Bristol-Myers Squibb

AZACTAM®
(aztreonam injection)
in GALAXY Plastic Container (PL 2040)
for Intravenous Use

Rx only

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

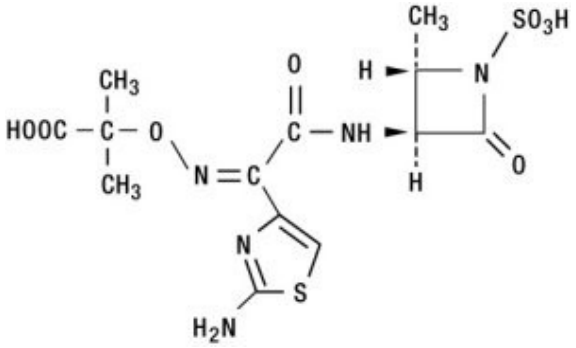
DESCRIPTION

AZACTAM® (aztreonam injection) 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 (eg, 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:

Reference ID: 3326494



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

AZACTAM in the GALAXY plastic container (PL 2040) is a frozen, iso-osmotic, sterile, sodium-free, nonpyrogenic intravenous solution. Each 50 mL of solution contains 1 g, or 2 g aztreonam with approximately 1.7 g, or 700 mg Dextrose Hydrous, USP added to adjust osmolality, and approximately 780 mg, or 1.6 g of arginine added for pH adjustment, respectively. Thawed solutions have a pH in the range of 4.5 to 7.5. The solution is for intravenous administration following thawing at room temperature or under refrigeration.

This GALAXY container is fabricated from a specially designed multilayer plastic (PL 2040). Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability of the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers as well as by tissue culture toxicity studies.

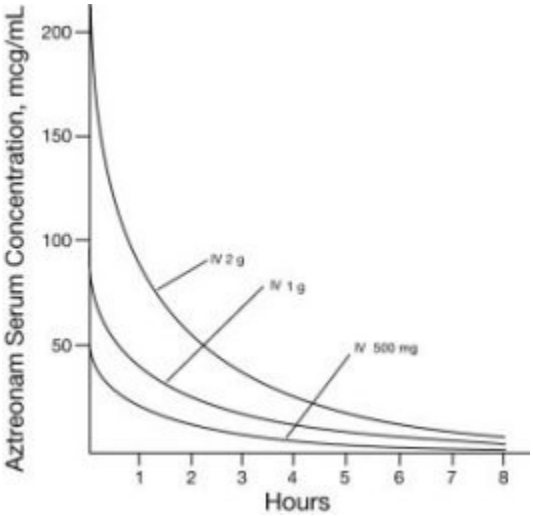
CLINICAL PHARMACOLOGY

Single 30-minute intravenous infusions of 500 mg, 1 g, and 2 g doses of AZACTAM in healthy subjects produced aztreonam peak serum levels of 54 mcg/mL, 90 mcg/mL, and 204 mcg/mL, respectively, immediately after administration; at 8 hours, serum levels were 1 mcg/mL, 3 mcg/mL, and 6 mcg/mL, respectively (Figure 1). Single 3-minute intravenous injections of the same doses resulted in serum levels of 58 mcg/mL, 125 mcg/mL, and 242 mcg/mL at 5 minutes following completion of injection.

Serum concentrations of aztreonam following completion of single intravenous infusions of 500 mg, 1 g, and 2 g doses are depicted in Figure 1.

Reference ID: 3326494

FIGURE 1



The serum levels of aztreonam following single 500 mg, 1 g, or 2 g intravenous doses of AZACTAM 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 AZACTAM 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 (1.5-2.0) in subjects with normal renal function, independent of the dose. 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 AZACTAM 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.

