Bristol Myers Squibb

AZACTAM*

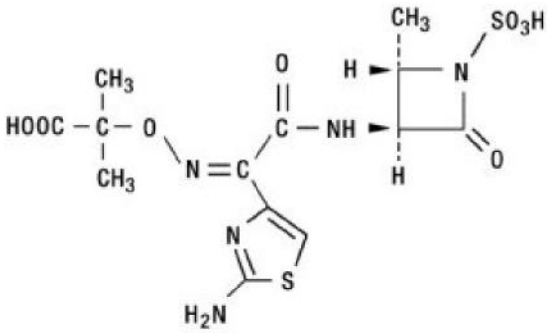
(Aztreonam)

DESCRIPTION

AZACTAM is a totally synthetic bactericidal antibiotic classified as a monobactam. It has activity against a wide spectrum of gram-negative aerobic pathogens.

The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other beta-lactam antibiotics (e.g., penicillins, cephalosporins, cephamycins, carbapenems). 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. The structural formula is:



$C_{13}H_{17}N_5O_8S_2$ MW 435.42 CAS-78110-38-0

CLINICAL PHARMACOLOGY

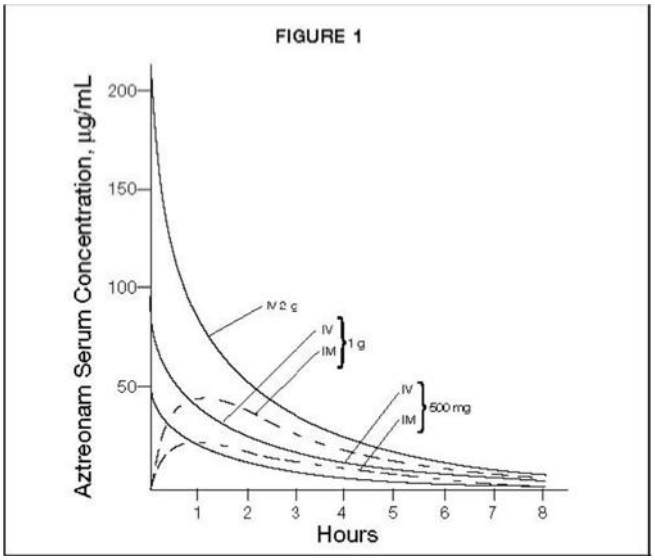
Adult Pharmacokinetics

Single 30 minute intravenous infusions of 500 mg, 1 g and 2 g doses of AZACTAM in healthy subjects produced peak serum levels of 54, 90, and 204 µg/mL, respectively, immediately after administration; at eight hours, serum levels were 1, 3, and 6 µg/mL, respectively (Figure 1). Single 3-minute intravenous injections of the same doses resulted

in serum levels of 58, 125 and 242 µg/mL at five minutes following completion of injection.

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

FIGURE 1



The serum levels of aztreonam following single 500 mg, or 1 g (intramuscular or intravenous) or 2 g (intravenous) doses of AZACTAM exceed the MIC_{90} for *Neisseria* sp., *H. influenza* and most genera of the *Enterobacteriaceae* for eight hours (for *Enterobacter* sp., the eight hour serum levels exceed the MIC for 80 percent of strains). For *P. 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.

The serum half-life of aztreonam averaged 1.7 hours (1.5 to 2.0) in subjects with normal renal function, independent of the dose and route of administration. In healthy subjects, based on a 70 kg person, the serum clearance was 91 mL/min and renal clearance was 56 mL/min; the apparent mean volume of distribution at steady-state averaged 12.6 liters, approximately equivalent to extra-cellular fluid volume.

In patients with impaired renal function, the serum half-life of aztreonam is prolonged. (See **DOSAGE AND ADMINISTRATION, Renal Impairment**). 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 µg/mL within the first two 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 µg/mL. After intramuscular injection of single 500 mg and 1 g doses of AZACTAM, urinary levels were approximately 500 and 1200 µg/mL, respectively, within the first two hours, declining to 180 and 470 µg/mL in the six to eight hour specimens. In healthy subjects, aztreonam is excreted in the urine about equally by active tubular secretion and glomerular filtration. Approximately 60 to 70 percent of an intravenous or intramuscular dose was recovered in the urine by eight hours. Urinary excretion of a single parenteral dose was essentially complete by 12 hours after injection. About 12 percent 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 AZACTAM every eight hours for seven days to healthy subjects produced no apparent accumulation of aztreonam or modification of its disposition characteristics; serum protein binding averaged 56 percent and was independent of dose. An average of about 6 percent of a 1 g intramuscular dose was excreted as a microbiologically inactive open beta-lactam ring hydrolysis product of aztreonam in the zero to eight 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-3-glucosaminidase, alanine aminopeptidase, and 3_2-microglobulin) were used. No abnormal results were obtained.

