes the "15 mL vial capacity" in the following portion of the labeling.
(b) (4)

DOSAGE AND ADMINISTRATION
i Intravenous (IV) Solutions
A) For Bolus Injection –first paragraph.
B) For Infusion – second paragraph.

Generic firms should be requested to include the vial sizes (b) (4) on the labels and in the PI, since they differ from the RLD.
Note: In the 12/5/09 submission the firm indicates that their product uses the same volume for constitution.

- From Team Leader, Captain Lillie Golson:
I contacted DMETs with your proposal and they have no problem as long as the strengths are clearly differentiated. So your proposal to use 20 mL and 30 mL size vials with this product is acceptable.

2. The listing of the active and inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the composition statement listed in the application.
[Vol. 1.1, p. 86]

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)

NOTE: The firm indicates that the drug product is lyophilized.

[Vol. 1.1, p. 86]

3. Physical Description

Dry: Slightly yellow solids
Solution: Light yellow
[Chemistry review]

4. Manufacturing Facility of the Drug Product

Abraxis Pharmaceutical Products
Grand Island, New York
[Vol. 1.1, p. 99]

5. Patent/ Exclusivities

Patent Data – ---

No	Expiration	Use Code	Use	File
None				

Exclusivity Data – ---

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

6. Package Sizes

RLD- Single-dose 15 mL capacity vials:
[Note: The RLD previously marketed a 500 mg/vial – 10s]
1 g/vial – 10s
2 g/vial - 10s

ANDA - Single-dose 20 mL and 30 mL capacity vials:
500 mg/vial – 10s [20 mL]
1 g/vial – 10s [20 mL]
2 g/vial - 10s [30 mL]

7. Container/Closure

The configuration of container/closure system used for packaging the drug product (is summarized below:
[Vol. 1.1, p. 275 to 278]

Container/Closure	Description
20 mL and 30 mL vial	Type I USP glass
Closure	Gray rubber stoppers
Seal	Flip-off Aluminum Seals
Color	Mist gray, green and blue

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. Solution pH

USP – between 4.5 and 7.5, in a solution containing 100 mg of aztreonam per mL.
NDA – 4.5 to 7.5
ANDA – 4.5 to 7.5 [insert labeling] (b) (4) [chemistry review]
[Vol. 1.1, p. 285]

10. The firm provided the supporting documents that verify the statement, “Vial stoppers do not contain natural rubber latex” in the 3/13/09 submission.

Appears this way on original.

Date of Review: 3/30/09

Date of Submission: 3/13/09

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

Team Leader:
Captain Lillie Golson Date:

cc: ANDA: 65-439
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSAM\ABRAXIS PHARMACEUTICAL PRODUCTS\LTRS&REV\65439ap.ll.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
4/16/2009 01:14:48 PM
LABELING REVIEWER

Michelle Dillahunt
4/16/2009 03:05:26 PM
LABELING REVIEWER
M.Dillahunt for Lillie Golson

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

ANDA Number: 65-439

Dates of Submission: December 5, 2008 and February 2, 2009

Applicant's Name: Abraxis Pharmaceutical Products

Established Name: Aztreonam for Injection USP, 500 mg, 1 gram and 2 grams

---

1. CONTAINER

   Please provide supporting documents that verify the statement, "Vial stoppers do not contain natural rubber latex".

2. INSERT

   a. DOSAGE AND ADMINISTRATION

      i. Renal Impairment in Adult Patients

         Revise to read, "… between 10 mL/min/1.73 m^2 and…".

      ii. Intravenous (IV) Solutions

         A) Use separate Tables for "IV bolus" and "IV infusion".

            Use the following titles for each Table.

            CONSTITUTION for IV BOLUS

            CONSTITUTION for IV INFUSION

         B) After constitution, further dilution is not required for IV bolus. Therefore, in the Table for "IV bolus" revise the column heading to read "Amount of Diluent to be added (mL)". In addition, do not add the statement, "(b) (4) (b) (4)" at the bottom of the Table.

         C) Revise the statement below the Table for "Constitution for IV Infusion to read, "(b) (4) (b) (4). Further…".

      iii. For Bolus Injection

         Revise the first sentence to read, "…for injection vial should…".

      iv. Intramuscular (IM) Solutions

         A) After constitution, further dilution is not required for IM administration. Therefore, in the Table for "Intramuscular (IM)

Solutions" revise the column heading to read "Amount of Diluent to be added (mL)".

B) For IM administration the constituted solution should not be further diluted therefore, delete the statement beneath the Table or IM administration, "(b) (4)

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 with the enclosed copy of the 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 [The chemist has to review the firm's response to chemist before all of the questions are answered].

1. The firm revised the description of the drug product to read, "Aztreonam for injection is a sterile, nonpyrogenic, sodium-free, lyophilized, (b) (4) containing approximately 780 mg arginine per gram of aztreonam." Is this now accurate?
2. The innovator's vial size is "15 mL" and the ANDA's vial sizes are "20 mL" and "30 mL". Is this acceptable?
3. The firm has the statements, "Sodium free-nonpyrogenic" and "Vial stoppers do not contain natural rubber latex". Do you concur?
4. The firm informed us that their "formulation" differs from the innovator, "powder fill" vs. "lyophilized".
   Is it acceptable for the ANDA to have a lyophilized drug product which differs from the innovator's formulation?
5. The firm indicates that the "vial sizes" differs from the innovator's because of the difference in formulation. (b) (4)

6. Intramuscular use
   a. Has the firm submitted data to support the recommended volume for reconstitution for IM use, "i.e., 3 mL"?
   b. Does the lyophilized product and the powder filled product usually require the different volumes for diluent?
7. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION section of the insert labeling, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]? See text below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 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 USP 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection USP 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 aztreonam for injection should be constituted with 6 to 10 mL Sterile Water for Injection USP.

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 USP. Further dilution may be obtained with one of the following intravenous infusion solutions: Sodium Chloride Injection USP, 0.9%, Ringer's Injection USP
Lactated Ringer's Injection USP, Dextrose Injection USP, 5% or 10%,
Dextrose and Sodium Chloride Injection USP, 5%:0.9%,5%:0.45% or 5%:0.2%

Sodium Lactate Injection USP (M/6 Sodium Lactate),Ionosol® B and 5% Dextrose
Isolyte® E, Isolyte® E with 5% Dextrose, Isolyte® M with 5% Dextrose, Normosol®-R
Normosol®-R and 5% Dextrose, Normosol®-M and 5% Dextrose, Mannitol Injection USP, 5% or 10%, Lactated Ringer's and 5% Dextrose Injection, Plasma-Lyte® M and 5% Dextrose, 10% Travert® Injection, 10% Travert® and Electrolyte No. 1 Injection
10% Travert® and Electrolyte No. 2 Injection, 10% Travert® and Electrolyte No. 3 Injection

Intramuscular (IM) Solutions

The contents of aztreonam for injection 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 USP, Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and propylparabens), Sodium Chloride Injection USP, 0.9%, Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol)

Stability of IV and IM Solutions

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

(b) (4)

[redacted]

Aztreonam for injection, USP solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection USP or Sodium Chloride Injection USP, 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.

Preparation of Parenteral Solutions/General

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

Appears this way on original.

FOR THE RECORD:

1. Labeling model

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

- The ANDA vial sizes differ from the innovator's. The RLD vial capacity is 15 mL for all three strengths, 500 mg, 1 gram and 2 grams. The ANDA vial sizes are 20 mL for the 500 mg and 1 gram strengths and 30 mL for 2 gram strength.
The RLD includes the "15 mL vial capacity" in the following portion of the labeling.
(b) (4)

DOSAGE AND ADMINISTRATION
i Intravenous (IV) Solutions
A) For Bolus Injection –first paragraph.
B) For Infusion – second paragraph.

Generic firms should be requested to include the vial sizes (b) (4) on the labels and in the PI, since they differ from the RLD.
Note: In the 12/5/09 submission the firm indicates that their product uses the same volume for constitution.

- From Team Leader, Captain Lillie Golson:
I contacted DMETs with your proposal and they have no problem as long as the strengths are clearly differentiated. So your proposal to use 20 mL and 30 mL size vials with this product is acceptable.

2. The listing of the active and inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the composition statement listed in the application.
[Vol. 1.1, p. 86]

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)

NOTE: The firm indicates that the drug product is lyophilized.

[Vol. 1.1, p. 86]

3. Physical Description

Dry: Slightly yellow solids
Solution: Light yellow
[Chemistry review]

4. Manufacturing Facility of the Drug Product

Abraxis Pharmaceutical Products
Grand Island, New York
[Vol. 1.1, p. 99]

5. Patent/ Exclusivities

Patent Data – ---

No	Expiration	Use Code	Use	File
None				

Exclusivity Data – ---

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					

6. Package Sizes

RLD- Single-dose 15 mL capacity vials:
[Note: The RLD previously marketed a 500 mg/vial – 10s]
1 g/vial – 10s
2 g/vial - 10s

ANDA - Single-dose 20 mL and 30 mL capacity vials:
500 mg/vial – 10s [20 mL]
1 g/vial – 10s [20 mL]
2 g/vial - 10s [30 mL]

7. Container/Closure

The configuration of container/closure system used for packaging the drug product (is summarized below:
[Vol. 1.1, p. 275 to 278]

Container/Closure	Description
20 mL and 30 mL vial	Type I USP glass
Closure	Gray rubber stoppers
Seal	Flip-off Aluminum Seals
Color	Mist gray, green and blue

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. Solution pH

USP – between 4.5 and 7.5, in a solution containing 100 mg of aztreonam per mL.
NDA – 4.5 to 7.5
ANDA – 4.5 to 7.5 [insert labeling] (b) (4) [chemistry review]
[Vol. 1.1, p. 285]

9. CONTAINER: 500 mg, 1 gram and 2 grams
Satisfactory as of the December 5, 2008 submission
Tray label: 500 mg, 1 gram and 2 grams
Satisfactory as of the December 5, 2008 submission

Future revisions: Increase the size of the asterisk on the side panel.

Appears this way on original.

Date of Review: 2/11/09

Date of Submission: 12/5/08 and 2/2/09

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

Team Leader:
Captain Lillie Golson Date:

cc: ANDA: 65-439
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSAM\ABRAXIS PHARMACEUTICAL PRODUCTS\LTRS&REV\65439na4.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
2/26/2009 01:44:48 PM
LABELING REVIEWER

Michelle Dillahunt
2/26/2009 04:07:38 PM
LABELING REVIEWER
M. Dillahunt for Wm. Peter Rickman

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

ANDA Number: 65-439

Dates of Submission: March 14, 2008

Applicant's Name: Abraxis Pharmaceutical Products

Established Name: Aztreonam for Injection USP, 500 mg, 1 gram and 2 grams

---

1. CONTAINER: 500 mg, 1 gram and 2 grams

   a. You indicate your drug product differs from the innovator's in that it is "lyophilized" and not "powder filled". In addition, you indicate that your "vial size" and (b) (4) as previously requested.

   b. The color or your 1 and 2 g container labels are similar. Please further differentiate the color of the strength by using contrasting colors.

2. INSERT

   a. DESCRIPTION

      Powder color

      Is the color of your product in the dry state "white" or "yellow"? Please provide documentation.

   b. DOSAGE AND ADMINISTRATION

      i. As previously requested, include the following information in the DOSAGE AND ADMINISTRATION section due to the differences of your drug product from the innovator.

         A) The vial size for each strength.

            [You may include a statement that your vial size differs from the innovator's because your product is "lyophilized"].

         B) The volume required for reconstitution for each strength.

Please provide this information in a Table format, such as follows:

Strength	Vial size	Volume of Sterile Water for Injection [mL] for reconstitution	Final volume [mL]

ii. We note that you included the same volume of diluent for reconstitution as the innovator. However, you previously informed us that your "vial sizes" [i.e., 20 mL and 30 mL] and (b) (4) . Please explain. In addition, provide supporting documents that provide the volume of Sterile Water for Injection required for reconstitution for each strength.

iii. Although your product is "lyophilized" and not "powder filled", you recommend your drug product to be reconstituted with the same volume as the innovator for IM use," 3 mL". Please verify with supporting documentation.

iv. Admixtures with Other Antibiotics

In the first sentence delete "(b) (4)".

v. Stability of IV and IM Solutions

In the first sentence delete "(b) (4)"

b. HOW SUPPLIED

i. Add "single dose vials" beneath the established name.

ii. Include the vial sizes for each strength.

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 with the enclosed copy of the 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

1. The firm revised the description of the drug product to read, "Aztreonam for injection is a sterile, nonpyrogenic, sodium-free, lyophilized, (b) (4) containing approximately 780 mg arginine per gram of aztreonam." Is this now accurate?
2. The innovator's vial size is "15 mL" and the ANDA's vial sizes are "20 mL" and "30 mL". Is this acceptable?
3. The firm has the statements, "Sodium free-nonpyrogenic" and "Vial stoppers do not contain natural rubber latex". Do you concur?
4. The firm informed us that their "formulation" differs from the innovator, "powder fill" vs. "lyophilized".
   Is it acceptable for the ANDA to have a lyophilized drug product which differs from the innovator's formulation?
5. The firm indicates that the "vial sizes" differs from the innovator's because of the difference in formulation. (b) (4)

6. Intramuscular use
   a. Has the firm submitted data to support the recommended volume for reconstitution for IM use, "i.e., 3 mL"?
   b. Does the lyophilized product and the powder filled product usually require the different volumes for diluent?

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

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 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 USP 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection USP 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 aztreonam for injection should be constituted with 6 to 10 mL Sterile Water for Injection USP.

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 USP. Further dilution may be obtained with one of the following intravenous infusion solutions: Sodium Chloride Injection USP, 0.9%, Ringer's Injection USP
Lactated Ringer's Injection USP, Dextrose Injection USP, 5% or 10%,
Dextrose and Sodium Chloride Injection USP, 5%:0.9%,5%:0.45% or 5%:0.2%
Sodium Lactate Injection USP (M/6 Sodium Lactate),Ionosol® B and 5% Dextrose
Isolyte® E, Isolyte® E with 5% Dextrose, Isolyte® M with 5% Dextrose, Normosol®-R
Normosol®-R and 5% Dextrose, Normosol®-M and 5% Dextrose, Mannitol Injection USP, 5% or 10%, Lactated Ringer's and 5% Dextrose Injection, Plasma-Lyte® M and 5% Dextrose, 10% Travert® Injection, 10% Travert® and Electrolyte No. 1 Injection
10% Travert® and Electrolyte No. 2 Injection, 10% Travert® and Electrolyte No. 3 Injection

Intramuscular (IM) Solutions

The contents of aztreonam for injection 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 USP, Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and propylparabens), Sodium Chloride Injection USP, 0.9%, Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol)

Stability of IV and IM Solutions

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

(b) (4)

Aztreonam for injection, USP solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection USP or Sodium Chloride Injection USP, 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.

Preparation of Parenteral Solutions/General

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

From: Cohran, Carolyn
Sent: Monday, July 30, 2007 10:37 AM
To: Council, Jacqueline
Subject: 65-439 Aztreonam for Injection

We called the firm today about the (b) (4) infusion solution study you had asked about. They said they did have the data, and they would submit it in their response to our deficiency letter.

Carolyn

Carolyn Cohran, Ph.D.
Regulatory Review Chemist
FDA/CDER/OPS/OGD/DCIII
7500 Standish Place, Room E148
MPN 2, HFD-643
Rockville, MD 20855
Tel. 301-827-5745
carolyn.cohran@fda.hhs.gov

FOR THE RECORD:

1. Labeling model

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

- The ANDA vial sizes differ from the innovator's. The RLD vial capacity is 15 mL for all three strengths, 500 mg, 1 gram and 2 grams. The ANDA vial sizes are 20 mL for the 500 mg and 1 gram strengths and 30 mL for 2 gram strength.
The RLD includes the "15 mL vial capacity" in the following portion of the labeling.
(b) (4)

DOSAGE AND ADMINISTRATION
i Intravenous (IV) Solutions
A) For Bolus Injection –first paragraph.
B) For Infusion – second paragraph.

Generic firms should be requested to include the vial sizes (b) (4) on the labels and in the PI, since they differ from the RLD.

- From Team Leader, Captain Lillie Golson:
I contacted DMETs with your proposal and they have no problem as long as the strengths are clearly differentiated. So your proposal to use 20 mL and 30 mL size vials with this product is acceptable.

2. The listing of the active and inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the composition statement listed in the application.
[Vol. 1.1, p. 86]

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)

NOTE: The firm indicates that the drug product is lyophilized.

[Vol. 1.1, p. 86]

3. Physical Description

Dry: Slightly yellow solids
Solution: Light yellow
[Chemistry review]

4. Manufacturing Facility of the Drug Product

Abraxis Pharmaceutical Products
Grand Island, New York
[Vol. 1.1, p. 99]

5. Patent/ Exclusivities

Patent Data –

No	Expiration	Use Code	Use	File
None				

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 - Single-dose 20 mL and 30 mL capacity vials:
500 mg/vial – 10s [20 mL]
1 g/vial – 10s [20 mL]
2 g/vial - 10s [30 mL]
[See comment to the chemist]

7. Container/Closure

The configuration of container/closure system used for packaging the drug product (is summarized below:
[Vol. 1.1, p. 275 to 278]

Container/Closure	Description
20 mL and 30 mL vial	Type I USP glass
Closure	Gray rubber stoppers
Seal	Flip-off Aluminum Seals
Color	Mist gray, green and blue

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. Solution pH

USP – between 4.5 and 7.5, in a solution containing 100 mg of aztreonam per mL.
NDA – 4.5 to 7.5
ANDA – 4.5 to 7.5 [insert labeling] (b) (4) [chemistry review]
[Vol. 1.1, p. 285]

Appears this way on original.

Date of Review: 10/8/08

Date of Submission: 3/14/08

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

Team Leader:
Captain Lillie Golson Date:

cc: ANDA: 65-439
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
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Review

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/s/

Jacqueline Council
10/31/2008 08:01:46 AM
LABELING REVIEWER

Lillie Golson
10/31/2008 03:57:05 PM
LABELING REVIEWER

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

ANDA Number: 65-439

Dates of Submission: September 11, 2007

Applicant's Name: Abraxis Pharmaceutical Products

Established Name: Aztreonam for Injection USP, 500 mg, 1 gram and 2 grams

---

Labeling Deficiencies:

1. CONTAINER: 500 mg, 1 gram and 2 grams

   a. Front panel

      i. 500 mg, 1 gram and 2 grams

         Add an asterisk following the strength, "1 gram*/vial".

      ii. 2 grams

         Replace "2 gram/vial" with "2 grams*/vial"

   b. Side panel

      i. Add an asterisk prior to the "*Each vial contains …" statement.

      ii. We note that you indicate your drug product differs from the innovator's in that it is "lyophilized" and not "powder filled". In addition, you indicate that your "vial size" and "(b) (4)

2. (b) (4)

3. INSERT

   a. GENERAL COMMENTS

      i. Decrease the prominence of your company name printed at the top of your insert labeling

      ii. Please revise your labeling to be in accord with the current approved labeling of the reference listed drug. We refer you to

the FDA website at
http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

b. DOSAGE AND ADMINISTRATION

i. We request that you include the following information in the DOSAGE AND ADMINISTRATION section due to the differences of your drug product from the innovator. [See comment 1(b)(ii) under CONTAINER].