Reference ID: 3326494

Average urine concentrations of aztreonam were approximately 1100 mcg/mL, 3500 mcg/mL, and 6600 mcg/mL within the first 2 hours following single 500 mg, 1 g, and 2 g intravenous doses of AZACTAM (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. 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 dose was recovered in the urine by 8 hours. Urinary excretion of a single intravenous 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 administration of a single 500 mg or 1 g dose of AZACTAM 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.

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

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

Reference ID: 3326494

Table 1: Extravascular Concentrations of Aztreonam After a Single Intravenous Dose (IV)[a]

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

[a] 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; in amniotic fluid at 6 to 8 hours after a single 1 g intravenous dose (5 patients), 2 mcg/mL. The concentration of aztreonam in peritoneal fluid obtained 1 to 6 hours after multiple 2 g intravenous doses ranged between 12 mcg/mL and 90 mcg/mL in 7 of 8 patients studied.

Reference ID: 3326494

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 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

Mechanism of Action

Aztreonam is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Aztreonam has activity in the presence of some beta-lactamases, both penicillinases and cephalosporinases, of Gram-negative and Gram-positive bacteria.

Mechanism of Resistance

Resistance to aztreonam is primarily through hydrolysis by beta-lactamase, alteration of penicillin-binding proteins (PBPs), and decreased permeability.

Interaction with Other Antimicrobials

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.

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**[5] section.

Reference ID: 3326494

Aerobic Gram-negative microorganisms:

Citrobacter species
Enterobacter species
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. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for aztreonam. However, the efficacy of aztreonam in treating clinical infections due to these microorganisms has 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, eg, *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*.)

Reference ID: 3326494

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution Techniques

Quantitative methods are used to determine antimicrobial MICs.[1-3] 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[6] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of aztreonam powder. The MIC values should be interpreted according to the criteria in Table 2.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.[6,7] This procedure uses paper disks impregnated with 30 mcg aztreonam to test the susceptibility of microorganisms to aztreonam. The disk diffusion interpretive criteria are provided in Table 2.

Table 2: Susceptibility Test Interpretive Criteria for Aztreonam

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion Zone Diameters (mm)		
	(S) Susceptible	(I) Intermediate	(R) Resistant	(S) Susceptible	(I) Intermediate	(R) Resistant
Enterobacteriaceae	≤4	8	≥16	≥21	18-20	≤17
Haemophilus influenzae[a]	≤2	-	-	≥26	-	-
Pseudomonas aeruginosa	≤8	16	≥32	≥22	16-21	≤15

[a] The current absence of data on resistant isolates precludes defining any category other than "Susceptible." If isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for additional testing.

Reference ID: 3326494

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individual performing the test.[6-8] Standard aztreonam powder should provide the following range of MIC values noted in Table 3. For the diffusion technique using the 30 mcg disk, the criteria in Table 3 should be achieved.

Table 3: Acceptable Quality Control Ranges for Aztreonam

QC Strain	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion Zone Diameters (mm)
Escherichia coli ATCC 25922	0.06-0.25	28-36
Haemophilus influenzae ATCC 49247	0.12-5	30-38
Pseudomonas aeruginosa ATCC 27853	2-8	23-29

INDICATIONS AND USAGE

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

AZACTAM is indicated for the treatment of the following infections caused by susceptible Gram-negative microorganisms:

Reference ID: 3326494

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

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

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

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

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

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

AZACTAM 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. AZACTAM is effective against most of the commonly encountered Gram-negative aerobic pathogens seen in general surgery.

Concurrent Therapy

Concurrent initial therapy with other antimicrobial agents and AZACTAM is recommended before the causative organism(s) is known in seriously ill patients who are

---

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

Reference ID: 3326494

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 AZACTAM (see **DOSAGE AND ADMINISTRATION**). Certain antibiotics (eg, 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 AZACTAM (aztreonam 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 (eg, 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 (eg, 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 AZACTAM, 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*.

Reference ID: 3326494

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 2 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 AZACTAM 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.