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

EXTRAVASCULAR CONCENTRATIONS OF AZTREONAM AFTER A SINGLE PARENTERAL DOSE*

Fluid or Tissue	Dose (g)	Route	Hours Post-injection	Number of Patients	Mean Concentration (µg/mL or µg/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 - adults)	2	IV	0.9-4.3	16	3
(inflamed meninges - pediatric)	30 or 50mg/kg	IV	1.2 -3.5	6	4**
pericardial fluid	2	IV	1	6	33
pleural fluid	2	IV	1.1-3.0	3	51
synovial fluid	2	IV	0.8-1.9	11	83
Tissues					
atrial appendage	2	IV	0.9-1.6	12	22
endometrium	2	IV	0.7-1.9	4	9
fallopian tube	2	IV	0.7-1.9	8	12
fat	2	IV	1.3-2.0	10	5
femur	2	IV	1.0-2.1	15	16
gallbladder	2	IV	0.8-1.3	4	23
kidney	2	IV	2.4-5.6	5	67
large intestine	2	IV	0.8-1.9	9	12
liver	2	IV	0.9-2.0	6	47
lung	2	IV	1.2-2.1	6	22
myometrium	2	IV	0.7-1.9	9	11
ovary	2	IV	0.7-1.9	7	13
prostate	1	IM	0.8-3.0	8	8
skeletal muscle	2	IV	0.3-0.7	6	16
skin	2	IV	0.0-1.0	8	25
sternum	2	IV	1	6	6

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

** Range of CSF concentrations are 2.5 to 8.7 µg/mL. CSF concentrations are 5 to 10% of serum concentrations drawn within 30 minutes.

The concentration of aztreonam in saliva at 30 minutes after a single 1 g intravenous dose was 0.2 µg/mL; in breast milk at two hours after a single 1 g intravenous dose, 0.2 µg/mL, and at six hours after a single 1 g intramuscular dose, 0.3 µg/mL; in amniotic fluid at six to eight hours after a single 1 g intravenous dose, 2 µg/mL. The concentrations of aztreonam in peritoneal fluid obtained one to six hours after multiple 2 g intravenous doses ranged between 12 and 90 µg/mL in most 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.

Pharmacokinetics (elderly): In a study of healthy elderly male subjects (65-75 years of age) the average elimination half-life of aztreonam (2.1 hr) was slightly longer than that found in young healthy males. This finding is consistent with normally diminished renal function in healthy elderly subjects. Age *per se* is not an indication for dosage reduction, which should be based on other factors, primarily parameters of renal function.

Pharmacokinetics (pediatric): The pharmacokinetics of aztreonam in pediatric patients varies with age. Data obtained after single doses for various patient sub-groups are listed in the following table. There were no significant changes in pharmacokinetic parameters after multiple dosing (30 mg/kg) for 5-9 days. Data on safety and effectiveness in neonates younger than one week are limited; use in this population needs to be carefully assessed. (See **DOSAGE AND ADMINISTRATION.**)

Mean (± SEM) Pharmacokinetic Parameters for 30 mg/kg or 50 mg/kg single doses

	Number	Dose (mg/kg)	Infusion rate (min)	Peak serum conc. (µg/mL)	$t_{1/2}$ (hr)	Serum clearance (mL/min/kg)
Newborn 1wk-1mo	5	30	3	83.7 (13.9)	2.4	1.68 (0.16)
Infant >1mo-2yr	6	30	3	115.5 (7.2)	1.7	1.87 (0.31)
Children >2yr-12yr	5	30	3	140.8 (45.8)	1.7	2.50 (0.15)
Children 11-12 yr	4	30	30	108.8 (12.9)	1.6	1.81 (0.40)

Children* 10-18 yr	10	30	3	175.0 (10.9)	1.5	2.46 (0.22)
Children 3-12 yr	5	50	3	214.0 (34.7)	2.0	1.94 (0.24)
Children 2-12 yr	5	50	30	186.0 (24.8)	1.2	2.51 (0.29)

* Patients with cystic fibrosis

Approximately three-fourths of an administered dose is excreted unchanged in the urine during the 24 hours following administration.