A) The vial size for each strength.

B) The volume required for reconstitution for each strength.

ii. We note that you included the same text as the innovator," …6 to 10 mL Sterile Water…" in this section. However, you informed us that your (b) (4) Please revise accordingly.

iii. Intramuscular use

Although your product is "lyophilized" and not "powder filled", you recommend your drug product to be reconstituted with the same volume as the innovator for IM use," 3 mL". Has this been verified?

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 with the enclosed copy of the 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

1. The innovator's vial size is "15 mL" and the ANDA's vial sizes are "20 mL" and "30 mL". Is this acceptable?
2. The firm has the statements, "Sodium free-nonpyrogenic" and "Vial stoppers do not contain natural rubber latex". Do you concur?
4. The firm informed us that their "formulation" differs from the innovator, "powder fill" vs. "lyophilized".
   Is it acceptable for the ANDA to have a lyophilized drug product which differs from the innovator's formulation?
5. The firm indicates that the "vial sizes" differs from the innovator's because of the difference in formulation. [redacted] (b) (4)

6. Intramuscular use
   a. Has the firm submitted data to support the recommended volume for reconstitution for IM use, "i.e., 3 mL"?
   b. Does the lyophilized product and the powder filled product usually require the different volumes for diluent?
7. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION section of the insert labeling, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]? See text below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 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 USP 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection USP 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 aztreonam for injection should be constituted with 6 to 10 mL Sterile Water for Injection USP.

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 USP. Further dilution may be obtained with one of the following intravenous infusion solutions: Sodium Chloride Injection USP, 0.9%, Ringer's Injection USP
Lactated Ringer's Injection USP, Dextrose Injection USP, 5% or 10%,
Dextrose and Sodium Chloride Injection USP, 5%:0.9%,5%:0.45% or 5%:0.2%
Sodium Lactate Injection USP (M/6 Sodium Lactate),Ionosol® B and 5% Dextrose
Isolyte® E, Isolyte® E with 5% Dextrose, Isolyte® M with 5% Dextrose, Normosol®-R
Normosol®-R and 5% Dextrose, Normosol®-M and 5% Dextrose, Mannitol Injection USP, 5% or 10%, Lactated Ringer's and 5% Dextrose Injection, Plasma-Lyte® M and 5% Dextrose, 10%
Travert® Injection, 10% Travert® and Electrolyte No. 1 Injection

10% Travert® and Electrolyte No. 2 Injection, 10% Travert® and Electrolyte No. 3 Injection

Intramuscular (IM) Solutions

The contents of aztreonam for injection 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 USP, Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and propylparabens), Sodium Chloride Injection USP, 0.9%, Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol)

Stability of IV and IM Solutions

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

(b) (4)

Aztreonam for injection, USP solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection USP or Sodium Chloride Injection USP, 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.

Preparation of Parenteral Solutions/General

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

From: Cohran, Carolyn
Sent: Monday, July 30, 2007 10:37 AM
To: Council, Jacqueline
Subject: 65-439 Aztreonam for Injection

We called the firm today about the (b) (4) infusion solution study you had asked about. They said they did have the data, and they would submit it in their response to our deficiency letter.

Carolyn

Carolyn Cohran, Ph.D.
Regulatory Review Chemist
FDA/CDER/OPS/OGD/DCIII
7500 Standish Place, Room E148
MPN 2, HFD-643
Rockville, MD 20855
Tel. 301-827-5745
carolyn.cohran@fda.hhs.gov

Appears this way on original.

FOR THE RECORD:

1. Labeling model

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

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].

- The ANDA vial sizes differ from the innovator's. The RLD vial capacity is 15 mL for all three strengths, 500 mg, 1 gram and 2 grams. The ANDA vial sizes are 20 mL for the 500 mg and 1 gram strengths and 30 mL for 2 gram strength.
The RLD includes the "15 mL vial capacity" in the following portion of the labeling.

DOSAGE AND ADMINISTRATION
i Intravenous (IV) Solutions
A) For Bolus Injection –first paragraph.
B) For Infusion – second paragraph.

Generic firms should be requested to include the vial szies (b) (4) on the labels and in the PI, since if they differ from the RLD.

- The firm added the CDAD text which has not been approved yet by the RLD.

Therefore, we and either ask to delete the text prior to approval or wait until RLD approves it.

2. The listing of the active and inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the composition statement listed in the application.
[Vol. 1.1, p. 86]

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)

NOTE: The firm indicates that the drug product is lyophilized.

[Vol. 1.1, p. 86]

3. Physical Description

Dry: Slightly yellow solids
Solution: Light yellow
[Chemistry review]

4. Manufacturing Facility of the Drug Product

Abraxis Pharmaceutical Products
Grand Island, New York
[Vol. 1.1, p. 99]

5. Patent/ Exclusivities

Patent Data –

No	Expiration	Use Code	Use	File
None				

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 - Single-dose 20 mL and 30 mL capacity vials:
500 mg/vial – 10s [20 mL]
1 g/vial – 10s [20 mL]
2 g/vial - 10s [30 mL]
[See comment to the chemist]

7. Container/Closure

The configuration of container/closure system used for packaging the drug product (is summarized below:
[Vol. 1.1, p. 275 to 278]

Container/Closure	Description
20 mL and 30 mL vial	Type I USP glass
Closure	Gray rubber stoppers
Seal	Flip-off Aluminum Seals
Color	Mist gray, green and blue

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. Solution pH

USP – between 4.5 and 7.5, in a solution containing 100 mg of aztreonam per mL.
NDA – 4.5 to 7.5
ANDA – 4.5 to 7.5 [insert labeling] (b) (4) [chemistry review]
[Vol. 1.1, p. 285]

Date of Review: 12/19/07

Date of Submission: 9/11/07

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

Team Leader:
Captain Lillie Golson Date:

cc: ANDA: 65-439
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
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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
1/25/2008 07:29:30 PM
LABELING REVIEWER

Lillie Golson
1/29/2008 05:23:25 PM
LABELING REVIEWER

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

ANDA Number: 65-439

Dates of Submission: October 5, 2006

Applicant's Name: Abraxis Pharmaceutical Products

Established Name: Aztreonam for Injection USP, 500 mg, 1 gram and 2 grams

---

Labeling Deficiencies:

1. CONTAINER: 500 mg, 1 gram and 2 grams

   a. General Comment

      We note that your vial sizes are "20 mL" and "30 mL". Your vial size should be the same size as the innovator "15 mL". Revise your labels and labeling accordingly.

   b. Front panel

      i. Use the same background color for the entire established name.

      ii. Delete "/vial".

      iii. Delete "(b) (4)".

   c. Side panel

      i. (b) (4)

2. (b) (4)

   (b) (4)

3. INSERT

   a. GENERAL COMMENTS

      i. Throughout the insert labeling use the abbreviation "mcg" for micrograms instead of "µg".

      ii, We note that you have your company name printed at the top of your insert labeling. When printing final print, ensure that the established name in the Title is the most prominent text at the top of your labeling.

b. DESCRIPTION

Add the “Each vial contains…” statements to this section as seen on your container labels.

c. WARNINGS

Second paragraph

Start a new paragraph with the sentence, “While cross-reactivity …”.

d. DOSAGE AND ADMINISTRAION

i. AZTREONAM FOR INJECTION DOSAGE GUIDELINES – Tables

Add a horizontal line underneath “PEDIATRIC PATIENTS ** as seen under ADULTS”.

ii. 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.

e. HOW SUPPLIED

See comment regarding your vial size under CONTAINER.

f. At the end of your insert labeling you list Abbott Laboratories and M^{c}Graw Inc., in association with the trade name of some intravenous solution. Please ensure these are the correct manufacturers.

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://www.fda.gov/cder/cdernew/listserv.html

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 the enclosed copy of the 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

1. The innovator's vial size is "15 mL" and the ANDA's vial sizes are "20 mL" and "30 mL". We plan to inform the ANDA that the vial sizes should be the same as the innovator's, "15 mL". Do you concur with this plan?
2. The firm has the statements, "Sodium free-nonpyrogenic" and "Vial stoppers do not contain natural rubber latex". Do you concur?
3. Has the firm submitted stability data to verify the claims found in the following subsections of the DOSAGE AND ADMINISTRATION section of the insert labeling, [i.e., dilution volumes, concentration, admixture with other antibiotics and diluents]? See text below.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 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 USP 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in Dextrose Injection USP 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 aztreonam for injection should be constituted with 6 to 10 mL Sterile Water for Injection USP.

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 USP. Further dilution may be obtained with one of the following intravenous infusion solutions: Sodium Chloride Injection USP, 0.9%, Ringer's Injection USP
Lactated Ringer's Injection USP, Dextrose Injection USP, 5% or 10%,
Dextrose and Sodium Chloride Injection USP, 5%:0.9%,5%:0.45% or 5%:0.2%
Sodium Lactate Injection USP (M/6 Sodium Lactate),Ionosol® B and 5% Dextrose
Isolyte® E, Isolyte® E with 5% Dextrose, Isolyte® M with 5% Dextrose, Normosol®-R
Normosol®-R and 5% Dextrose, Normosol®-M and 5% Dextrose, Mannitol Injection USP, 5% or 10%, Lactated Ringer's and 5% Dextrose Injection, Plasma-Lyte® M and 5% Dextrose, 10% Travert® Injection, 10% Travert® and Electrolyte No. 1 Injection
10% Travert® and Electrolyte No. 2 Injection, 10% Travert® and Electrolyte No. 3 Injection

Intramuscular (IM) Solutions

The contents of aztreonam for injection 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 USP, Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and propylparabens), Sodium Chloride Injection USP, 0.9%, Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol)

Stability of IV and IM Solutions

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

(b) (4)

Aztreonam for injection, USP solutions at concentrations exceeding 2% w/v, except those prepared with Sterile Water for Injection USP or Sodium Chloride Injection USP, 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 statement listed in the application.
   [Vol. 1.1, p. 86]

   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)

   NOTE: The firm indicates that the drug product is lyophilized.

   [Vol. 1.1, p. 86]

3. Physical Description

   Dry: Slightly yellow solids
   Solution: Light yellow
   [Chemistry review]

4. Manufacturing Facility of the Drug Product

   Abraxis Pharmaceutical Products
   Grand Island, New York
   [Vol. 1.1, p. 99]

5. Patent/ Exclusivities

   Patent Data –

No	Expiration	Use Code	Use	File
None				

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 - Single-dose 20 mL and 30 mL capacity vials:
500 mg/vial – 10s [20 mL]
1 g/vial – 10s [20 mL]
2 g/vial - 10s [30 mL]
[See comment to the firm].

7. Container/Closure

The configuration of container/closure system used for packaging the drug product (is summarized below:
[Vol. 1.1, p. 275 to 278]

Container/Closure	Description
20 mL and 30 mL vial	Type I USP glass
Closure	Gray rubber stoppers
Seal	Flip-off Aluminum Seals
Color	Mist gray, green and blue

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. Solution pH

USP – between 4.5 and 7.5, in a solution containing 100 mg of aztreonam per mL.
NDA – 4.5 to 7.5
ANDA – 4.5 to 7.5 [insert labeling] (b) (4) [chemistry review]
[Vol. 1.1, p. 285]

Date of Review: 6/25/06

Date of Submission: 10/5/06

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

Team Leader:
Captain Lillie Golson Date:

cc: ANDA: 65-439
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSAM\ABRAXIS PHARMACEUTICAL PRODUCTS\LTRS&REV\65439na1.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
7/17/2007 03:38:20 PM
LABELING REVIEWER

Lillie Golson
7/23/2007 05:02:09 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065439

CHEMISTRY REVIEWS

ANDA 65-439

Aztreonam for Injection, USP
500 mg/vial, 1 g/vial, 2 g/vial

APP Pharmaceuticals, LLC

Carolyn Cohran, Ph.D.
Chemistry Division III
Office of Generic Drugs
Team 6

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 65-439

2. REVIEW #: 4

3. REVIEW DATE: December 9, 2009; updated 12/21/09, 1/21/10

4. REVIEWER: Carolyn Cohran, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Gratuitous Amendment	January 22, 2009
CMC Amendment	July 23, 2008
Minor Amendment	December 7, 2007
Gratuitous Amendment	April 13, 2007
Original	October 5, 2006 (letter date 12/20/06)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone amendment	January 19, 2010
Telephone amendment	December 18, 2009
Telephone amendment	December 9, 2009 in DARRTS 12/14/09 (Attachment 02)
Telephone amendment	December 7, 2009 in DARRTS 12/14/09 (Attachment 01)
Gratuitous amendment	November 3, 2009
Telephone amendment	September 11, 2009
CMC Amendment	April 10, 2009

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	APP Pharmaceuticals, LLC
Address:	1501 East Woodfield Road Suite 300E Schaumburg, Illinois 60173
Representative:	Georgia Hizon
Telephone:	(847) 330-3950
Fax:	(847) 413-8570

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Aztreonam for Injection, USP
   c) Code Name/# (ONDC only): N/A
   d) Chem. Type/Submission Priority (ONDC only): N/A
      - Chem. Type:
      - Submission Priority:

9. LEGAL BASIS FOR SUBMISSION: The RLD is Azactam® 500 mg/vial, 1 g/vial, and 2 g/vial, manufactured by Bristol Myers Squibb under NDA 50-580. According to the Orange Book, there are no unexpired patents and no unexpired exclusivity for this product.

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Lyophilized powder

12. STRENGTH/POTENCY: 500 mg/vial, 1 g/vial, 2 g/vial

13. ROUTE OF ADMINISTRATION: IV or IM

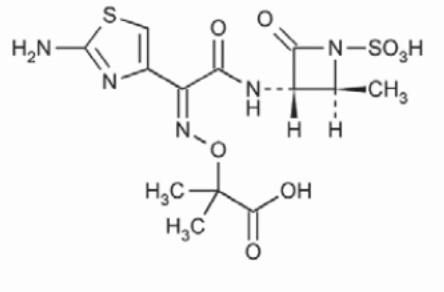
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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:

Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]oxy]-2-methyl-[2S-[2α, 3β(Z)]]-



Molecular Formula: $C_{13}H_{17}N_5O_8S_2$
Molecular Weight: 435.44 g/mole

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	A	12/3/09	C. Cohran
	III			3	A	12/15/2005	
	III			3	A	2/22/07	
	III			3	A	8/17/2006	
	III			3	A	11/12/2006	
	V			3	A	3/7/2007	

[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

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	11/26/08	J. Wells
EES	Acceptable	3/26/09	S. Ferguson
Methods Validation	N/A		
Labeling	Acceptable	10/21/09	J. Council
Bioequivalence	Bio waiver approved	2/20/2007	S. Mazzella
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only)

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 65-439

This application was a QbR submission, but there were technical difficulties with the electronic documents. As a result, it was reviewed in the CTD format.

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval is recommended.

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)

The drug product is Aztreonam for Injection, USP, 500 mg/vial, 1 g/vial, and 2 g/vial. This antibiotic is a sterile, lyophilized powder that will be reconstituted and administered by intravenous (IV) or intramuscular (IM) injection. The drug product formulation contains Aztreonam (b) (4), L-Arginine, (b) (4)

Aztreonam for Injection USP is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms: urinary tract, lower respiratory tract, septicemia, skin and skin-structure, intra-abdominal, and gynecologic infections. It is also indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscous perforations, cutaneous infections, and infections of serous surfaces. Aztreonam for Injection is packaged as strengths of 500 mg/vial, 1 g/vial, and 2 g/vial. The drug product complies with the USP monograph.

The drug substance is Aztreonam, USP, manufactured under (b) (4) DMF # (b) (4) The DMF was reviewed and found adequate. The drug substance complies with the USP monograph. The API is a synthetic bactericidal antibiotic. Aztreonam has (b) (4)

(b) (4)

.

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

Aztreonam for Injection 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.

Admixtures with other antibiotics

Aztreonam for Injection can also be prepared as an admixture with other antibiotics. Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 5%, to which clindamycin phosphate, gentamicin sulfate, tobramycin sulfate, or cefazolin sodium have been added at concentrations usually used clinically. Ampicillin sodium admixtures with aztreonam in Sodium Chloride Injection USP 0.9% are used, as well as in Dextrose Injection USP 5%. Aztreonam - cloxacillin sodium and aztreonam - vancomycin hydrochloride admixtures are stable in Dianeal® 137 with 4.25% Dextrose at certain conditions. 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 Aztreonam for Injection should be constituted with 6 – 10 ml Sterile Water for Injection.

For Infusion

The contents are to be transferred to an appropriate infusion solution, each gram of Aztreonam should be initially constituted with at least 3 ml SWFI, USP. Further dilution may be obtained with one of the following intravenous infusion solutions:

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

- Normosol®-R and 5% Dextrose
- Normosol®-M and 5% Dextrose
- Mannitol Injection USP, 5% or 10%
- Lactated Ringer's and 5% Dextrose Injection
- Plasma-Lyte® M and 5% Dextrose
- 10% Travert® Injection
- 10% Travert® and Electrolyte No. 1 Injection
- 10% Travert® and Electrolyte No. 2 Injection
- 10% Travert® and Electrolyte No. 3 Injection

Intramuscular (IM) solutions

The contents of Aztreonam for Injection 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 USP
- Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and polyparabens)
- Sodium Chloride Injection USP, 0.9%
- Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol)

The **Maximum Daily Dose** of Aztreonam is 8 g/day (2 g every 6 to 8 hours).

Information for Labeling reviewer:

The drug product is Aztreonam for Injection, USP, 500 mg/vial, 1 g/vial, and 2 g/vial. This antibiotic is a sterile, lyophilized powder that will be reconstituted and administered by intravenous (IV) or intramuscular (IM) injection. Aztreonam for Injection is packaged as strengths of 500 mg/vial, 1 g/vial, and 2 g/vial in glass vials with (b) (4) rubber stopper. The stopper is stated to not contain natural rubber (latex).