Reference ID: 3326494

Information for Patients

Patients should be counseled that antibacterial drugs including AZACTAM should only be used to treat bacterial infections. They do not treat viral infections (eg, the common cold). When AZACTAM 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 AZACTAM 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 with aztreonam have not been conducted using an intravenous route of administration. A 104-week rat inhalation toxicology study to assess the carcinogenic potential of aztreonam demonstrated no drug-related increase in the incidence of tumors. Rats were exposed to aerosolized aztreonam for up to 4 hours per day. Peak plasma levels of aztreonam averaging approximately 6.8 mcg/mL were measured in rats at the highest dose level.

Genetic toxicology studies performed with aztreonam *in vitro* (Ames test, mouse lymphoma forward mutation assay, gene conversion assay, chromosome aberration assay in human lymphocytes) and *in vivo* (mouse bone marrow cytogenetic assay) did not reveal evidence of mutagenic or clastogenic potential.

A two-generation reproduction study in rats at daily doses of 150, 600, or 2400 mg/kg given prior to and during gestation and lactation, revealed no evidence of impaired fertility. Based on body surface area, the high dose is 2.9-fold greater than the maximum recommended human dose (MRHD) for adults of 8 g per day. There was a slightly reduced survival rate during the lactation period in the offspring of rats that received the high dose, but not in offspring of rats that received lower doses of aztreonam.

Reference ID: 3326494

Pregnancy

Pregnancy Category B

In pregnant women, aztreonam crosses the placenta and enters the fetal circulation.

Developmental toxicity studies in pregnant rats and rabbits with daily doses of aztreonam up to 1800 and 1200 mg/kg, respectively, revealed no evidence of embryotoxicity or fetotoxicity or teratogenicity. These doses, based on body surface area, are 2.2- and 2.9-fold greater than the MRHD for adults of 8 g per day. A peri/postnatal study in rats revealed no drug-induced changes in any maternal, fetal, or neonatal parameters. The highest dose used in this study, 1800 mg/kg/day, is 2.2 times the MRHD based on body surface area.

There are no adequate and well-controlled studies of aztreonam on human pregnancy outcomes. 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 AZACTAM have been established in the age groups 9 months to 16 years. Use of AZACTAM in these age groups is supported by evidence from adequate and well-controlled studies of AZACTAM in adults with additional efficacy, safety, and pharmacokinetic data from noncomparative 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 AZACTAM may be warranted. (See **CLINICAL PHARMACOLOGY**, **DOSAGE AND ADMINISTRATION**, and **CLINICAL STUDIES**.)

Geriatric Use

Clinical studies of AZACTAM did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

Reference ID: 3326494

Other reported clinical experience has not identified differences in responses between the elderly and younger patients.[9-12] 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**).

AZACTAM contains no sodium.

ADVERSE REACTIONS

Local reactions (eg, phlebitis/thrombophlebitis; discomfort/swelling) following intravenous administration occurred at rates of approximately 1.9%.

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

Reference ID: 3326494

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 AZACTAM 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 (1.0%). 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 every 6 hours. 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 every 6 hours.

Reference ID: 3326494

The increased frequency of these reported laboratory adverse events may be due to either increased severity of illness treated or higher doses of AZACTAM 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

AZACTAM, an intravenous solution in GALAXY plastic containers (PL 2040), is intended for intravenous use only. Dosage should be determined by susceptibility of the causative organisms, severity and site of infection, and the condition of the patient.

Table 4: Azactam Dosage Guidelines for Adults*

Type of Infection	Dose	Frequency (hours)
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.

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

Reference ID: 3326494

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

The duration of therapy depends on the severity of infection. Generally, AZACTAM 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 AZACTAM should be halved in patients with estimated creatinine clearances between 10 and 30 mL/min/1.73 m^2 after an initial loading dose of 1 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.

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

$$\text{Females: } 0.85 \times \text{above value}$$

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.

Reference ID: 3326494

Dosage in Pediatric Patients

AZACTAM 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**.)