Studies *in vitro* demonstrated that aztreonam, at concentrations up to 660 µg/mL, did not displace bilirubin from albumin, either in a purified bilirubin-albumin solution or in hyperbilirubinemic neonatal serum.

IMMUNOLOGY

There is no evidence to support IgE-mediated cross-reactivity between aztreonam and other beta-lactam antibiotics. However, rare cases of *de novo* sensitization to AZACTAM have occurred in patients who are already at high risk for such reactions, including those with multiple exposures to beta-lactam antibiotics such as patients with cystic fibrosis. (See **CONTRAINDICATIONS and PRECAUTIONS).**

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 (ie, penicillinases and cephalosporinases) produced by most gram-negative and gram-positive pathogens; it is therefore, usually active against gram-negative aerobic organisms that are resistant to antibiotics hydrolyzed by beta-lactamases. 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 is active *in vitro* against most strains of the following

organisms, including many that are multiply-resistant to other antibiotics (i.e., certain cephalosporins, penicillins, and aminoglycosides):

Escherichia coli

Enterobacter species

Klebsiella species including *K. pneumoniae* and *K. oxytoca*

Proteus mirabilis

Proteus vulgaris

Morganella morganii (formerly *Proteus morganii*)

Providencia species, including *P. stuartii* and *P. rettgeri* (formerly *Proteus rettgeri*)

Pseudomonas species including *P. aeruginosa*

Serratia marcescens

Neisseria gonorrhoeae (including penicillinase-producing strains)

Haemophilus influenzae (including ampicillin-resistant and other penicillinase-producing strains)

Citrobacter species

Some strains of *Acinetobacter calcoaceticus*

Aztreonam is also active *in vitro* against a variety of other aerobic gram-negative pathogens, although the clinical significance of this finding has not been established. These organisms include:

Salmonella species

Shigella species

Pasteurella multocida

Yersinia enterocolitica

Aeromonas hydrophila

Neisseria meningitidis

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. Due to the induction of beta-lactamases, certain antibiotics (e.g., cefoxitin, imipenem) have been found to cause antagonism with many beta-lactams, including

aztreonam, for certain gram-negative aerobes, such as *Enterobacter* species and *Pseudomonas* species.

Alterations of the anaerobic intestinal flora by broad spectrum antibiotics may permit overgrowth of potential pathogens, e.g., *Candida* and *Clostridia* 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 Testing

Diffusion Technique: Quantitative procedures that require measurement of zone diameters give precise estimates of microbial susceptibility to antibiotics. One such method, recommended for use with the aztreonam 30 µg disc, is the National Committee of Clinical Laboratory Standards (NCCLS) approved procedure. Only a 30 µg aztreonam disc should be used; there are no suitable surrogate discs.

Results of laboratory tests using 30 µg aztreonam discs should be interpreted using the following criteria:

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

Dilution Technique: Broth, agar microdilution methods or equivalent (eg., E test™), may be used to determine the minimal inhibitory concentration (MIC) of aztreonam.

MIC test results should be interpreted according to the concentrations of aztreonam that can be attained in serum, tissues and body fluids.

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

For any susceptibility test, a report of "susceptible" indicates that the pathogen is likely to respond to AZACTAM therapy; a report of "resistant" indicates that the pathogen is not likely to respond. A report of "intermediate" (moderate susceptibility) indicates that the pathogen is expected to be susceptible to AZACTAM (aztreonam) if high dosages are used,

or if the infection is confined to tissues and fluids (e.g., urine, bile) in which high aztreonam levels are attained.

The quality control cultures should have the following assigned daily ranges for aztreonam:

		Discs	**Mode MIC (µg/mL)**
E. coli	(ATCC 25922)	28-36 mm	0.06-0.25
P. aeruginosa	(ATCC 27853)	23-29 mm	2.0-8.0

INDICATIONS

AZACTAM is indicated for the treatment of the infections listed below when caused by susceptible gram-negative microorganisms.

Before initiating treatment with AZACTAM, appropriate specimens should be obtained for isolation of the causative organism(s) and for determination of susceptibility to aztreonam. Treatment may be started empirically before results of susceptibility testing are available. In infections where gram-positive or anaerobic pathogens are suspected or are shown to be present, AZACTAM must be used with another antibiotic to provide appropriate coverage. See **Concurrent Therapy**.

Urinary Tract Infections (complicated and uncomplicated), including pyelonephritis and cystitis (initial and recurrent) and asymptomatic bacteriuria.

Lower Respiratory Tract Infections, including pneumonia and bronchitis. In the treatment of acute pulmonary exacerbations in patients with cystic fibrosis, clinical improvement is usually noted.