Aztreonam solutions exceeding 2% w/v concentration were prepared for IV bolus injection or IM injection. Finished products of 500 mg/vial and 2 g/vial were reconstituted with 1.5 ml and 6 ml diluents, respectively. The reconstituted solution stability of the RLD (2 g/vial) and APP's Aztreonam for Injection (500 mg/vial) using SWFI and Sodium chloride Injection as diluents were tested. The study design is provided. The duration of storage was zero time control, 48 hours at 25 ± 2°C and 7 days at 5 ± 3°C. For the reconstituted solution stability study, four parameters were studied: Visual inspection, pH, Assay, and Impurities. For the Reconstituted solution stability study, all samples passed the visual inspection test, the pH did not change significantly and was comparable with the RLD, the assay values met the label claim

limits, and while slightly higher than the RLD, impurity levels were comparable. The data was acceptable.

Abraxis also tested the LVP admixture stability of the drug product for the 500 mg/vial strength. Representative diluents, in terms of electrolytes and sugar, were tested for admixture compatibility. Diluents used in the study are as follows: Dextrose Injection USP, 10%, Dextrose and Sodium Chloride Injection USP (5%:0.9%), Sodium Lactate Injection USP (M/6 Sodium Lactate), Ionosol® B and 5% Dextrose, Lactated Ringer's and 5% Dextrose Injection, and Plasma-Lyte® M and 5% Dextrose. These same diluents were used for the (b) (4) infusion studies. LVP admixture solutions were prepared with 1.5 ml SWFI followed by dilution with secondary diluents at a final concentration of 20 mg/ml. The LVP preparations were tested at zero time point, after storage for 48 hours at 25 ± 2°C and 7 days at 5 ± 3°C. Samples were also (b) (4) (b) (4) and test performed after storage for 24 hours at 48 hours at 25 ± 2°C and 72 hours at 5 ± 3°C. For the LVP Admixture Compatibility Study, the vials parameters studied were visual inspection, pH, and assay. For the LVP Admixture stability study, the samples passed the visual inspection except for (b) (4) found in a sample. (Note: The firm was asked about issues regarding (b) (4) found in the sample, and the firm has put procedures in place to prevent reoccurrence See stability section for further details). No other (b) (4) or precipitate was found. The pH values did not change significantly from the zero time point, and the aztreonam assay concentrations met the limit. For the (b) (4) samples, samples also passed visual inspection, pH values were comparable to the zero time point, and passed the assay specifications. The data was acceptable.

C. Basis for Approvability or Not-Approval Recommendation

All questions regarding Manufacture of Drug Substance, Control of the Drug Substance Control of Excipients, Control of the Drug Product, Container Closure System of Drug Product, and Stability of the Drug Product have been adequately addressed. The ANDA is recommended for approval.

Following this page, 67 pages withheld in full - (b)(4)

cc: ANDA 65439
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/CCohran /12/9/09; 12/21/09

HFD-630/SZuk/12/17/09; 12/21/09

HFD-617/RSzydlo/12/22/09

V:\Chemistry Division III\Team 6\Final Version for DARRTS Folder\65439.R04.ap.doc

TYPE OF LETTER: APPROVABLE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-65439	ORIG-1	APP PHARMACEUTICALS LLC	AZTREONAM

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

/s/

CAROLYN F COHRAN
01/22/2010

SUSAN ZUK
01/22/2010

ROBERTA T SZYDLO
01/22/2010

ANDA 65-439

Aztreonam for Injection, USP
500 mg/vial, 1 g/vial, 2 g/vial

APP Pharmaceuticals, LLC

Carolyn Cohran, Ph.D.
Chemistry Division III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 65-439

2. REVIEW #: 3

3. REVIEW DATE: March 19, 2009

4. REVIEWER: Carolyn Cohran, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Minor Amendment	07-Dec-2007
Original	05-Oct-2006 (letter date 12/20/06)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Gratuitous Amendment	January 22, 2009
CMC Amendment	July 23, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	APP Pharmaceuticals, LLC
Address:	1501 East Woodfield Road Suite 300E Schaumburg, Illinois 60173
Representative:	Georgia Hizon
Telephone:	(847) 330-3950
Fax:	(847) 413-8570

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Aztreonam for Injection, USP
   c) Code Name/# (ONDC only): N/A
   d) Chem. Type/Submission Priority (ONDC only): N/A
      - Chem. Type:
      - Submission Priority:

9. LEGAL BASIS FOR SUBMISSION: The RLD is Azactam® 500 mg/vial, 1 g/vial, and 2 g/vial, manufactured by Bristol Myers Squibb under NDA 50-580. According to the Orange Book, there are no unexpired patents and no unexpired exclusivity for this product.

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Lyophilized powder

12. STRENGTH/POTENCY: 500 mg/vial, 1 g/vial, 2 g/vial

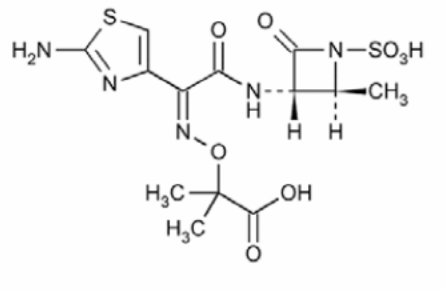
13. ROUTE OF ADMINISTRATION: IV or IM

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:
    Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]oxy]-2-methyl-[2S-[2α, 3β(Z)]]-



Molecular Formula: $C_{13}H_{17}N_5O_8S_2$
Molecular Weight: 435.44 g/mole

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	I	3/19/09	C. Cohran
	III			3	A	12/15/2005	
	III			3	A	2/22/07	
	III			3	A	8/17/2006	
	III			3	A	11/12/2006	
	V			3	A	3/7/2007	

[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

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	11/26/08	J. Wells *Not yet in Micro database*
EES	Acceptable	4/19/07	S. Ferguson
Methods Validation	N/A		
Labeling	Pending		J. Council
Bioequivalence	Bio waiver approved	2/20/2007	S. Mazzella
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only)

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 65-439

This application was a QbR submission, but there were technical difficulties with the electronic documents. As a result, it was reviewed in the CTD format.

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval is not recommended.

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)

The drug product is Aztreonam for Injection, USP, 500 mg/vial, 1 g/vial, and 2 g/vial. This antibiotic is a sterile, lyophilized powder that will be reconstituted and administered by intravenous (IV) or intramuscular (IM) injection. The drug product formulation contains Aztreonam (b) (4), L-Arginine, (b) (4) (b) (4). It is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms: urinary tract, lower respiratory tract, septicemia, skin and skin-structure, intra-abdominal, and gynecologic infections. It is also 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 for Injection is packaged as strengths of 500 mg/vial, 1 g/vial, and 2 g/vial.

The drug substance is Aztreonam, USP, manufactured under (b) (4) DMF # (b) (4) The DMF was reviewed and found inadequate. The API is a synthetic bactericidal antibiotic. Aztreonam has (b) (4)

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

Aztreonam for Injection 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.

Admixtures with other antibiotics

Aztreonam for Injection can also be prepared as an admixture with other antibiotics. Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 5%, to which clindamycin phosphate, gentamicin sulfate, tobramycin sulfate, or cefazolin sodium have been added at concentrations usually used clinically. Ampicillin sodium admixtures with aztreonam in Sodium Chloride Injection USP 0.9% are used, as well as in Dextrose Injection USP 5%. Aztreonam - cloxacillin sodium and aztreonam - vancomycin hydrochloride admixtures are stable in Dianeal® 137 with 4.25% Dextrose at certain conditions. 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 Aztreonam for Injection should be constituted with 6 – 10 ml Sterile Water for Injection.

For Infusion

The contents are to be transferred to an appropriate infusion solution, each gram of Aztreonam should be initially constituted with at least 3 ml SWFI, USP. Further dilution may be obtained with one of the following intravenous infusion solutions:

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

- Plasma-Lyte® M and 5% Dextrose
- 10% Travert® Injection
- 10% Travert® and Electrolyte No. 1 Injection
- 10% Travert® and Electrolyte No. 2 Injection
- 10% Travert® and Electrolyte No. 3 Injection

Intramuscular (IM) solutions

The contents of Aztreonam for Injection 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 USP
- Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and polyparabens)
- Sodium Chloride Injection USP, 0.9%
- Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol)

The **Maximum Daily Dose** of Aztreonam is 8 g/day (2 g every 6 to 8 hours).

Information for Labeling reviewer:

The drug product is Aztreonam for Injection, USP, 500 mg/vial, 1 g/vial, and 2 g/vial. This antibiotic is a sterile, lyophilized powder that will be reconstituted and administered by intravenous (IV) or intramuscular (IM) injection. Aztreonam for Injection is packaged as strengths of 500 mg/vial, 1 g/vial, and 2 g/vial in glass vials with (b) (4) rubber stopper. The stopper is stated to not contain natural rubber (latex).

Aztreonam solutions exceeding 2% w/v concentration were prepared for IV bolus injection or IM injection. Finished products of 500 mg/vial and 2 g/vial were reconstituted with 1.5 ml and 6 ml diluents, respectively. The reconstituted solution stability of the RLD (2 g/vial) and APP's Aztreonam for Injection (500 mg/vial) using SWFI and Sodium chloride Injection (NS) as diluents were tested. The study design is provided. The duration of storage was zero time control, 48 hours at 25 ± 2°C and 7 days at 5 ± 3°C. For the reconstituted solution stability study, four parameters were studied: Visual inspection, pH, Assay, and Impurities. For the Reconstituted solution stability study, all samples passed the visual inspection test, the pH did not change significantly and was comparable with the RLD, the assay values met the label claim limits, and while slightly higher than the RLD, impurity levels were comparable. The data was acceptable.

Abraxis also tested the LVP admixture stability of the drug product for the 500 mg/vial strength. Representative diluents, in terms of electrolytes and sugar, were tested for

admixture compatibility. Diluents used in the study are as follows: Dextrose Injection USP, 10%, Dextrose and Sodium Chloride Injection USP (5%:0.9%), Sodium Lactate Injection USP (M/6 Sodium Lactate), Ionosol® B and 5% Dextrose, Lactated Ringer's and 5% Dextrose Injection, and Plasma-Lyte® M and 5% Dextrose. These same diluents were used for the (b) (4) infusion studies. LVP admixture solutions were prepared with 1.5 ml SWFI followed by dilution with secondary diluents at a final concentration of 20 mg/ml. The LVP preparations were tested at zero time point, after storage for 48 hours at 25 ± 2°C and 7 days at 5 ± 3°C. Samples were also (b) (4) (b) (4) and test performed after storage for 24 hours at 48 hours at 25 ± 2°C and 72 hours at 5 ± 3°C. For the LVP Admixture Compatibility Study, the vials parameters studied were visual inspection, pH, and assay. For the LVP Admixture stability study, the samples passed the visual inspection except for (b) (4) found in a sample. No other (b) (4) or precipitate was found. The pH values did not change significantly from the zero time point, and the aztreonam assay concentrations met the limit. For the (b) (4) samples, samples also passed visual inspection, pH values were comparable to the zero time point, and passed the assay specifications. The data was acceptable.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not recommended for approval for the following deficiencies:

1. Manufacture of Drug Substance
2. Control of the Drug Substance
3. Control of Excipients
4. Control of the Drug Product
5. Container Closure System of Drug Product
6. Stability of the Drug Product

Following this page, 57 pages withheld in full - (b)(4)

R3 **Methods Validation Package** See Module 3 evaluation above.

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

A. Labeling & Package Insert

The structure, description, ingredients, and "How Supplied" section match information provided in the RLD insert and in Module 3 of this application.

B. Environmental Assessment Or Claim Of Categorical Exclusion

III. List Of Deficiencies To Be Communicated

See letter.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-439 APPLICANT: APP Pharmaceuticals, LLC

DRUG PRODUCT: Aztreonam for Injection USP, 500 mg/vial, 1 g/vial, and 2 g/vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

Following this page, 1 page 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. DMF # [redacted] (b) (4) was reviewed and found not adequate. The deficiencies have been communicated to the DMF holder. Please be aware this ANDA cannot be approved until all DMF deficiencies are resolved satisfactorily.

2. Please provide updated stability data from on-going stability studies.

Sincerely yours,

{See appended electronic signature page}

Vilayat Sayeed
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 65439
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/CCohran /03/19/09

HFD-630/SZuk/3/20/09

HFD-617/RSzydlo/3/24/09

V:\Chemistry Division III\Team 6\Final Version for DFS Folder\65439.R03.na.doc

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/

Carolyn Cohran
3/25/2009 09:50:34 AM
CHEMIST

Roberta Szydlo
3/25/2009 10:33:24 AM
CSO

Susan Zuk
3/25/2009 11:56:55 AM
CHEMIST

ANDA 65-439

Aztreonam for Injection, USP
500 mg/vial, 1 g/vial, 2 g/vial

Carolyn Cohran, Ph.D.
Chemistry Division III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 65-439

2. REVIEW #: 2

3. REVIEW DATE: June 8, 2008

4. REVIEWER: Carolyn Cohran, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	05-Oct-2006 (letter date 12/20/06)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	07-DEC-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	APP Pharmaceuticals, LLC
Address:	1501 East Woodfield Road Suite 300E Schaumburg, Illinois 60173
Representative:	Georgia Hizon
Telephone:	(847) 330-3950
Fax:	(847) 413-8570

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Aztreonam for Injection, USP
   c) Code Name/# (ONDC only): N/A
   d) Chem. Type/Submission Priority (ONDC only): N/A
      - Chem. Type:
      - Submission Priority:

9. LEGAL BASIS FOR SUBMISSION: The RLD is Azactam® 500 mg/vial, 1 g/vial, and 2 g/vial, manufactured by Bristol Myers Squibb under NDA 50-580. According to the Orange Book, there are no unexpired patents and no unexpired exclusivity for this product.

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Lyophilized powder

12. STRENGTH/POTENCY: 500 mg/vial, 1 g/vial, 2 g/vial

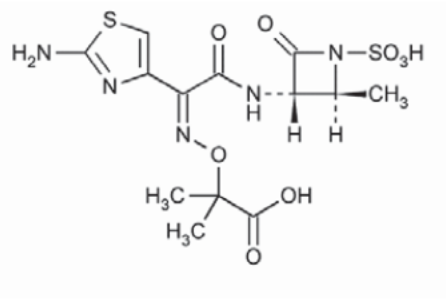
13. ROUTE OF ADMINISTRATION: IV or IM

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:
    Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]oxy]-2-methyl-[2S-[2α, 3β(Z)]]-



Molecular Formula: $C_{13}H_{17}N_5O_8S_2$
Molecular Weight: 435.44 g/mole

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	2	I	5/19/08	C. Cohran
	III			3	A	12/15/2005	
	III			3	A	2/22/07	
	III			3	A	8/17/2006	
	III			3	A	11/12/2006	
	V			3	A	3/7/2007	

[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

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Acceptable	4/19/07	S. Ferguson
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Bio waver approved	2/20/2007	S. Mazzella
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only)

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 65-439

This application was a QbR submission, but there were technical difficulties with the electronic documents. As a result, it was reviewed in the CTD format.

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval is not recommended.

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)

The drug product is Aztreonam for Injection, USP, 500 mg/vial, 1 g/vial, and 2 g/vial. This antibiotic is a sterile, lyophilized powder that will be reconstituted and administered by intravenous (IV) or intramuscular (IM) injection. The drug product formulation contains Aztreonam, L-Arginine, (b) (4) (b) (4). It is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms: urinary tract, lower respiratory tract, septicemia, skin and skin-structure, intra-abdominal, and gynecologic infections. It is also 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 for Injection is packaged as strengths of 500 mg/vial, 1 g/vial, and 2 g/vial.

The drug substance is Aztreonam, USP, manufactured under (b) (4) DMF # (b) (4). The DMF was reviewed and found inadequate. The API is a synthetic bactericidal antibiotic. Aztreonam has (b) (4)

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

Aztreonam for Injection 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.

Admixtures with other antibiotics

Aztreonam for Injection can also be prepared as an admixture with other antibiotics. Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 5%, to which clindamycin phosphate, gentamicin sulfate, tobramycin sulfate, or cefazolin sodium have been added at concentrations usually used clinically. Ampicillin sodium admixtures with aztreonam in Sodium Chloride Injection USP 0.9% are used, as well as in Dextrose Injection USP 5%. Aztreonam - cloxacillin sodium and aztreonam - vancomycin hydrochloride admixtures are stable in Dianeal® 137 with 4.25% Dextrose at certain conditions. 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 Aztreonam for Injection should be constituted with 6 – 10 ml Sterile Water for Injection.

For Infusion

The contents are to be transferred to an appropriate infusion solution, each gram of Aztreonam should be initially constituted with at least 3 ml SWFI, USP. Further dilution may be obtained with one of the following intravenous infusion solutions:

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

- Plasma-Lyte® M and 5% Dextrose
- 10% Travert® Injection
- 10% Travert® and Electrolyte No. 1 Injection
- 10% Travert® and Electrolyte No. 2 Injection
- 10% Travert® and Electrolyte No. 3 Injection

Intramuscular (IM) solutions

The contents of Aztreonam for Injection 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 USP
- Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and polyparabens)
- Sodium Chloride Injection USP, 0.9%
- Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol)

The **Maximum Daily Dose** of Aztreonam is 8 g/day (2 g every 6 to 8 hours).

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not recommended for approval for the following deficiencies:

1. Control of the Drug Substance
2. Manufacture of the Drug Substance
3. Control of the Drug Product
4. Stability of the Drug Product

Following this page, 60 pages withheld in full - (b)(4)

(b) (4)

See batch analysis section above for COA information.

Please provide (b) (4) stability data from APP's drug product (b) (4) (b) (4).(Please note that this request was made by the Agency via telephone communication between Susan Zuk, FDA and Georgia Hizon, APP on 7/30/07
RESPONSE: The (b) (4) ***stability data from APP's drug product is provided in the protocol amendment 1 final report for Reconstituted Solution Stability and LVP Admixture Compatibility Studies of Aztronam for Injection. – This report data is summarized above. The response is acceptable.***

R2 Comparability Protocols
R3 Methods Validation Package See Module 3 evaluation above.

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

A. Labeling & Package Insert

The structure, description, ingredients, and "How Supplied" section match information provided in the RLD insert and in Module 3 of this application.