Table 5: Azactam Dosage Guidelines for Pediatric Patients*

Type of Infection	Dose	Frequency (hours)
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.

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.

Directions for Use of AZACTAM (aztreonam injection) in GALAXY Plastic Container (PL 2040).

AZACTAM is to be administered as an intermittent intravenous infusion only.

Storage

Store in a freezer capable of maintaining a temperature of −20°C (−4°F).

Thawing of Plastic Containers

Thaw frozen container at room temperature, 25°C (77°F) or in a refrigerator, 2°C to 8°C (36°F-46°F). After thawing is complete, invert the container to assure a well-mixed solution. **(DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.)**

Check for minute leaks by squeezing container firmly. If leaks are detected, discard solution as sterility may be impaired.

The container should be visually inspected. Thawed solutions should not be used unless clear; solutions will be colorless to yellow. Components of the solution may precipitate in

Reference ID: 3326494

the frozen state and will dissolve upon reaching room temperature with little or no agitation. If after visual inspection the solution remains discolored, cloudy, or if an insoluble precipitate is noted or if any seals or outlet ports are not intact, the container should be discarded.

DO NOT ADD SUPPLEMENTARY MEDICATION.

The thawed solution in GALAXY plastic container (PL 2040) remains chemically stable for either 14 days under refrigeration (2°C-8°C/36°F-46°F) or for 48 hours at room temperature (25°C/77°F). **DO NOT REFREEZE THAWED ANTIBIOTICS**.

Preparation for Intravenous Administration

Use aseptic technique.

1. Suspend container(s) from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

Additives or other medication should not be added to AZACTAM or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of several different drugs, it should be flushed before and after infusion of AZACTAM with an infusion solution compatible with AZACTAM (aztreonam injection) in GALAXY plastic container (PL 2040)* and any other drug(s) administered via this common line.

It is recommended that the intravenous administration apparatus be replaced at least once every 48 hours.

CAUTION: Do not use plastic containers in series connections. Such use could result in an embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Intravenous Administration

Infusion of AZACTAM should be completed within a 20- to 60-minute period. The plastic container is a single-dose unit; discard any unused portion remaining in the container.

Reference ID: 3326494

*The following infusion solutions are compatible with AZACTAM (aztreonam injection) in GALAXY plastic container (PL 2040):

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

HOW SUPPLIED

AZACTAM® (aztreonam injection) in GALAXY plastic container (PL 2040) is supplied as a frozen, 50 mL single-dose intravenous solution as follows:

1 g aztreonam/50 mL container:
Packages of 24 NDC 0003-2230-11

2 g aztreonam/50 mL container:
Packages of 24 NDC 0003-2240-11

Store at or below −20°C (−4°F) [see **Directions for Use of AZACTAM (aztreonam injection) in GALAXY Plastic Container (PL 2040)**].

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.

Reference ID: 3326494

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. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Ninth Edition. CLSI document M07-A9, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.

6. 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.

7. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition CLSI document M02-A11, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.

8. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Twenty-third Informational Supplement, CLSI document M100-S23. CLSI document M100-S23, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2013.

9. 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.

10. 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.

11. Roelandts F. Clinical use of aztreonam in a psychogeriatric population. *Acta Clin Belg* 1992;47:251-255.

Reference ID: 3326494

12. Andrews R, Fasoli R, Scoggins WG, et al. Combined aztreonam and gentamicin therapy for pseudomonal lower respiratory tract infections. *Clin Therap* 1994;16:236-252.

AZACTAM and the Bristol-Myers Squibb logo are registered trademarks of Bristol-Myers Squibb Company.

All other trademarks are the property of their respective owners.

AZACTAM® (aztreonam injection) in GALAXY plastic container (PL 2040) is manufactured to Bristol-Myers Squibb specifications
by:
Baxter Healthcare Corporation
Deerfield, IL 60015
for:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

TBD Rev TBD

Reference ID: 3326494