Bacteremia/Septicemia

Meningitis caused by *Haemophilus influenzae* and *Neisseria meningitidis.*

Bone and Joint Infections

Skin and Skin-Structure Infections, including those associated with post-operative wounds, ulcers and burns.

Intra-abdominal Infections, including peritonitis.

Gynecologic Infections, including pelvic inflammatory disease, endometritis and pelvic cellulitis.

Gonorrhea (acute uncomplicated urogenital or anorectal infections due to beta-lactamase producing or non-producing strains of *N. gonorrhoeae*).

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 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. 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.

Some patients with serious infections due to *Pseudomonas* may benefit from concurrent use of AZACTAM and an aminoglycoside because of synergistic action. These agents are also synergistic *in vitro* against many strains of *Enterobacteriaceae*, and other gram-negative aerobic bacilli. However, this enhanced activity is not predictable.

CONTRAINDICATIONS

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

PRECAUTIONS

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

Antibiotics, like other drugs, should be given with caution to any patient with a history of allergic reaction to structurally related compounds. If an allergic reaction occurs, discontinue the drug and institute supportive treatment as appropriate **(**See

IMMUNOLOGY). Serious hypersensitivity reactions may require epinephrine and other emergency measures.

Use of beta-lactam containing therapies, including aztreonam, can cause encephalopathy (e.g. confusion, impairment of consciousness, epilepsy, movement disorders); particularly in patients with renal impairment and in association with beta-lactam overdose. AZACTAM can have an important impact on the ability to drive and use machines should encephalopathy occur.

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. 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. Treatment with medication that inhibits intestinal peristalsis should not be given.

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 and fungi. Should superinfection occur during therapy, appropriate measures should be taken.

Drug Interactions

Concomitant administration of probenecid or furosemide and AZACTAM cause clinically insignificant increases in the serum levels of aztreonam. Single-dose pharmacokinetic studies have not shown any significant interaction between aztreonam and 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.

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.

Pregnancy

Aztreonam crosses the placenta and enters the fetal circulation.

Studies in pregnant rats and rabbits, with daily doses up to 15 and 5 times the maximum recommended human dose respectively, 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 breast milk in concentrations that are less than 1 percent of concentrations determined in simultaneously obtained maternal serum. Consideration should be given to temporary discontinuation of nursing during treatment with AZACTAM.

Pediatric Use

Data on safety and effectiveness in neonates younger than one week are limited; use in this population needs to be carefully assessed. (See **DOSAGE AND ADMINISTRATION.)**

AZACTAM contains arginine. Studies in low birth weight infants have demonstrated that arginine administered in the AZACTAM formulation may result in increases in serum arginine, insulin and indirect bilirubin. The consequences of exposure to this amino acid during treatment of neonates have not been fully ascertained.

ADVERSE REACTIONS

In clinical studies, adverse effects were infrequent with about 2% of patients having therapy discontinued. Effects considered related or of uncertain relationship to AZACTAM therapy are:

Hypersensitivity: Anaphylaxis, angioedema, bronchospasm.

Dermatologic: Rash, pruritus, petechiae, purpura, diaphoresis, flushing, urticaria, erythema multiforme, toxic epidermal necrolysis and exfoliative dermatitis.

Hematologic: Eosinophilia, increases in prothrombin and partial thromboplastin time, thrombocytosis, thrombocytopenia, leukocytosis, neutropenia, anemia, pancytopenia, bleeding and positive Coombs Test have occurred rarely.

Hepatobiliary: Elevations of hepatic transaminases and alkaline phosphatase levels usually reversing during therapy and without overt signs or symptoms of hepatobiliary dysfunction. Clinical diagnoses of jaundice and hepatitis were reported rarely.

Gastrointestinal: Diarrhea, nausea and/or vomiting, abdominal cramps, mouth ulcer and altered taste. Rare cases of *C. difficile*-associated diarrhea, including pseudomembranous colitis, or gastro-intestinal bleeding have occurred.

Local Reactions: Discomfort at the IV injection site and phlebitis/thrombophlebitis; mild discomfort was noted at the IM injection site.

Nervous System Disorders: Encephalopathy (e.g. confusion, impairment of consciousness, epilepsy, movement disorders (see **PRECAUTIONS**).

Miscellaneous: Rare instances of the following reactions have been reported. Vaginitis, vaginal candidiasis, hypotension, seizure, diplopia, weakness, paresthesia, confusion, dizziness, vertigo, insomnia, ECG changes, tinnitus, headache, breast tenderness, halitosis, muscle aches, fever, malaise, sneezing and nasal congestion, wheezing, dyspnea and chest pain. Increases in serum creatinine were uncommon.