B. Environmental Assessment Or Claim Of Categorical Exclusion

III. List Of Deficiencies To Be Communicated

See letter.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

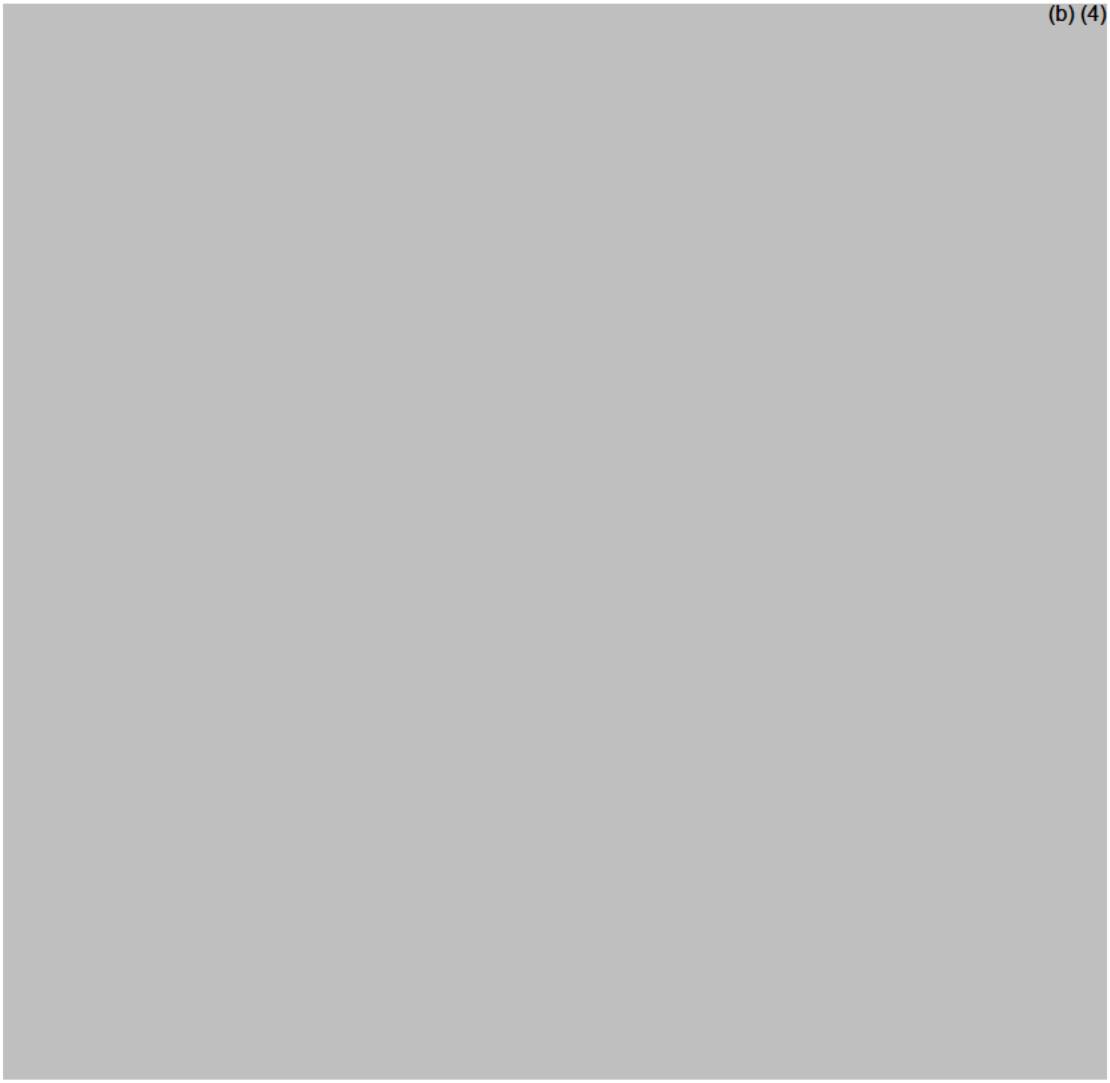
ANDA: 65-439 APPLICANT: APP Pharmaceuticals, LLC

DRUG PRODUCT: Aztreonam for Injection, USP

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)



B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. DMF [redacted] (b) (4) was reviewed and found not adequate. The deficiencies have been communicated to the DMF holder. Please be aware this ANDA cannot be approved until all DMF deficiencies are resolved satisfactorily.

2. Please provide updated stability data for the stability batches.

Sincerely yours,

{See appended electronic signature page}

Vilayat Sayeed
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 65439
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/CCohran /6/8/08

HFD-630/SZuk/6/10/08

HFD-617/RSzydlo/6/12/08

V:\Chemistry Division III\Team 6\Final Version for DFS Folder\65439.R02.na.doc

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/

Carolyn Cohran
6/13/2008 03:24:04 PM
CHEMIST

Roberta Szydlo
6/13/2008 03:32:18 PM
CSO

Susan Zuk
6/13/2008 03:34:00 PM
CHEMIST

ANDA 65-439

Aztreonam for Injection, USP
500 mg/vial, 1 g/vial, 2 g/vial

Carolyn Cohran, Ph.D.
Chemistry Division III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 65-439

2. REVIEW #: 1

3. REVIEW DATE: April 26, 2007

4. REVIEWER: Carolyn Cohran, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	---

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	05-Oct-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Abraxis Pharmaceutical Products
Address:	6133 North River Road, Suite 500, Rosemont, Illinois 60018
Representative:	Georgia Hizon
Telephone:	(847) 939-8110

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Aztreonam for Injection, USP
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only): N/A

- Chem. Type:
- Submission Priority:

9. LEGAL BASIS FOR SUBMISSION: The RLD is Azactam® 500 mg/vial, 1 g/vial, and 2 g/vial, manufactured by Bristol Myers Squibb under NDA 50-580. According to the Orange Book, there are no unexpired patents and no unexpired exclusivity for this product.

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Lyophilized powder

12. STRENGTH/POTENCY: 500 mg/vial, 1 g/vial, 2 g/vial

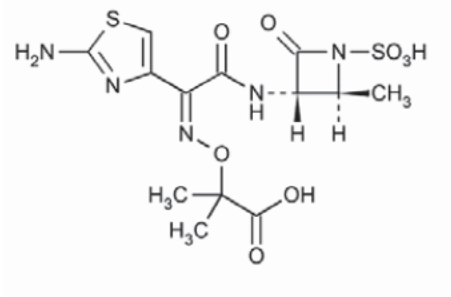
13. ROUTE OF ADMINISTRATION: IV or IM

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:
Propanoic acid, 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]oxy]-2-methyl-[2S-[2α, 3β(Z)]]-



Molecular Formula: $C_{13}H_{17}N_5O_8S_2$
Molecular Weight: 435.44 g/mole

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	I	4/9/07	C. Cohran
	III			3	A	12/15/2005	
	III			3	A	2/22/07	
	III			3	A	8/17/2006	
	III			3	A	11/12/2006	
	V			3	A	3/7/2007	

[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

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending	–	
EES	Inspection pending	12/19/2006	
Methods Validation	N/A		
Labeling	Pending	–	
Bioequivalence	Bio waver approved	2/20/2007	
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only)

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 65-439

This application was a QbR submission, but there were technical difficulties with the electronic documents. As a result, it was reviewed in the CTD format.

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval is not recommended.

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)

The drug product is Aztreonam for Injection, USP, 500 mg/vial, 1 g/vial, and 2 g/vial. This antibiotic is a sterile, lyophilized powder that will be reconstituted and administered by intravenous (IV) or intramuscular (IM) injection. The drug product formulation contains Aztreonam, L-Arginine, (b) (4) (b) (4). It is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms: urinary tract, lower respiratory tract, septicemia, skin and skin-structure, intra-abdominal, and gynecologic infections. It is also 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 for Injection is packaged as strengths of 500 mg/vial, 1 g/vial, and 2 g/vial.

The drug substance is Aztreonam, USP, manufactured under (b) (4) DMF # (b) (4) The DMF was reviewed and found inadequate. The API is a synthetic bactericidal antibiotic. Aztreonam has (b) (4)

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

Aztreonam for Injection 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.

Admixtures with other antibiotics

Aztreonam for Injection can also be prepared as an admixture with other antibiotics. Intravenous infusion solutions of aztreonam for injection not exceeding 2% w/v prepared with Sodium Chloride Injection USP 0.9% or Dextrose Injection USP 5%, to which clindamycin phosphate, gentamicin sulfate, tobramycin sulfate, or cefazolin sodium have been added at concentrations usually used clinically. Ampicillin sodium admixtures with aztreonam in Sodium Chloride Injection USP 0.9% are used, as well as in Dextrose Injection USP 5%. Aztreonam - cloxacillin sodium and aztreonam - vancomycin hydrochloride admixtures are stable in Dianeal® 137 with 4.25% Dextrose at certain conditions. 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 Aztreonam for Injection should be constituted with 6 – 10 ml Sterile Water for Injection.

For Infusion

The contents are to be transferred to an appropriate infusion solution, each gram of Aztreonam should be initially constituted with at least 3 ml SWFI, USP. Further dilution may be obtained with one of the following intravenous infusion solutions:

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

- Plasma-Lyte® M and 5% Dextrose
- 10% Travert® Injection
- 10% Travert® and Electrolyte No. 1 Injection
- 10% Travert® and Electrolyte No. 2 Injection
- 10% Travert® and Electrolyte No. 3 Injection

Intramuscular (IM) solutions

The contents of Aztreonam for Injection 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 USP
- Sterile Bacteriostatic Water for Injection, USP (with benzyl alcohol or with methyl- and polyparabens)
- Sodium Chloride Injection USP, 0.9%
- Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol)

The **Maximum Daily Dose** of Aztreonam is 8 g/day (2 g every 6 to 8 hours).

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not recommended for approval for the following deficiencies:

1. Manufacture of the Drug Substance
2. Characterization of the Drug Substance
3. Control of the Drug Substance
4. Control of the Drug Product
5. Stability of the Drug Product

Following this page, 55 pages withheld in full - (b)(4)

III. List Of Deficiencies To Be Communicated

See letter.

Appears this way on original.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-439 APPLICANT: Abraxis Pharmaceutical Products

DRUG PRODUCT: Aztreonam for Injection USP, 500 mg/vial, 1 g/vial, and 2 g/vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

Following this page, 1 page withheld in full - (b)(4)

(b) (4)

20.

21.

22.

23.

24.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. DMF # (b) (4) was reviewed and found not adequate. The deficiencies have been communicated to the DMF holder. Please be aware this ANDA cannot be approved until all DMF deficiencies are resolved satisfactorily.

2. Please provide updated stability data for the stability batches.

Chemistry Assessment Section

OGD is changing its CMC review process though our question based review (QbR) initiative, which is described in more detail on the OGD website: http://www.fda.gov/cder/ogd/QbR.htm.

OGD's QbR was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD), a submission format adopted by multiple regulatory bodies including the FDA. Generic firms are strongly recommended to submit their ANDAs in the CTD format (either eCTD or paper) to facilitate the implementation of the QbR and to avoid undue delays in the review of their applications.

Because of the increasing number of ANDA submissions OGD receives each year, the Quality Overall Summary (QOS) part of the CTD format is extremely important to making our new review process more efficient. Beginning in January 2007, all ANDA applicants are recommended to provide an electronic copy of a QOS that addresses OGD's QbR questions. The QbR-Quality Overall Summary Outline posted on our webpage http://www.fda.gov/cder/ogd/ contains all the questions to prepare the QOS. The QOS should be submitted in both MS Word and pdf format along with the paper or electronic submission. The QOS should be provided even if the remainder of the application is not in CTD format. OGD has prepared QOS models that can be found on the OGD web site. We ask you to use these as a guide for your submissions.

If you are already submitting QbR-based applications, we would like to take this opportunity to thank you for supporting this very important initiative.

Sincerely yours,

{See appended electronic signature page}

Vilayat Sayeed
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 65-439
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/CCohran /04/26/07/

HFD-643/SZuk/5/1/07/

HFD-630/RNguyen/5/4/07/

F/T by

V:\Chemistry Division III\Team 6\Final Version for DFS Folder\65439.R01.na.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

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/s/

Carolyn Cohran
5/4/2007 12:30:05 PM
CHEMIST

Ryan Nguyen
5/4/2007 05:06:00 PM
CSO

Susan Zuk
5/4/2007 05:11:00 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065439

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	65-439
Drug Product Name	Aztrenonam for Injection, USP
Strength	500 mg/vial, 1g/vial, and 2 g/vial
Applicant Name	Abraxis Pharmaceutical Products
Address	Rosemont, IL
Submission Date(s)	October 5, 2006
Amendment Date(s)	
Reviewer	Steven Mazzella,R.Ph.
First Generic	NO

I. Submission Summary

A. Drug Product Information

Test Product	Aztrenonam for Injection USP, 500 mg/vial, 1g/vial, and 2 g/vial
Reference Product	Azactam® Aztrenonam for Injection USP , 500 mg/vial, 1g/vial, and 2 g/vial
RLD Manufacturer	Bristol Myers Squibb
NDA No.	050580
RLD Approval Date	December 31, 1986 (per Orange Book)
Indication	Infections caused by susceptible gram negative microorganisms

B. Formulation

Ingredients/Formulation 1	Test (mg/vial)	Reference (mg/vial)
Aztreonam, USP	**500**	**500**
L-Arginine, USP	**390**	**390**

Ingredients/Formulation 2	Test (g/vial)	Reference (g/vial)
Aztreonam, USP	**1**	**1**
L-Arginine, USP	**0.780**	**0.780**

Ingredients/Formulation 3	Test (g/vial)	Reference (g/vial)
Aztreonam, USP	**2**	**2**
L-Arginine, USP	**1.560**	**1.560**

Recommendations

The Division of Bioequivalence agrees that the information submitted by Abraxis Pharmaceutical Products demonstrates that its test product, Aztrenonam for Injection USP, 500 mg/vial, 1g/vial, and 2 g/vial , fall under the criteria set forth in 21 CFR 320.22(b)(1) of the Bioavailability/ Bioequivalence Regulations. The waiver is granted.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-439 APPLICANT: Abraxis Pharmaceutical Products

DRUG PRODUCT: Aztrenonam for Injection USP, 500 mg/vial, 1g/vial, and 2 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

ANDA 65-439
BIOEQUIVALENCE – ACCEPTABLE
Submission date: October 5, 2006

1. **WAIVER** (WAI)

Strengths:
500 mg/vial, 1g/vial, and 2 g/vial
Outcome:AC

Outcome: AC- Acceptable

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/s/

Steven Mazzella
2/16/2007 06:58:09 AM
BIOPHARMACEUTICS

Lizzie Sanchez
2/16/2007 04:23:53 PM
BIOPHARMACEUTICS

Dale Conner
2/20/2007 01:21:58 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065439

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

05 Nov 2008

ANDA: 65-439

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
10/29/08	10/30/08	N/A	11/4/08

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
10/5/06	1	4/19/08

Applicant/Sponsor
Name: APP
Address: 1501 East Woodfield Rd, Suite 300E, Schaumburg, IL 60173
Representative: Georgia Hizon
Telephone: (847) 330-3950

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 to original ANDA

2. **SUBMISSION PROVIDES FOR:** Response to microbiology deficiencies

3. **MANUFACTURING SITE:** Abraxis Pharmaceutical Products, 3159 Staley Road, Grand Island, New York 14072

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile lyophilized powder for IM or IV injection, 500 mg/ vial and 1 g/vial in 20 mL vials and 2 g/vial in 30 mL vials, single dose.

5. **METHOD(S) OF STERILIZATION:** (b) (4) (b) (4).

6. **PHARMACOLOGICAL CATEGORY:** Indicated for the treatment of infections caused by susceptible gram negative organisms.

B. **SUPPORTING/RELATED DOCUMENTS:**
ANDA 78-651 and associated microbiology reviews 78-651a1.doc and 78-651a2 by P. Dexter, dated 7/10/2008 and 8/27/2008, respectively

C. **REMARKS:** The same (b) (4) validation information provided in the subject amendment was provided in the amendments to ANDA 78-651.

filename: 65-439a1.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)

[redacted]

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/ LCDR Paul Dexter, M.S.

C. CC Block

cc: Field Copy

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/s/

Jesse Wells
11/25/2008 10:38:01 AM
MICROBIOLOGIST

Mark Anderson
11/25/2008 11:14:34 AM
MICROBIOLOGIST

checked for correct linking

Neal Sweeney
11/25/2008 11:19:56 AM
MICROBIOLOGIST

Paul Dexter
11/26/2008 07:48:24 AM
MICROBIOLOGIST

Product Quality Microbiology Review

19 Apr 2008

ANDA: 65-439

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
10/5/2006	10/6/2006	N/A	4/15/2008

Submission History (for amendments only)
None

Applicant/Sponsor
Name: Abraxis Pharmaceutical Products
Address: 6133 North River Road, Suite 500, Rosemont, IL 60018
Representative: Georgia Hizon
Telephone: (847) 939-8110

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 a sterile drug product

3. **MANUFACTURING SITE:** Abraxis Pharmaceutical Products, 3159 Staley Road, Grand Island, New York 14072

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile lyophilized powder for IM or IV injection, 500 mg/ vial and 1 g/vial in 20 mL vials and 2 g/vial in 30 mL vials, single dose.

5. **METHOD(S) OF STERILIZATION:** (b) (4) (b) (4).

6. **PHARMACOLOGICAL CATEGORY:** Indicated for the treatment of infections caused by susceptible gram negative organisms.

B. **SUPPORTING/RELATED DOCUMENTS:**

DMF (b) (4). LOA p. 341

ANDA 78-718 and associated microbiology review 78-718.doc by P. Dexter, dated 3/10/2008.

ANDA 78-052 and associated microbiology reviews 78-052 and 78-052a1 by L. Shelton, dated 1/4/07 and 3/26/07, respectively.

C. **REMARKS:** Some of the validation information for equipment and (b) (4) (b) (4) in the subject ANDA is the same as that submitted for ANDAs 78-718 and 78-052.

filename: 65-439.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 can be found in the "Product Quality Microbiology Review" and "List of Comments and Deficiencies" 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) validation information.

C. Assessment of Risk Due to Microbiology Deficiencies – The safety risk due to microbiology deficiencies is considered moderate.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist /Jesse Wells, Ph.D.
Microbiology Supervisor/Neal Sweeney, Ph.D.

C. CC Block

cc: Field Copy

Following this page, 18 pages withheld in full - (b)(4)

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 65-439 APPLICANT: Abraxis Pharmaceutical Products

DRUG PRODUCT: Aztreonam for Injection, USP

A. Microbiology Deficiencies:

1. (b) (4)
2.
3.
4.
5.
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8.