OVERDOSAGE

If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis. Aztreonam has been shown to be cleared from the serum by continuous arterio-venous hemofiltration.

Use of beta-lactam containing therapies, including aztreonam, can cause encephalopathy (e.g. confusion, impairment of consciousness, epilepsy, movement disorders); particularly in patients with renal impairment and in association with beta-lactam overdose.

DOSAGE AND ADMINISTRATION

AZACTAM 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.

ADULT DOSAGE GUIDELINES

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.

A single dose of 1 g of AZACTAM administered intramuscularly is effective in the treatment of acute uncomplicated gonorrhea and acute uncomplicated cystitis.

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. 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.

Pediatric

The usual dosage for patients older than one week is 30 mg/kg every six to eight hours. For severe infections in patients two years or older, 50 mg/kg every six to eight hours is recommended. The recommended dose for all patients in the treatment of infections due to *P. aeruginosa* is 50 mg/kg every six to eight hours.

The maximum daily pediatric dose should not exceed the maximum recommended dose for adults.

Renal Impairment

Prolonged serum levels of aztreonam may occur in patients with transient or persistent renal insufficiency. Therefore, after an initial usual dose, the dosage of AZACTAM should

be halved in patients with estimated creatinine clearances between 10 and 30 mL/min/1.73 m^2.

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.

Males:

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

Females: 0.85 × 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 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.

CONSTITUTION AND STABILITY

Preparation of Parenteral Solutions

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 AZACTAM 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.

Each gram of AZACTAM reconstituted with 3 mL of an appropriate solution (see **Preparation of Parenteral Solutions**) provides 1 gram of AZACTAM in a total volume of approximately 4 mL.

Intramuscular (IM) Administration

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

Sterile Water for Injection USP

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

Sodium Chloride Injection USP

Bacteriostatic Sodium Chloride Injection USP (with benzyl alcohol*)

*Diluents containing benzyl alcohol are not suitable for use in the newborn.

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. Solutions prepared for intramuscular injection must be used within 24 hours if stored under controlled room temperature (15°-30°C), or within 3 days if refrigerated (2°-8°C).

Intravenous (IV) Administration

For *Bolus Injection*: The selected dose of AZACTAM should be constituted with 6 to 10 mL Sterile Water for Injection USP and be **slowly** injected directly into a vein, or the tubing of a suitable administration set, over a period of 3 to 5 minutes.

For *Infusion*: Each gram of aztreonam should be initially constituted with at least 3 mL Sterile Water for Injection USP. Further dilution, to a final concentration not exceeding 2% w/v (at least 50 mL of solution per gram of aztreonam), 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, 5% or 10%

Lactated Ringer's and 5% Dextrose Injection

Plasma-Lyte® M and 5% Dextrose

* Diluents containing benzyl alcohol are not suitable for use in the newborn.

Alternatively, contents of the 100 mL bottle may be constituted to a final concentration not exceeding 2% w/v (at least 50 mL of solution per gram of aztreonam) with appropriate infusion listed above. These solutions may be frozen immediately.

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 AZACTAM 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 AZACTAM into a compatible infusion solution during administration; in this case, the final dilution of aztreonam should provide a concentration not exceeding 2% w/v.

AZACTAM solutions for IV infusion at concentrations not exceeding 2% w/v must be used within 24 hours following constitution if kept at controlled room temperature (59°-86°F/15°-30°C) or within 3 days if refrigerated (36°-46°F/2°-8°C).

AZACTAM solutions at concentrations exceeding 2% w/v (1 gram aztreonam per 50 mL) should be used promptly after preparation; except if prepared in sterile water for injection or sodium chloride injection. These solutions must be used within 24 hours if stored at controlled room temperature or within 3 days if refrigerated.

Admixtures with Other Antibiotics

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

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

Other drug admixtures, or admixtures of the above drugs in concentrations outside of those specified, are not recommended since compatibility data are not available.

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

HOW SUPPLIED

AZACTAM For injection is available in the following presentations:

- Single-dose vial (15 mL capacity) containing 1 g of product for intramuscular or intravenous administration.
- Single-dose vial (15 mL capacity) containing 0.5 grams of product for intramuscular or intravenous injection.

The product, like all medicines, must be kept away from children.

The expiration date applies to the product contained into an intact and properly stored package

Storage

Store original packages at room temperature (not to exceed 30°C); avoid excessive heat.

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