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}

Neal J. Sweeney, Ph.D.
Microbiology Supervisor
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Jesse Wells
9/16/2008 08:30:26 AM
MICROBIOLOGIST

Mark Anderson
9/16/2008 12:14:10 PM
MICROBIOLOGIST

checked for correct linking

Neal Sweeney
9/16/2008 12:40:10 PM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 065439

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 065439 Applicant APP Pharmaceuticals, LLC
Drug Aztreonam for Injection Strength(s)500 mg/vial, 1 g/vial, and 2 g/vial

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch
Date5 January 2010 Date 6/18/10
InitialsMHS Initials rlw

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
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked N/A
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days:Yes ☐ No ☐ Study Submitted ☐
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:Full Approval.
Comments:ANDA submitted on 10/6/2006, BOS=Azactam NDA 50-580, PI cert provided. ANDA ack for filing on 10/6/2006(LO dated 12/20/2006). There are no listed patents which protect the RLD. It is noted that the 500 mg/vial strength of the RLD is currently in the D/C'd section of the OB. Technically, per the regulations, the Agency should make a determination that the 500 mg/vial product of NDA 50-580 was not discontinued for reasons of safety or efficacy prior to approving an ANDA for the 500 mg/vial strength. Since the 1 g/vial and 2 g/vial strengths remain in the active section of the OB it appears unlikely that the 500 mg/vial strength was D/C'd for reasons of S or E. Upper management from within OGD can decide whether to proceed with approval of all three strength without the FR notice. If it is decided that the FR notice is needed then the sponsor can w/d the 500 mg strength and OGD can move forward with approving the 1 g/vial and 2 g/vial presentations.

2. Project Manager, Roberta Szydlo Team6
Review Support Branch
Date12/23/09 Date_____
Initialsrts Initials_____

Original Rec'd date10/5/06
Date Acceptable for Filing10/6/06
Patent Certification (type)1
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio review tabbed Yes ☒ No ☐
Bio Review Filed Electronically: Yes ☒ No ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 3/26/09
Date of Office Bio Review 2/20/07
Date of Labeling Approv. Sum 10/21/09
Labeling Acceptable Email Rec'd Yes ☐ No ☐
Labeling Acceptable Email filed Yes ☐ No ☐
Date of Sterility Assur. App. 11/26/08
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:First generic under expedited review status due to shortage and medical necessity.

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date1/4/10 Date 6/18/10
Name/Initialsrts for JC Name/Initials rlw/for

Comments:
Good afternoon Roberta and Lillie,

The approval summary is still current, [no new RLD labeling].

Jacqueline

From: Szydlo, Roberta
Sent: Wednesday, December 23, 2009 8:40 AM
To: Council, Jacqueline; Golson, Lillie D
Subject: Labeling concurrence, ANDA 65439, Aztreonam FIJ, APP Pharmaceuticals

Hello Jacqueline and Lillie,

Please provide labeling concurrence for ANDA 65439, Aztreonam for Injection USP, 500 mg/vial, 1 g/vial, and 2 g/vial from APP Pharmaceuticals.

<< File: 65439.label.pdf >> << File: 65439.ap.ltr.doc >>

Thanks,
Roberta

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 6/18/10
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments: N/A. There are no patents listed in the current "Orange Book" for this drug product.

5. Div. Dir./Deputy Dir. Date1/21/10
Chemistry Div. III Initials DSG
Comments:cmc acceptable.

6. Frank Holcombe **First Generics Only** Date3/2/2010
Assoc. Dir. For Chemistry Initials RMP
Comments: (First generic drug review)
CMC is satisfactory.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Azactam for Injection, 500 mg/vial, i gram/vial and 2 grams/vial
Bristol Myers Squibb NDA 50-580

8. Peter Rickman Date 6/18/10
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Bioequivalence waiver grante dunder 21 CFR 320.22(b)(1). Drug product is "Q&Q" to the RLD. Office-level bio endorsed 2/20/07.

Microbiology/Sterility Assurance found acceptable for approval (Microbiology Review # 2) 11/26/08.

Final-printed labeling (FPL) found acceptable for approval 4/16/09, as endorsed 10/21/09.

CMC found acceptable for approval (Chemistry Review #4).

OR

8. Robert L. West — Date 6/18/10
Deputy Director, OGD — Initials RLWest
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 6/15/10 (Verified 6/18/10). No "OAI" Alerts noted.

There are no patents or exclusivity currently listed in the "Orange Book" for this drug product.

It is noted that the 500 mg strength of this product is currently listed in the "Discontinued" section of the "Orange Book". In view of the fact that this ANDA was granted "expedited review" status based upon multiple criteria stated in the CDER MaPP 5240.3, we will defer a determination as to whether the 500 mg strength was discontinued for reasons of safety or effectiveness. The retention of the 1 gram and 2 gram strengths provides evidence that it was not.

This ANDA is recommended for approval.

9. Gary Buehler — Date 6/18/10
Director, OGD — Initials rlw/for
Comments: for Keith Webber, Ph.D. Deputy Director, OPS
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Mark Gonitzke — Date6/18/10
Review Support Branch — Initials mg

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
6/18/10 Date notified of approval by phone
6/18/10 Date approval letter faxed

FDA Notification:
6/18/10 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
DARRTS Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

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ORANGE BOOK PRINT OFF:

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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 April, 2010
Patent and Generic Drug Product Data Last Updated: June 16, 2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-65439	ORIG-1	APP PHARMACEUTICALS LLC	AZTREONAM

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/s/

MARK A GONITZKE
06/18/2010

Consult Request for ANDA # 65-439

Aztreonam, 500 mg, 1 g and 2 g/vial

From: Wendelyn Schmidt, Ph.D, Pharmacology/Toxicology Supervisor, DAIOP

Through: Roberta Szydlo, Probject Manager

Date: August 17, 2009

Background:

Aztreonam has been used intravenously for the treatment of infection at up to 8 g/day for adults and 120 mg/kg/day for pediatric patients for a minimum of 2 days through several weeks, depending on the persistence and severity of infection. (b) (4)

No new toxicology studies were conducted to investigate (b) (4)

Conclusions: The main risk with (b) (4) of these impurities is (b) (4) (b) (4) of aztreonam. As always, the levels of impurities should be kept as low as feasible.

Recommendation: There does not appear to be an increased risk to patients with the proposed specifications of the impurities listed above.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
ANDA 65439	ORIG 1		AZTREONAM
ANDA 65439	ORIG 1		AZTREONAM
ANDA 65439	ORIG 1		AZTREONAM
ANDA 65439	ORIG 1		AZTREONAM
ANDA 65439	ORIG 1		AZTREONAM

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/s/

WENDELYN J SCHMIDT
08/17/2009

TELEPHONE CONFERENCE FAX

ANDA 65439

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: APP Pharmaceuticals, LLC TEL: 847-330-3950

ATTN: Georgia Hizon FAX: 847-413-8570

FROM: Roberta Szydlo FDA CONTACT PHONE: (240) 276-8476

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated October 5, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Aztreonam for Injection USP, 500 mg/vial, 1 g/vial, 2 g/vial.

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" within ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Roberta Szydlo at (240) 276-8476. Please submit documentation by fax to the attention of the Project Manager at (240) 276-8474. Please also submit official hard copies of any faxed documentation to the Document Room.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

Deficiencies for ANDA 65-439 **Aztreonam for Injection USP, 500 mg/vial, 1 g/vial, 2 g/vial**

1. (b) (4)
2.
3.
4.
5.
6.
7.

In addition to responding to the deficiencies presented above, please provide updated stability data.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-65439	ORIG-1	ABRAXIS PHARMACEUTICAL PRODUCTS	AZTREONAM
ANDA-65439	ORIG-1	ABRAXIS PHARMACEUTICAL PRODUCTS	AZTREONAM

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/s/

CAROLYN F COHRAN
09/04/2009

ROBERTA T SZYDLO
09/04/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2009-0325	
TO *(Division/Office)* DAIOP - HFD-520 Thru: David Roeder, ODEIV HFD-104			FROM: Roberta Szydlo	
DATE: 4/24/2009	IND NO.	ANDA NO. 065439	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 4/10/2009,7/23/08, 1/11/09
NAME OF DRUG AZTREONAM		PRIORITY CONSIDERATION 15 days	CLASSIFICATION OF DRUG OTHER ANTIBIOTICS - SYSTEMIC	DESIRED COMPLETION DATE 5/9/2009

NAME OF FIRM APP Pharmaceuticals LLC

REASON FOR REQUEST

I. GENERAL

- Γ NEW PROTOCOL
- Γ PROGRESS REPORT
- Γ NEW CORRESPONDENCE
- Γ DRUG ADVERTISING
- Γ ADVERSE REACTION REPORT
- Γ MANUFACTURING CHANGE/ADDITION
- Γ MEETING PLANNED BY _____
- Γ PRE NDA MEETING
- Γ END OF PHASE II MEETING
- Γ RESUBMISSION
- Γ SAFETY/EFFICACY
- Γ PAPER NDA
- Γ CONTROL SUPPLEMENT
- Γ RESPONSE TO DEFICPENCY LETTER
- Γ FINAL PRINTED LABELING
- Γ LABELING REVISION
- Γ ORIGINAL NEW CORRESPONDENCE
- Γ FORMULATIVE REVIEW
- X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

- □ DISSOLUTION
- □ PROTOCOL-- BIOPHARMACEUTICS
- □ IN--VIVO WAIVER REQUEST
- □ DEFICIENCY LETTER RESPONSE
- □ BIOAVAILABILITY STUDIES
- □ PHASE IV STUDIES

IV.DRUG EXPERIENCE

- □ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- □ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- □ CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
- □ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- □ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- □ SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

□ CLINICAL □ PRECLINICAL

COMMENTS

The Office of Generic Drugs is requesting a Pharm/Tox review for an application which is under ***expedited review due to a drug shortage (see attached medical necessity documentation).*** The drug product is Aztreonam for Injection, USP, 500 mg/vial, 1 g/vial, and 2 g/vial. The maximum recommended dose is 8 g per day for adults and 120 mg/kg/day for pediatric patients. Duration of therapy depends on severity of infection. According to the label, the drug product 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. The sponsor has (b) (4) mitted information regarding the presence of (b) (4) impurities in their drug product that are (b) (4) The firm has provided a (b) (4) toxicology study and toxicity assessment for th urities. The firm also proposes a level of (b) (4) for the drug product. Relevant data submitted by the firm is attached. These attachments can also be found in entirety in the EDR for the amendments dated 7/23/08, 1/22/09, and 4/10/09. Please provide your evaluation of the safety for this parenteral drug product for the proposed levels of (b) (4)

Please contact Susan Zuk, Division of Chemistry III, Team 6 Lead Chemist, at susan.suk@fda.hhs.gov or 240-276-8489, in the event that you have any questions.

Please cc Theresa Liu, HFD-617 (Theresa.Liu@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

SIGNATURE OF REQUESTER Roberta Szydlo	METHOD OF DE LIVERY *(Check one)* □ MAIL □ HAND Other - DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA

CENTER FOR DRUG EVALUATION AND RESEARCH
MEDICAL NECESSITY DETERMINATION

INSTRUCTIONS
Please evaluate the medical need for this product by answering the questions below. Keep in mind that a medically necessary drug product is a product that is used to treat or prevent a serious disease or medical condition for which there is no other alternative drug that is judged by medical staff to be an adequate substitute. Patient "inconvenience" alone is an insufficient basis to classify a product as medical necessity.

NAME AND HFD NUMBER OF DIVISION - __HFD-520_____
Name of person(s) making determination – __John Alexander, M.D., M.P.H._____
Date of Medical Necessity Request- _____1/25/04_____

PRODUCT(S): Aztreonam injection

MANUFACTURING FIRM: BMS

BACKGROUND: *CDER Drug Shortage informed week of 1/24/05 of a problem with the drug substance for this product at the bulk manufacturing facility (BMS – Latina facility).*

1. Is the product used to treat a serious disease or medical condition?

[ ] No
[X] Yes – Explain

Aztreonam is an intravenous antibiotic used to treat a variety of infections due to Gram-negative bacteria, including life-threatening infections of the blood. Aztreonam retains activity against some Gram-negative bacteria (particularly *E. coli, Acinetobacter, Klebsiella*, and *Pseudomonas* spp.) that are resistant to other typically used agents.

2. What are the labeled indications for this product?

The labeled indications include: Urinary Tract Infections (complicated and uncomplicated), Lower Respiratory Tract Infections, Septicemia, Skin and Skin Structure Infections, Intra-abdominal Infections, and Gynecologic Infections.

3. Are there important "off label" uses such as those for a serious medical condition?

The labeled indications cover most types of serious infections where aztreonam would be used. There have been some reports of its use for Gram-negative meningitis.

4. Are there generic forms of this product?
[X] No
[ ] Yes—Are there any special benefits/risks associated with the generic product(s)?

5. Are there alternative products available?

[ ] No
[X] Yes – Please explain the risk(s) and benefit(s) of this alternative product

There are a variety of agents approved to treat similar Gram-negative infections, but there are many instances where the bacteria causing the infections are resistant to these alternative agents. In some cases, aztreonam is the only marketed antibiotic that would be effective. Alternative agents include: broad-spectrum penicillins, 3rd and 4th generation cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems.

6. From the above assessment, is this product Medically Necessary? (Please note that this question refers only to the overall Medical Necessity of the product(s), not whether the specific (manufacturer's) product in question is appropriate for continued administration to patients. If the product is determined to be Medically Necessary, an assessment will then be made as to whether the product in question may be used (for instance with additional testing if necessary) to alleviate shortage situations. If it is not appropriate to administer such material to patients then alternative approaches will be examined. When necessary, a separate Health Hazard Evaluation [HHE] will be requested to address newly identified defects, impurities and/or risks associated with this drug.)

[ ] No
[X] Yes (Please state if this is only for specific indications)

The necessity for aztreonam is not limited to specific indications. Resistant Gram-negative bacteria could be found at any of the identified sites of infection and require treatment with aztreonam.

7. Additional comments:

8. Signature of person performing this medical necessity determination.

{See appended electronic signature page}

Medical Officer, Team Leader Date

{See appended electronic signature page}

Division Director Date

(MNForm-Revised 10/02)

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/s/

John Alexander
2/4/05 03:20:35 PM

Janice Soreth
2/4/05 03:46:49 PM

Following this page, 79 pages withheld in full - (b)(4)

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/s/

Theresa Liu

4/24/2009 02:58:55 PM

COMPLETE RESPONSE -- MINOR

ANDA 65-439

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: APP Pharmaceuticals, LLC TEL: 847-330-3950

ATTN: Georgia Hizon FAX: 847-413-8570

FROM: Roberta Szydlo FDA CONTACT PHONE: (240) 276-8476

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated October 5, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Aztreonam for Injection USP, 500 mg/vial, 1 g/vial, and 2 g/vial.

Reference is also made to your amendments dated July 23, 2008 and January 22, 2009.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (__**4**__ 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. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology 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: **65-439** APPLICANT: **APP Pharmaceuticals, LLC**

DRUG PRODUCT**: Aztreonam for Injection USP, 500 mg/vial, 1 g/vial, and 2 g/vial**

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

Following this page, 1 page 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. DMF # (b) (4) was reviewed and found not adequate. The deficiencies have been communicated to the DMF holder. Please be aware this ANDA cannot be approved until all DMF deficiencies are resolved satisfactorily.

2. Please provide updated stability data from on-going stability studies.

Sincerely yours,

{See appended electronic signature page}

Vilayat Sayeed
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Susan Zuk

3/25/2009 11:58:46 AM

Telephone Fax

ANDA 65-439

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301 827 8989

TO: Abraxis Pharmaceutical Products / [App Pharmaceuticals]

TEL: 847 330 - 3950

FAX: 847 413 - 8570

ATTN: Georgia Hizon

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, 500 mg, 1 grams and 2 grams

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling Comments for the December 5, 2008 and February 2, 2009 *submission.*

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

ANDA Number: 65-439

Dates of Submission: December 5, 2008 and February 2, 2009

Applicant's Name: Abraxis Pharmaceutical Products

Established Name: Aztreonam for Injection USP, 500 mg, 1 gram and 2 grams

---

1. CONTAINER

   Please provide supporting documents that verify the statement, "Vial stoppers do not contain natural rubber latex".

2. INSERT

   a. DOSAGE AND ADMINISTRATION

      i. Renal Impairment in Adult Patients

         Revise to read, "… between 10 mL/min/1.73 m^2 and…".

      ii. Intravenous (IV) Solutions

         A) Use separate Tables for "IV bolus" and "IV infusion".

            Use the following titles for each Table.

            CONSTITUTION for IV BOLUS

            CONSTITUTION for IV INFUSION

         B) After constitution, further dilution is not required for IV bolus. Therefore, in the Table for "IV bolus" revise the column heading to read "Amount of Diluent to be added (mL)". In addition, do not add the statement, "(b) (4) (b) (4))" at the bottom of the Table.

         C) Revise the statement below the Table for "Constitution for IV Infusion to read, (b) (4) (b) (4). Further…".

      iii. For Bolus Injection

         Revise the first sentence to read, "…for injection vial should…".

      iv. Intramuscular (IM) Solutions

         A) After constitution, further dilution is not required for IM administration. Therefore, in the Table for "Intramuscular (IM)

Solutions" revise the column heading to read "Amount of Diluent to be added (mL)".

B) For IM administration the constituted solution should not be further diluted therefore, delete the statement beneath the Table or IM administration, "(b) (4)

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 with the enclosed copy of the 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/

Michelle Dillahunt
2/26/2009 04:06:20 PM
Michelle Dillahunt for Wm. Peter Rickman

Szydlo, Roberta

From: West, Robert L
Sent: Wednesday, February 04, 2009 12:08 PM
To: Szydlo, Roberta; Shimer, Martin; CDER-DDR600
Cc: Greenberg, Harvey A; Skanchy, Jeanne
Subject: RE: Aztreonam FIJ - request for expedited review

Please grant "expedited review" status to ANDA 65-286 and ANDA 65-439 for Aztreonam for Injection. These appear to meet our criteria under MaPP 5240.3.

Thanks,

Bob

From: Szydlo, Roberta
Sent: Tuesday, February 03, 2009 9:47 AM
To: Shimer, Martin; West, Robert L
Cc: Greenberg, Harvey A; Skanchy, Jeanne
Subject: FW: Aztreonam FIJ - request for expedited review

Good morning Marty and Bob,

APP has requested expedited review status for ANDA 65-439 for Aztreonam FIJ. They referenced MaPP 5240.3 and also a potential shortage. The shortage has not been confirmed. There are no patents listed in the Orange Book for the RLD and no approved generics. There is also an application from Bedford for Aztreonam FIJ on Team 12 (ANDA 65-286). Please provide your recommendation on whether these applications should receive expedited status.

Thanks,
Roberta

From: Szydlo, Roberta
Sent: Monday, February 02, 2009 7:45 AM
To: Greenberg, Harvey A
Subject: Aztreonam FIJ

Hi Harvey,

Any news on whether Aztreonam FIJ qualifies as a drug shortage product?

thanks,
Roberta

From: Greenberg, Harvey A
Sent: Tuesday, January 27, 2009 2:21 PM
To: Szydlo, Roberta
Subject: RE: labeling deficiency ANDA 65-439 Aztreonam

Hi Roberta,
I am working on it--will update you when I get information from my group
Harvey

From: Szydlo, Roberta
Sent: Tuesday, January 27, 2009 2:11 PM
To: Greenberg, Harvey A
Subject: FW: labeling deficiency ANDA 65-439 Aztreonam

Hi Harvey,

Do you know anything about a drug shortage for Aztreonam FIJ?

Thanks,
Roberta

From: Golson, Lillie D
Sent: Tuesday, January 27, 2009 12:29 PM
To: Szydlo, Roberta
Cc: Council, Jacqueline; Golson, Lillie D
Subject: FW: labeling deficiency ANDA 65-439 Aztreonam

Hi Roberta,

Please advise on how to proceed on this one.

Thanks

From: Lisa McChesney Harris [mailto:LMcChesneyHarris@apppharma.com]
Sent: Tuesday, January 27, 2009 10:48 AM
To: Golson, Lillie D
Cc: (b) (6) Council, Jacqueline
Subject: RE: labeling deficiency ANDA 65-439 Aztreonam

Hi Lillie,

In response to (b) (6)'s e-mail below, Dr. Council called and left a voice message indicating that the Labeling Deficiency Response submitted on 12/05/08 had not yet been picked up for review and that she estimated the review period to be 3-6 months.

I would greatly appreciate reconsideration of this proposed timeframe for labeling review as this product can be considered a first generic product for which there are no blocking patents or exclusivities (please refer to the Orange Book wherein Azactam is the only listed drug product).

Additionally, this product has been on the ASHP's drug shortage list for most of 2008 and remains on the list as an allocation. Please refer to the weblink:
http://www.ashp.org/Import/PRACTICEANDPOLICY/PracticeResourceCenters/DrugShortages/Gettir
id=5

These circumstances may render it under a recurring nationwide shortage and, thus, potentially qualify this application for expedited review pursuant to MAPP 5240.3. Please let me know if I should present this information to another individual; perhaps in the Regulatory Support Branch, to seek their guidance regarding review queue priorities and / or to submit a request for expedited review.

Thank you for your consideration and guidance in this matter.

Best regards,

Lisa

Lisa L. McChesney-Harris, PhD
Vice President, Regulatory Affairs
APP Pharmaceuticals, LLC
1501 E Woodfield Road, Suite 300E
Schaumburg, IL 60173
(847) 330-3895
(847) 413-8570
lmcchesneyharris@APPpharma.com

Visit us at www.APPpharma.com!

From: (b) (6)
Sent: Monday, January 19, 2009 1:23 PM
To: "Council, Jacqueline"
Cc: "Golson, Lillie D"; Lisa McChesney Harris
Subject: labeling deficiency ANDA 65-439 Aztreonam
Importance: High

Dr. Council,
We are just following up to the labeling deficiency that we responded to on 12/5/08 for ANDA 65-439 (aztreonam). Hopefully by this time you have received the supplement. Could you please advise if the labeling was found acceptable as submitted?
Kindest Regards,
(b) (6)

(b) (6)
Regulatory Affairs
Labeling Associate

APP Pharmaceuticals, LLC.
1501 E. Woodfield Road, Suite 300E
Schaumburg, IL 60173
phone: (b) (6)
fax: 847-413-8570
(b) (6)@APPpharma.com

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/s/

Roberta Szydlo
2/5/2009 10:56:52 AM
CSO

Telephone Fax

ANDA 65-439

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301 827 8989

TO: Abraxis Pharmaceutical Products

TEL: 847 330 - 3950

ATTN: Georgia Hizon

FAX: 847 413 - 8570

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, 500 mg, 1 grams and 2 grams

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling Comments for the March 14. 2008 submission.

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

ANDA Number: 65-439

Dates of Submission: March 14, 2008

Applicant's Name: Abraxis Pharmaceutical Products

Established Name: Aztreonam for Injection USP, 500 mg, 1 gram and 2 grams

---

1. CONTAINER: 500 mg, 1 gram and 2 grams

   a. You indicate your drug product differs from the innovator's in that it is "lyophilized" and not "powder filled". In addition, you indicate that your "vial size" and (b) (4) as previously requested.

   b. The color or your 1 and 2 g container labels are similar. Please further differentiate the color of the strength by using contrasting colors.

2. INSERT

   a. DESCRIPTION

      Powder color

      Is the color of your product in the dry state "white" or "yellow"? Please provide documentation.

   b. DOSAGE AND ADMINISTRATION

      i. As previously requested, include the following information in the DOSAGE AND ADMINISTRATION section due to the differences of your drug product from the innovator.

         A) The vial size for each strength.

            [You may include a statement that your vial size differs from the innovator's because your product is "lyophilized"].

         B) The volume required for reconstitution for each strength.

Please provide this information in a Table format, such as follows:

Strength	Vial size	Volume of Sterile Water for Injection [mL] for reconstitution	Final volume [mL]

ii. We note that you included the same volume of diluent for reconstitution as the innovator. However, you previously informed us that your "vial sizes" [i.e., 20 mL and 30 mL] and (b) (4) Please explain. In addition, provide supporting documents that provide the volume of Sterile Water for Injection required for reconstitution for each strength.

iii. Although your product is "lyophilized" and not "powder filled", you recommend your drug product to be reconstituted with the same volume as the innovator for IM use," 3 mL". Please verify with supporting documentation.

iv. Admixtures with Other Antibiotics

In the first sentence delete (b) (4)".

v. Stability of IV and IM Solutions

In the first sentence delete " (b) (4)"

b. HOW SUPPLIED

i. Add "single dose vials" beneath the established name.

ii. Include the vial sizes for each strength.

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 with the enclosed copy of the 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
10/31/2008 03:57:38 PM
Lillie Golson 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 (240-276-8408)

TO: Georgia Hizon		**FROM:** Mark Anderson
APP Pharmaceuticals, LLC		Microbiology Project Manager
PHONE: 847-330-3950		**PHONE:** (240) 276-8831
FAX: 847-413-8570		**FAX:** (240) 276-8725

Total number of pages, excluding this cover sheet: **3**

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

Microbiology Deficiencies:

Enclosed are the microbiology deficiencies for ANDA 65-439 for Aztreonam for Injection USP, 500 mg, 1g, and 2 g vials. The submission reviewed was submitted on October 5, 2006. 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.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 65-439 APPLICANT: APP Pharmaceuticals, LLC

DRUG PRODUCT: Aztreonam for Injection USP, 500 mg, 1 g, and 2 g vials

A. Microbiology Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

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}

Neal J. Sweeney, Ph.D.
Microbiology Supervisor
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Neal Sweeney

9/16/2008 12:40:46 PM

MINOR AMENDMENT

ANDA 65-439

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: APP Pharmaceuticals, LLC TEL: 847-330-3950

ATTN: Georgia Hizon FAX: 847-413-8570

FROM: Roberta Szydlo FDA CONTACT PHONE: (240) 276-8476

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated October 5, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Aztreonam for Injection USP, 500 mg/vial, 1 g/vial, and 2 g/vial.

Reference is also made to your amendment dated December 7, 2007.

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: 65-439 APPLICANT: APP Pharmaceuticals, LLC

DRUG PRODUCT: Aztreonam for Injection USP, 500 mg/vial, 1 g/vial, and 2 g/vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. DMF (b) (4) was reviewed and found not adequate. The deficiencies have been communicated to the DMF holder. Please be

aware this ANDA cannot be approved until all DMF deficiencies are resolved satisfactorily.

2. Please provide updated stability data for the stability batches.

Sincerely yours,

{See appended electronic signature page}

Vilayat Sayeed
Director
Division of Chemistry III
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/

Susan Zuk
6/13/2008 03:34:42 PM

Telephone Fax

ANDA 65-439

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240 276 8400

TO: Abraxis Pharmaceutical Products . TEL: 847 939-8110

ATTN: Georgia Hizon FAX: 847 939-8212

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, 500 mg, 1 gram and 2 grams

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling Comments for the 9/11/07 submission

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

ANDA Number: 65-439

Dates of Submission: September 11, 2007

Applicant's Name: Abraxis Pharmaceutical Products

Established Name: Aztreonam for Injection USP, 500 mg, 1 gram and 2 grams

---

Labeling Deficiencies:

1. CONTAINER: 500 mg, 1 gram and 2 grams

   a. Front panel

      i. 500 mg, 1 gram and 2 grams

         Add an asterisk following the strength, "1 gram*/vial".

      ii. 2 grams

         Replace "2 gram/vial" with "2 grams*/vial"

   b. Side panel

      i. Add an asterisk prior to the "*Each vial contains …" statement.

      ii. We note that you indicate your drug product differs from the innovator's in that it is "lyophilized" and not "powder filled". In addition, you indicate that your "vial size" and "(b) (4) [redacted].

2. (b) (4) [redacted]

3. INSERT

   a. GENERAL COMMENTS

      i. Decrease the prominence of your company name printed at the top of your insert labeling

      ii. Please revise your labeling to be in accord with the current approved labeling of the reference listed drug. We refer you to

the FDA website at
http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

b. DOSAGE AND ADMINISTRATION

i. We request that you include the following information in the DOSAGE AND ADMINISTRATION section due to the differences of your drug product from the innovator. [See comment 1(b)(ii) under CONTAINER].

A) The vial size for each strength.

B) The volume required for reconstitution for each strength.

ii. We note that you included the same text as the innovator," …6 to 10 mL Sterile Water…" in this section. However, you informed us that your (b) (4) . Please revise accordingly.

iii. Intramuscular use

Although your product is "lyophilized" and not "powder filled", you recommend your drug product to be reconstituted with the same volume as the innovator for IM use," 3 mL". Has this been verified?

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 with the enclosed copy of the 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

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

/s/

Lillie Golson
1/29/2008 05:22:46 PM
Lillie Golson for Wm. Peter Rickman

Telephone Fax

ANDA 65-439

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301 827 5846

TO: Abraxis Pharmaceutical Products TEL: 847 993 1578

ATTN: Toni Glinsey FAX: 847 939 8212

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, 500 mg, 1 gram and 2 grams.

Pages (including cover): 5

SPECIAL INSTRUCTIONS:

Labeling Comments for the 10/5/06 submission.

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

ANDA Number: 65-439

Dates of Submission: October 5, 2006

Applicant's Name: Abraxis Pharmaceutical Products

Established Name: Aztreonam for Injection USP, 500 mg, 1 gram and 2 grams

---

Labeling Deficiencies:

1. CONTAINER: 500 mg, 1 gram and 2 grams

   a. General Comment

      We note that your vial sizes are "20 mL" and "30 mL". Your vial size should be the same size as the innovator "15 mL". Revise your labels and labeling accordingly.

   b. Front panel

      i. Use the same background color for the entire established name.

      ii. Delete "/vial".

      iii. Delete "(b) (4)".

   c. Side panel

      i. (b) (4)

2. (b) (4)

   (b) (4)

3. INSERT

   a. GENERAL COMMENTS

      i. Throughout the insert labeling use the abbreviation "mcg" for micrograms instead of "µg".

      ii, We note that you have your company name printed at the top of your insert labeling. When printing final print, ensure that the established name in the Title is the most prominent text at the top of your labeling.

b. DESCRIPTION

Add the “Each vial contains…” statements to this section as seen on your container labels.

c. WARNINGS

Second paragraph

Start a new paragraph with the sentence, “While cross-reactivity …”.

d. DOSAGE AND ADMINISTRAION

i. AZTREONAM FOR INJECTION DOSAGE GUIDELINES – Tables

Add a horizontal line underneath “PEDIATRIC PATIENTS ** as seen under ADULTS”.

ii. 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.

e. HOW SUPPLIED

See comment regarding your vial size under CONTAINER.

f. At the end of your insert labeling you list Abbott Laboratories and M^{c}Graw Inc., in association with the trade name of some intravenous solution. Please ensure these are the correct manufacturers.

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://www.fda.gov/cder/cdernew/listserv.html

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 the enclosed copy of the 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
7/23/2007 05:00:57 PM
Lillie Golson for Wm. Peter Rickman

MINOR AMENDMENT

ANDA 65-439

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: Abraxis Pharmaceutical Products TEL: 847-939-8105

ATTN: Brent Yurschak FAX: 847-939-8212

FROM: Ryan Nguyen, Pharm.D. PROJECT MANAGER: (301) 827-5737

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 5, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Aztreonam for Injection USP, 500 mg/vial, 1 g/vial, and 2 g/vial.

Reference is also made to your amendment dated April 13, 2007.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (5 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:

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-439 APPLICANT: Abraxis Pharmaceutical Products

DRUG PRODUCT: Aztreonam for Injection USP, 500 mg/vial, 1 g/vial, and 2 g/vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

1.

2.

3.

4.

5.

6.

7.

8.

9.

Following this page, 1 page withheld in full - (b)(4)

22. (b) (4)

23.

24.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. DMF # (b) (4) was reviewed and found not adequate. The deficiencies have been communicated to the DMF holder. Please be aware this ANDA cannot be approved until all DMF deficiencies are resolved satisfactorily.

2. Please provide updated stability data for the stability batches.

OGD is changing its CMC review process though our question based review (QbR) initiative, which is described in more detail on the OGD website: http://www.fda.gov/cder/ogd/QbR.htm.

OGD's QbR was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD), a submission format adopted by multiple regulatory bodies including the FDA. Generic firms are strongly recommended to submit their ANDAs in the CTD format (either eCTD or paper) to facilitate the implementation of the QbR and to avoid undue delays in the review of their applications.

Because of the increasing number of ANDA submissions OGD receives each year, the Quality Overall Summary (QOS) part of the CTD format is extremely important to making our new review process more efficient. Beginning in January 2007, all ANDA applicants are recommended to provide an electronic copy of a QOS that addresses OGD's QbR questions. The QbR-Quality Overall Summary Outline posted on our webpage http://www.fda.gov/cder/ogd/ contains all the questions to prepare the QOS. The QOS should be submitted in both MS Word and pdf format along with the paper or electronic submission. The QOS should be provided even if the remainder of the application is not in CTD format. OGD has prepared QOS models that can be found on the OGD web site. We ask you to use these as a guide for your submissions.

If you are already submitting QbR-based applications, we would like to take this opportunity to thank you for supporting this very important initiative.

Sincerely yours,

{See appended electronic signature page}

Vilayat Sayeed
Director
Division of Chemistry III
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/

Susan Zuk

5/4/2007 05:12:02 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 65-439

Abraxis Pharmaceutical Products
(a division of Abraxis BioScience, Inc.)
Attention: Georgia Hizon
6133 North River Road, Suite 500
Rosemont, IL 60018

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.

Reference is also made to your correspondence dated October 16, 2006 and to the telephone conversation dated December 15, 2006.

NAME OF DRUG: Aztreonam for Injection USP,
500 mg/vial, 1 g/vial and 2 g/vial

DATE OF APPLICATION: October 5, 2006

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 6, 2006

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
301-827-5739

Sincerely yours,

{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

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

/s/

Martin Shimer
12/20/2006 10:35:59 AM
Signing for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
*** **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 65-439 **FIRM NAME**: ABRAXIS PHARMACEUTICAL PRODUCTS

PIV: NO **Electronic or Paper Submission:** PAPER

RELATED APPLICATION(S): NA

First Generic Product Received? YES ON 500 MG/VIAL AND 2 G/VIAL

DRUG NAME: AZTREONAM
DOSAGE FORM: FOR INJECTION USP, 500 MG/VIAL, 1 G/VIAL AND 2 G/VIAL

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☒ **Micro Review**
☐ **BST**	☐ **BDI**	

Random Queue: 6
Chem Team Leader: Susan Zuk PM: Ryan Nguyen Labeling Reviewer: Jacqueline Council

Letter Date: OCTOBER 5, 2006 **Received Date**: OCTOBER 6, 2006

Comments: EC - 1 YES **On Cards:** YES
Therapeutic Code: 4010900 OTHER ANTIBIOTICS - SYSTEMIC

Archival copy: PAPER **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

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 Stanley Shepperson	**Recommendation:**
Date 05-DEC-2006	☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: Martin Shimer **Date: 20-DEC-2006**

ADDITIONAL COMMENTS REGARDING THE ANDA:
12-15-2006: Called Georgia Hizon of Abraxis to resubmit the Word version of the QOS, as it is not functional In our EDR.

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2** **Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: OCTOBER 5, 2006	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) NA	☒
1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2** **Patent Certification** 1. Patent number(s) NA 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☒ PII ☐ PIII ☐ PIV ☐ No Relevant Patents ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES. DMF (b) (4) b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) NA	☒

1.12.11	**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 or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients SAME 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): YES	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers (b) (4) with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES **HOW SUPPLIED:** Lyophilized Powder 500 mg/vial 1g/vial 1g/vial	☒

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: ___x PDF (archive) __x_ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) _x____ YES _____ NO** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** YES **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P** **Drug Product** YES **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence)- NO** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** **2.7.1.2** **Summary of Results of Individual Studies** **2.7.1.3** **Comparison and Analyses of Results Across Studies** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies Table 2. Statistical Summary of the Comparative BA Data Table 4. Summary of In Vitro Dissolution Studies **2.7.1.4** **Appendix**	☐

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature** YES **3.2.S.1.2** **Structure** YES **3.2.S.1.3** **General Properties** YES	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers YES 2. Manufacturing Responsibilities YES 3. Type II DMF number for API YES 4. CFN or FEI numbers YES	☒
3.2.S.3	**Characterization**- YES	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1** **Specification** Testing specifications and data from drug substance manufacturer(s) YES **3.2.S.4.2** **Analytical Procedures** YES **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) YES **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **3.2.S.4.5** **Justification of Specification-** YES	☒
3.2.S.5	**Reference Standards or Materials-** YES	☒
3.2.S.6	**Container Closure Systems** see DMF (b) (4)	☒
3.2.S.7	**Stability** see DMF (b) (4)	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition YES 2) Inactive ingredients are appropriate per IIG YES . Q1/Q2	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers YES **3.2.P.3.2** **Batch Formula** Batch Formulation YES **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3. If sterile product: (b) (4) 4. Reprocessing Statement YES **3.2.P.3.4** **Controls of Critical Steps and Intermediates**- YES **3.2.P.3.5** **Process Validation and/or Evaluation** 1. Microbiological sterilization validation YES (b) (4) **PROPOSED COMMERCIAL BATCH SIZES:** 500 mg/vial: (b) (4) 1g/vial: (b) (4) 2g/vial: (b) (4)	M

3.2.P.4	**Controls of Excipients (Inactive Ingredients) YES** Source of inactive ingredients identified YES **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2** **Analytical Procedures** YES - **3.2.P.4.3** **Validation of Analytical Procedures** YES **3.2.P.4.4** **Justification of Sepcifications** Applicant COA YES	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** YES **3.2.P.5.2** **Analytical Procedures** YES **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers YES **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form YES (ATTACHMENT 59) **3.2.P.5.5** **Characterization of Impurities** YES **3.2.P.5.6** **Justification of Specifications** YES	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period- No expiration date proposed until additional real-time stability data is accrued. **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch YES	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S** **Executed Batch Records for drug substance (if available) NO** **3.2.R.2.S** **Comparability Protocols no** **3.2.R.3.S** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 3
3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation -YES **500 mg/vial (Lot# 236-011)** TY: (b) (4) AY: (b) (4) Packaged: (b) (4) **1 g/vial (Lot# 236-010)** TY: (b) (4) AY: (b) (4) Packaged: (b) (4) **2 g/vial (Lot# 236-009)** TY: (b) (4) AY: (b) (4) Packaged: (b) (4) **3.2.R.1.P.2** **Information on Components - NO** **3.2.R.2.P** **Comparability Protocols** NO **3.2.R.3.P** **Methods Validation Package** -YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5
CLINICAL STUDY REPORTS- N/A

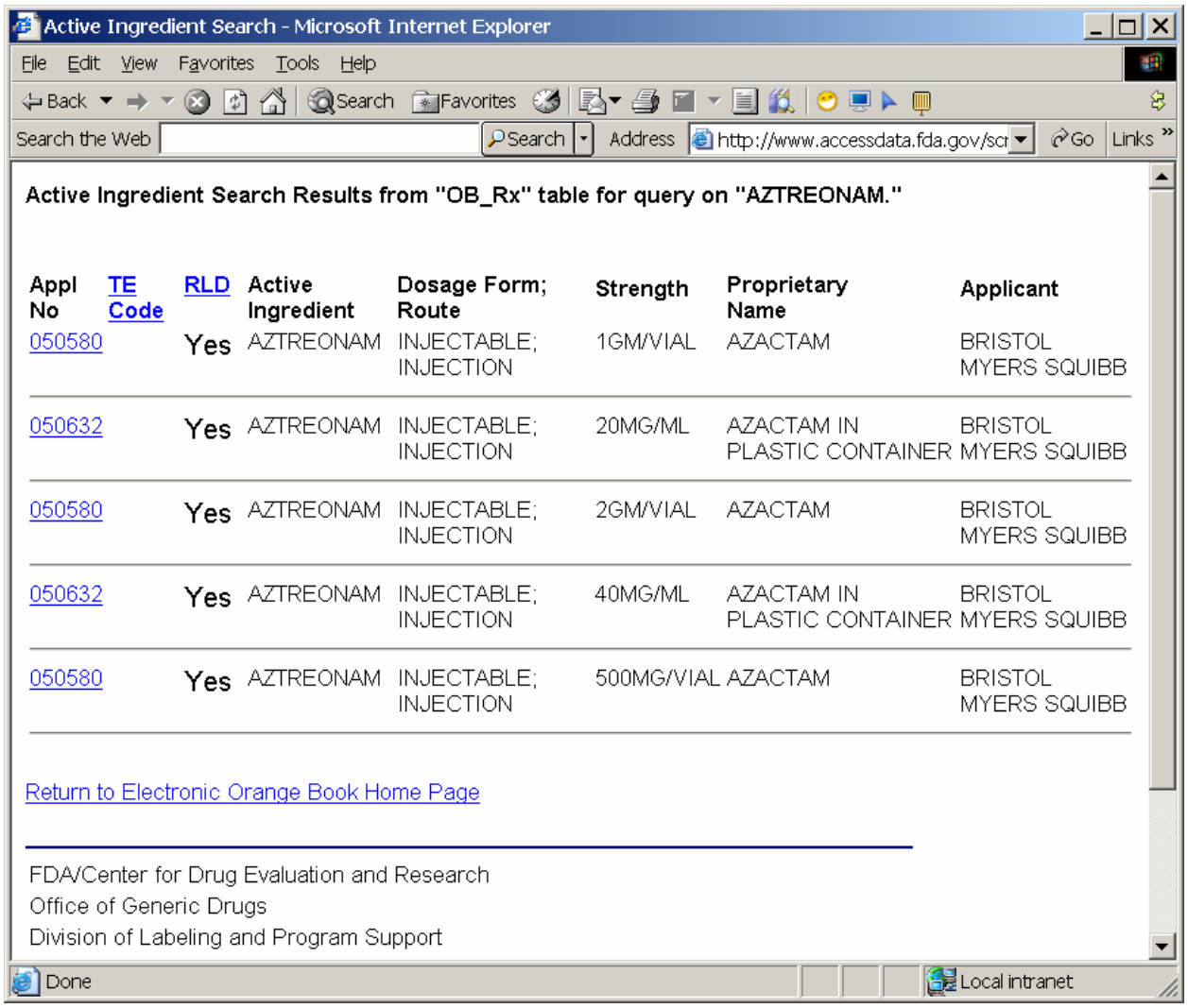
ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☐

	5.3.1.2 **Comparative BA/BE Study Reports** 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 6. Demographic Profile of Subjects Completing the Comparative BA Study Table 7. Incidence of Adverse Events in Individual Studies Table 8. Reanalysis of Study Samples **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies Table 5. Formulation Data **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation **5.3.7** **Case Report Forms and Individual Patient Listing**	☐
5.4	**Literature References**	
	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: NO	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. 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 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/10/2006 C. Bina



Active Ingredient Search Results from "OB_Rx" table for query on "AZTREONAM."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
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050632		Yes	AZTREONAM	INJECTABLE; INJECTION	20MG/ML	AZACTAM IN PLASTIC CONTAINER	BRISTOL MYERS SQUIBB
050580		Yes	AZTREONAM	INJECTABLE; INJECTION	2GM/VIAL	AZACTAM	BRISTOL MYERS SQUIBB
050632		Yes	AZTREONAM	INJECTABLE; INJECTION	40MG/ML	AZACTAM IN PLASTIC CONTAINER	BRISTOL MYERS SQUIBB
050580		Yes	AZTREONAM	INJECTABLE; INJECTION	500MG/VIAL	AZACTAM	BRISTOL MYERS SQUIBB

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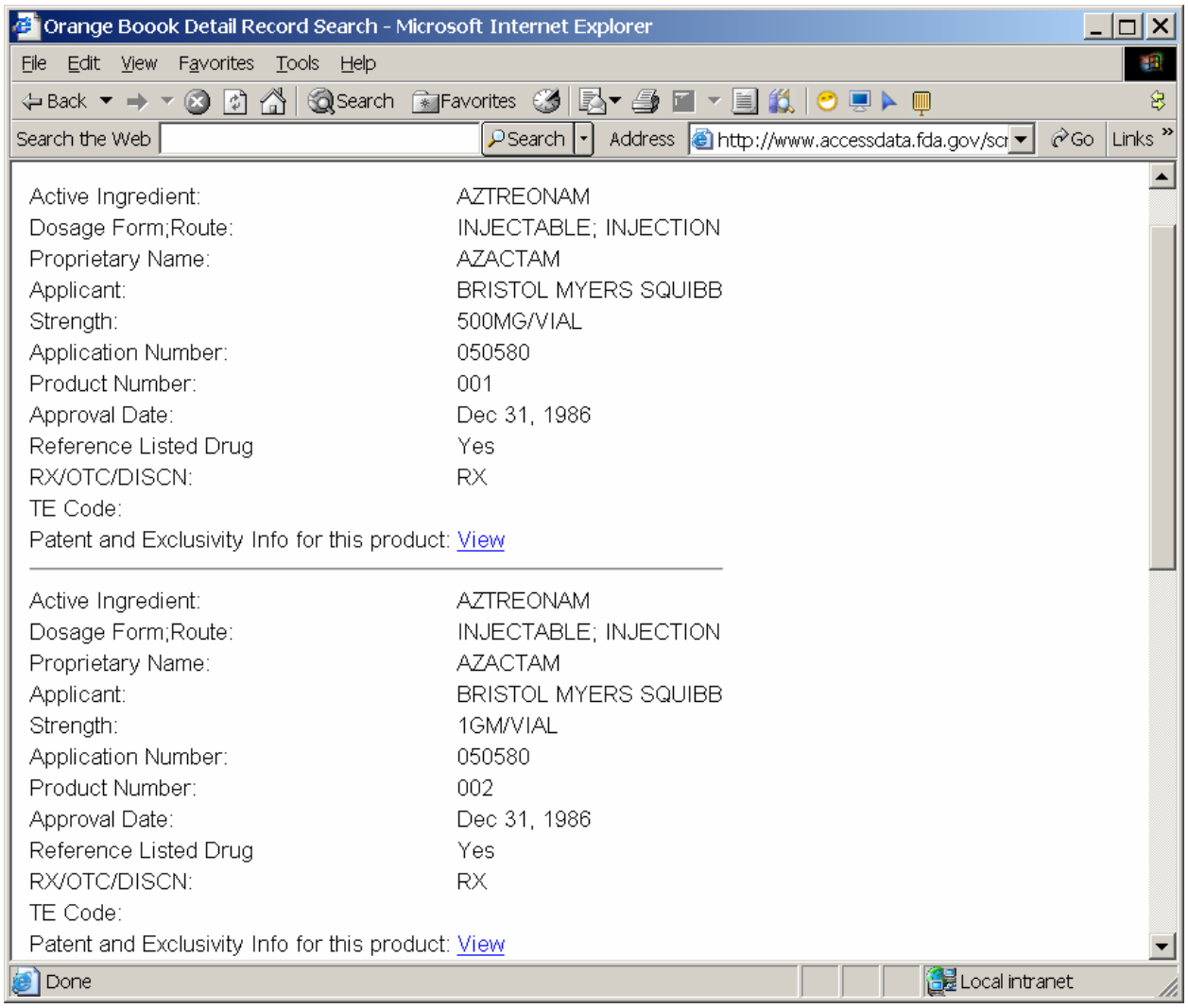
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Dosage Form;Route: INJECTABLE; INJECTION
Proprietary Name: AZACTAM
Applicant: BRISTOL MYERS SQUIBB
Strength: 500MG/VIAL
Application Number: 050580
Product Number: 001
Approval Date: Dec 31, 1986
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
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Dosage Form;Route: INJECTABLE; INJECTION
Proprietary Name: AZACTAM
Applicant: BRISTOL MYERS SQUIBB
Strength: 1GM/VIAL
Application Number: 050580
Product Number: 002
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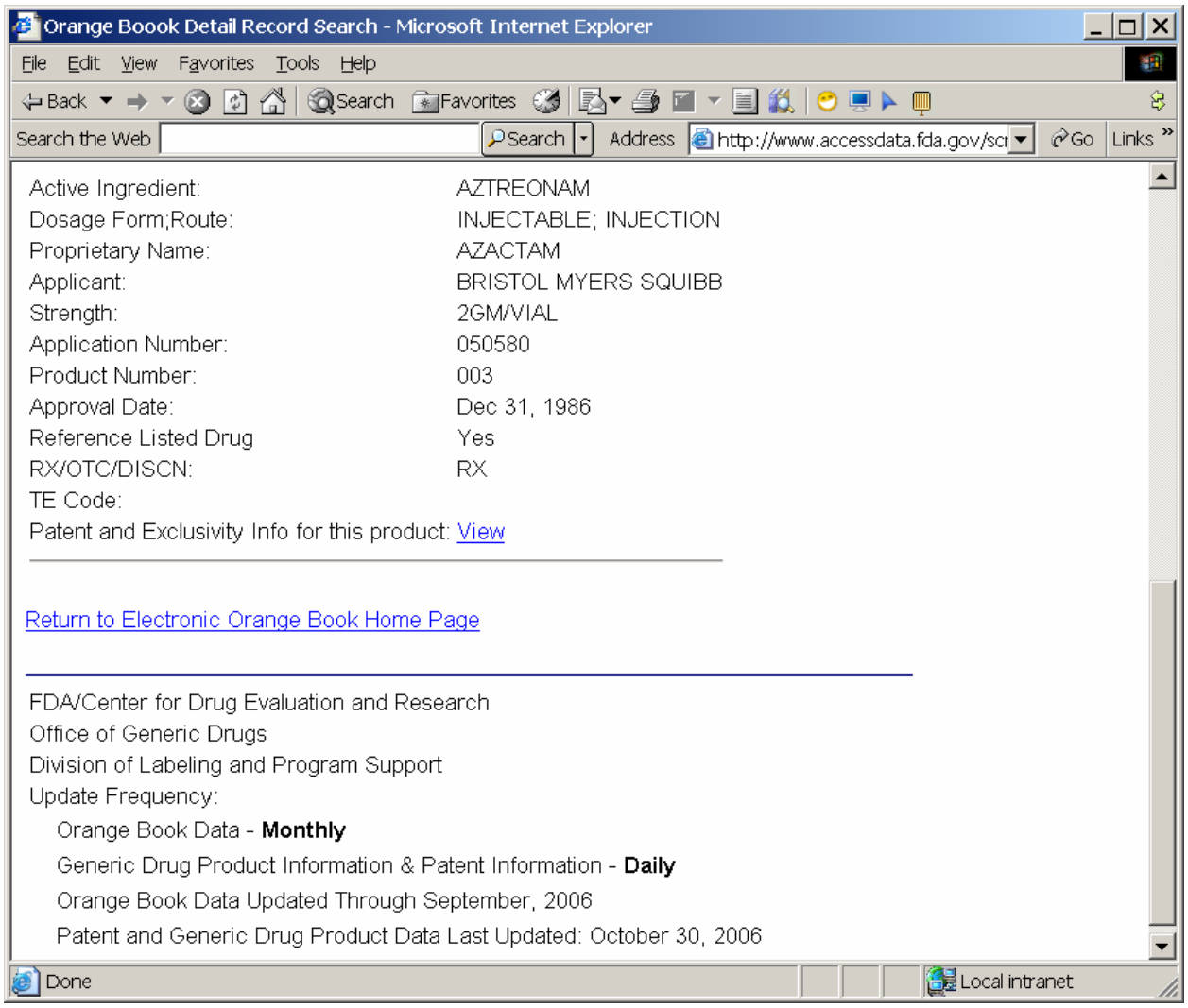
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Dosage Form;Route: INJECTABLE; INJECTION
Proprietary Name: AZACTAM
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Strength: 2GM/VIAL
Application Number: 050580
Product Number: 003
Approval Date: Dec 31, 1986
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
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Division of Labeling and Program Support
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Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through September, 2006
Patent and Generic Drug Product Data Last Updated: October 30, 2006
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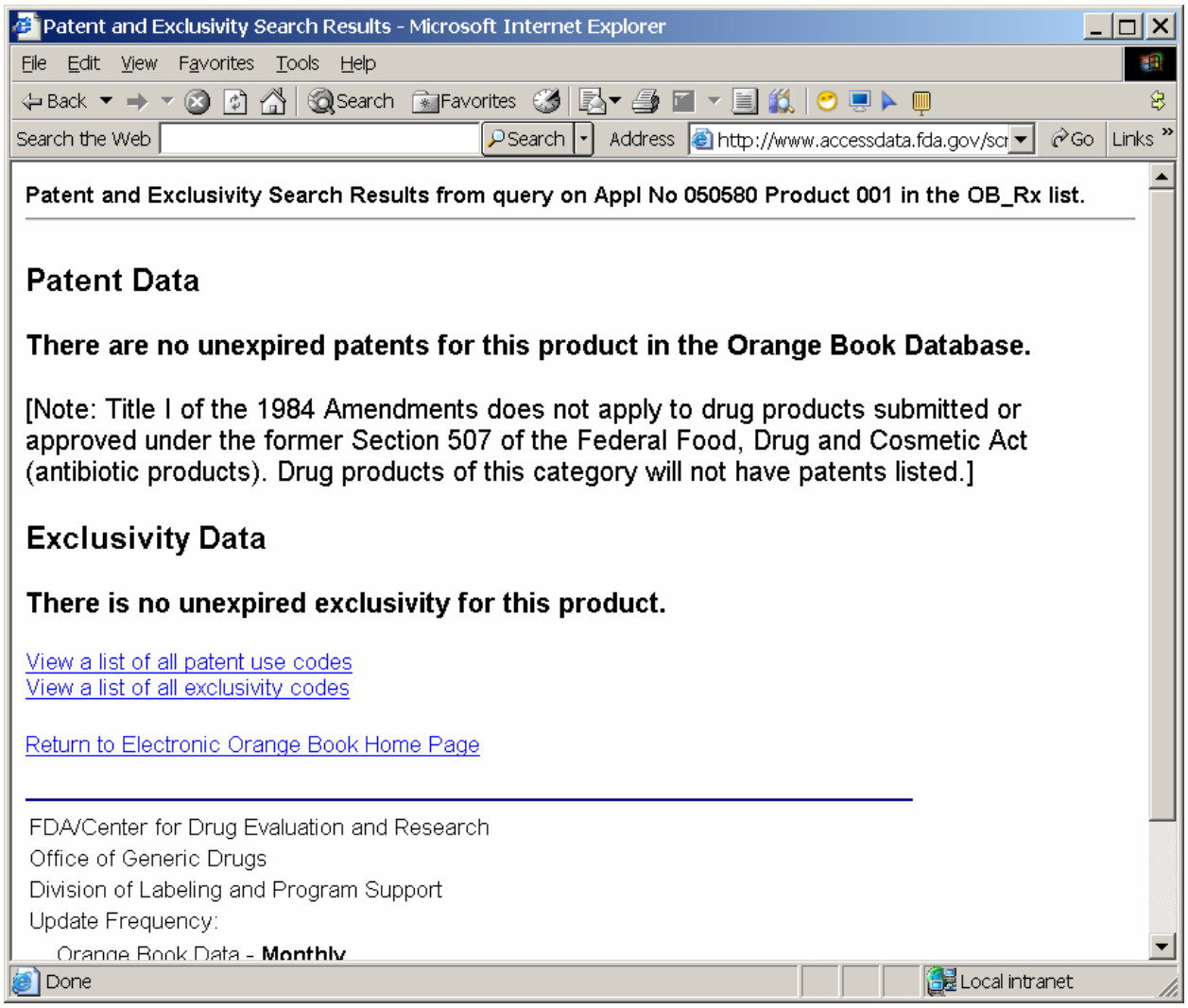
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Patent Data
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[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]
Exclusivity Data
There is no unexpired exclusivity for this product.
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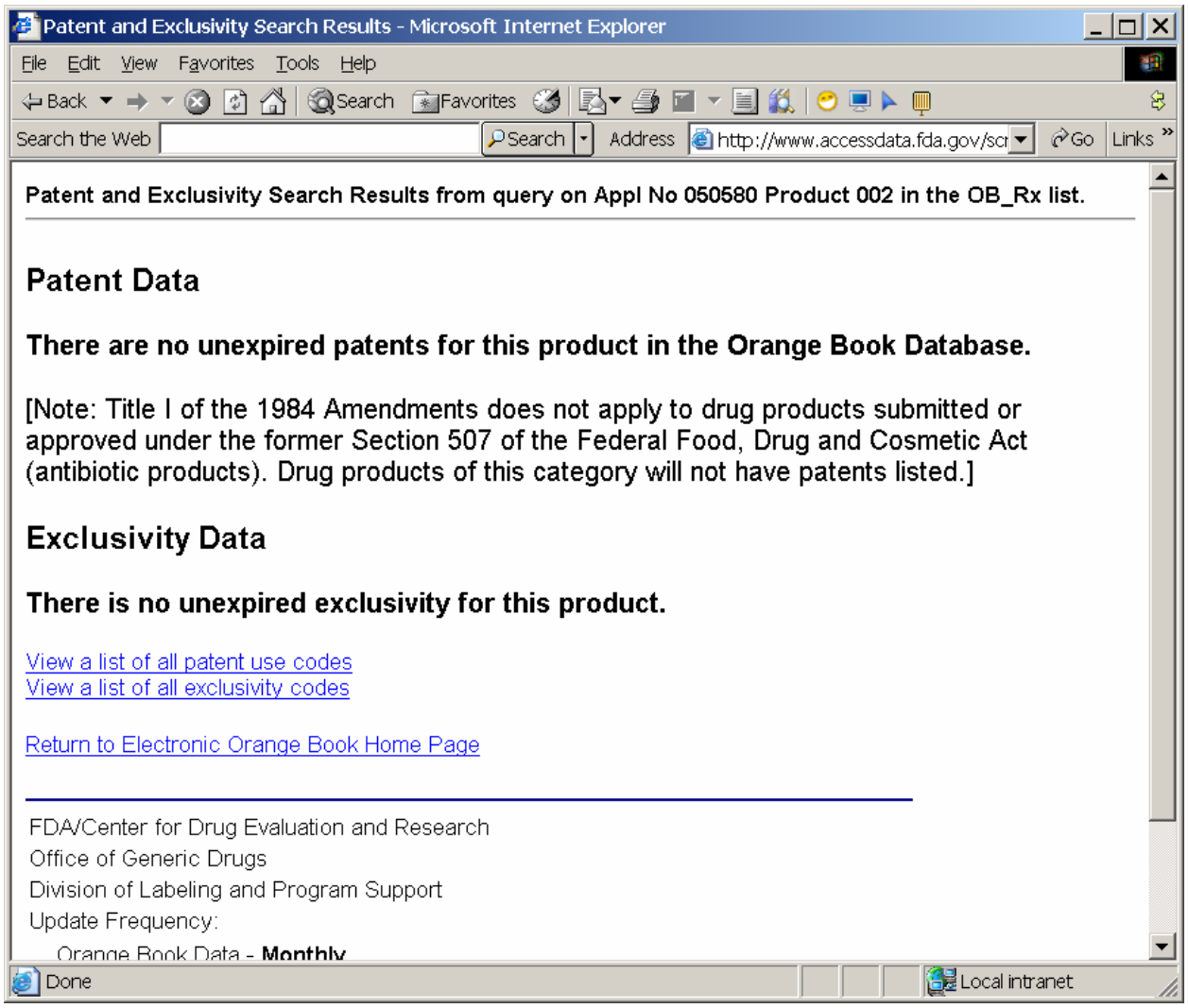
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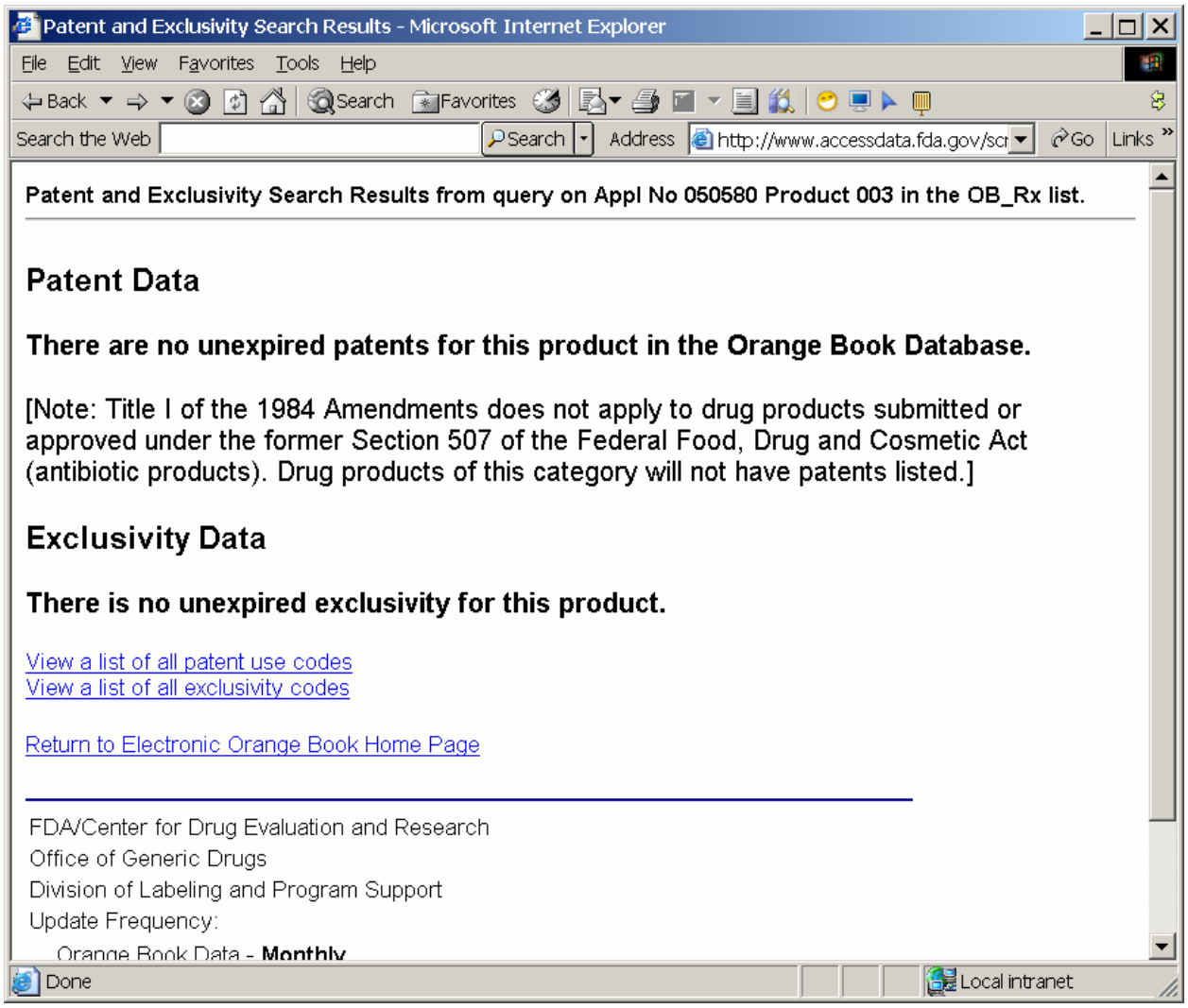
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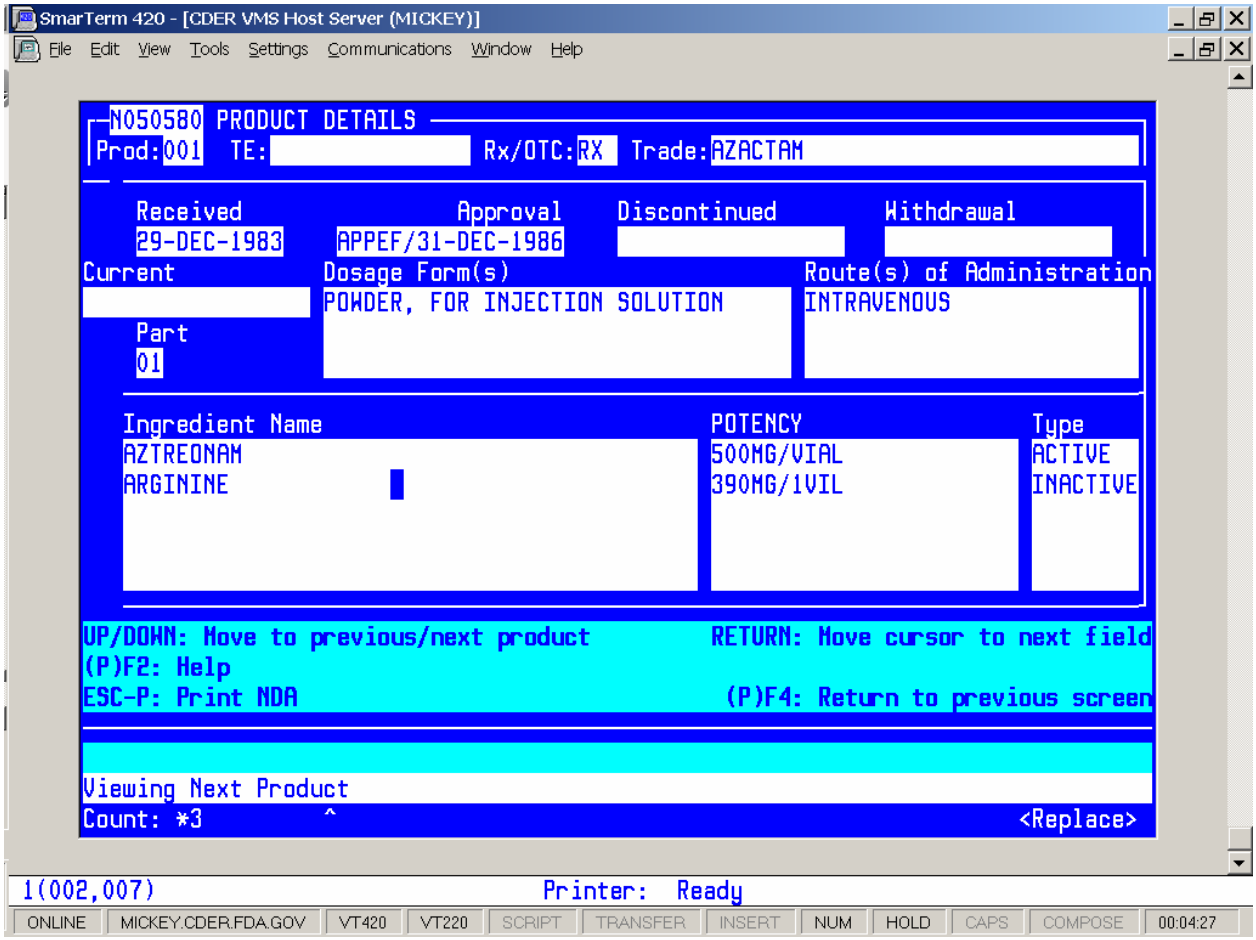
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Route(s) of Administration
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Ingredient Name
POTENCY
Type
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ARGININE
390MG/1VIL
INACTIVE
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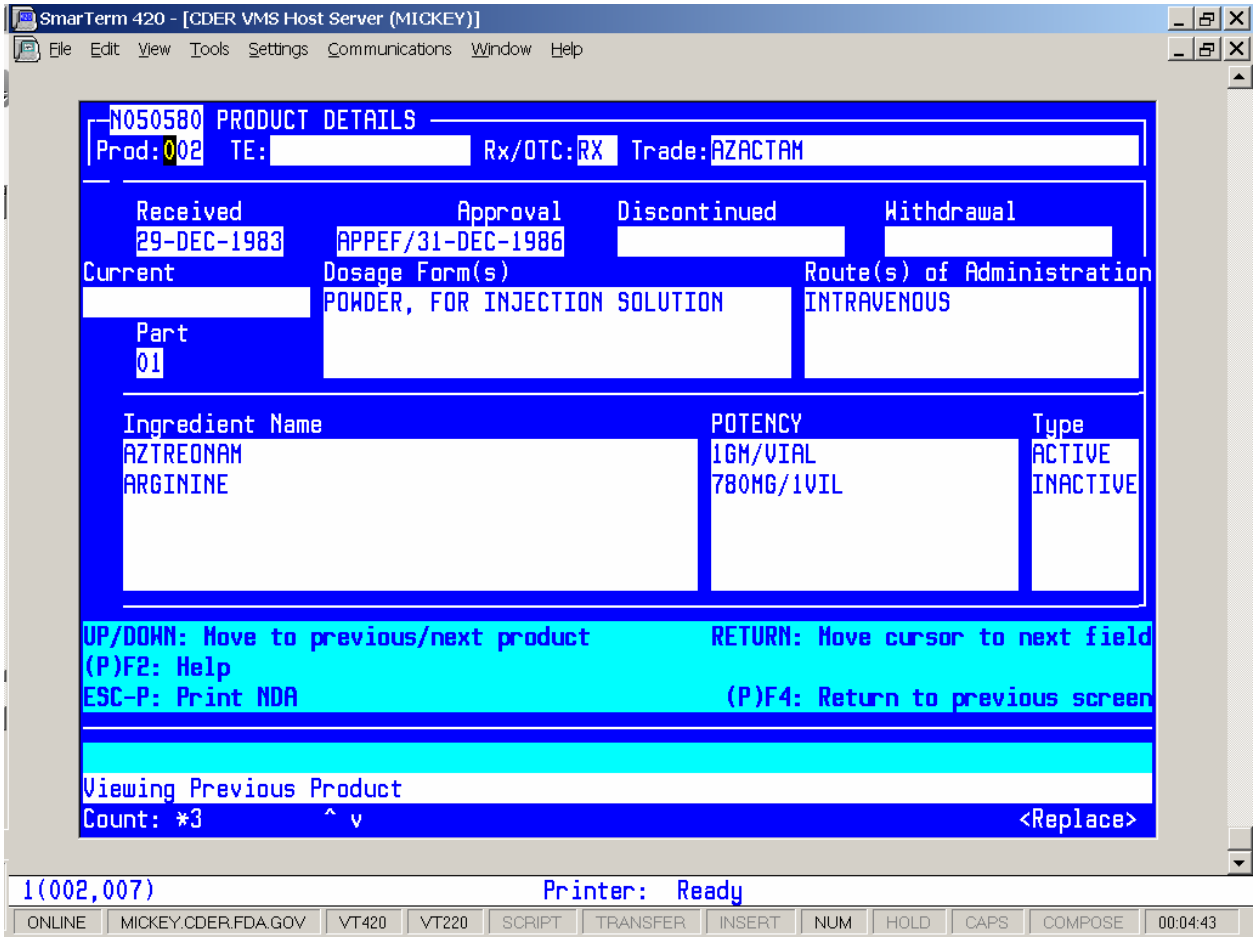
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INTRAVENOUS
Ingredient Name
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Type
AZTREONAM
1GM/VIAL
ACTIVE
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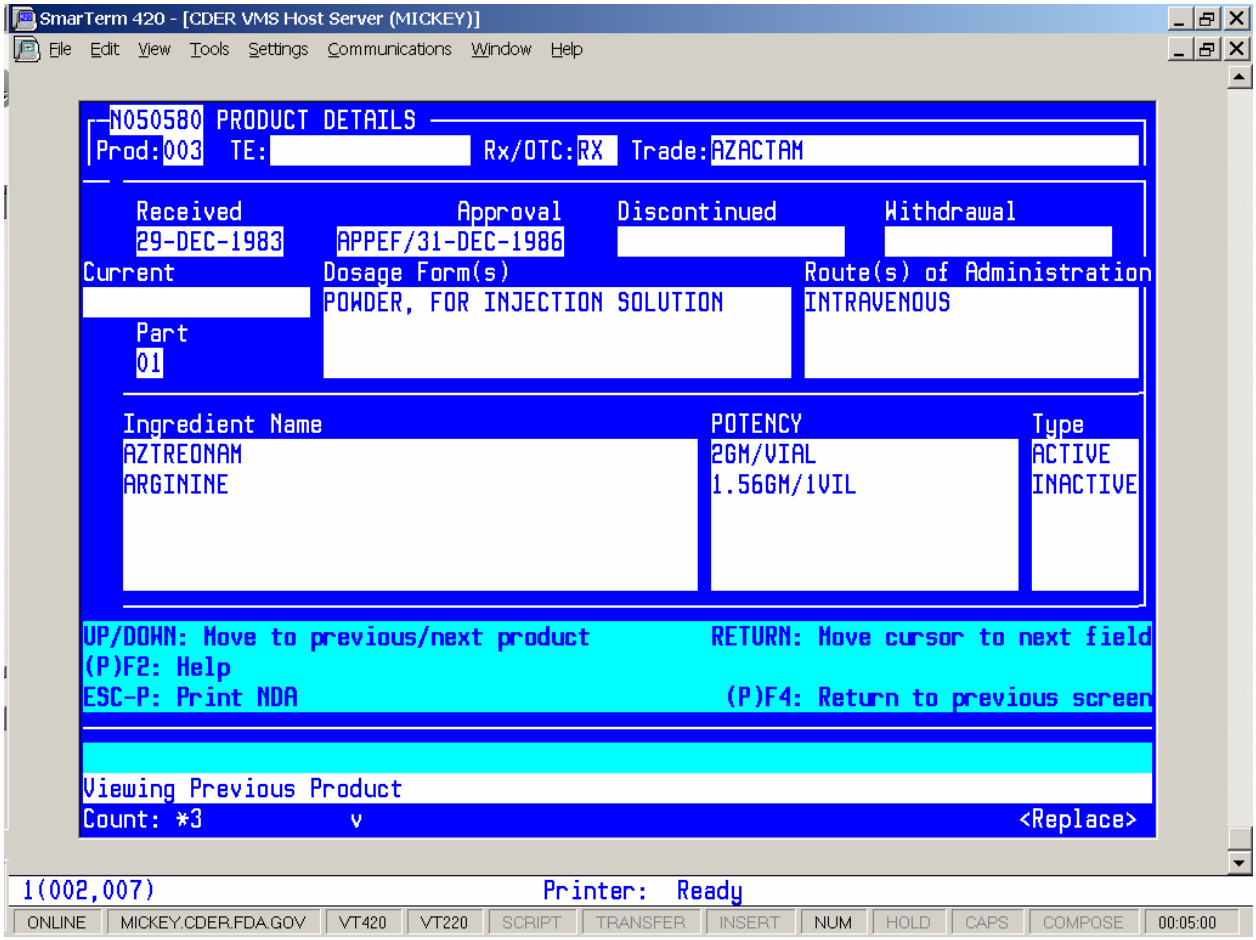
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Route(s) of Administration
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Ingredient Name
AZTREONAM
ARGININE
POTENCY
2GM/VIAL
1.56GM/1VIL
Type
ACTIVE
INACTIVE
UP/DOWN: Move to previous/next product
RETURN: Move cursor to next field
(P)F2: Help
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