AZACTAM® (aztreonam for injection, USP)

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 for injection, USP) contains the active ingredient aztreonam, a monobactam. It was originally isolated from Chromobacterium violaceum. It is a synthetic bacterial 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:

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

CLINICAL PHARMACOLOGY
Single 30-minute intravenous infusions of 500 mg, 1 g, and 2 g doses of 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 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 AZACTAM, 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.

The serum levels of aztreonam following single 500 mg or 1 g (intramuscular or intravenous) or 2 g (intravenous) doses of AZACTAM exceed the MIC₉₀ 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 MIC₉₀ for approximately 4 to 6 hours. All of the above doses of AZACTAM result in average urinary levels of aztreonam that exceed the MIC₉₀ 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 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. 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.

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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, netilmicin sodium, cephradine, cindamycin, 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 many 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 section.

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

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)

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 method4 (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 should provide an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.1-4 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>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum Inhibitory Concentrations (mcg/mL)</th>
<th>Disk Diffusion Zone Diameters (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(S)</td>
<td>(I)</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>≤4</td>
<td>8</td>
</tr>
<tr>
<td>Haemophilus influenzae*</td>
<td>≤2</td>
<td>-</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa*</td>
<td>≤8</td>
<td>16</td>
</tr>
</tbody>
</table>

* 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.

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.4 Standard aztreonam powder should provide the following range of MIC values noted in Table 3. For diffusion technique using the 30 mcg disk, the criteria in Table 3 should be achieved.

<table>
<thead>
<tr>
<th>QC Strain</th>
<th>Minimum Inhibitory Concentrations (mcg/mL)</th>
<th>Disk Diffusion Zone Diameters (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>0.06-0.25</td>
<td>28-36</td>
</tr>
<tr>
<td>Haemophilus influenza</td>
<td>0.12-5</td>
<td>30-38</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2-8</td>
<td>23-29</td>
</tr>
</tbody>
</table>

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AZACTAM (aztreonam for injection, USP) 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:

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*.

Sepsis or Septicemia caused by Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Serratia marcescens*.

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

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

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

* Efficacy for this organism in this organ system was studied in fewer than 10 infections.
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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 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 for injection, USP) 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.

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.

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 stopping 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 inhalation toxicity 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 toxicity 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 body weight 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.

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. Other reported clinical experience has not identified differences in response between the elderly and younger patients. 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. 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 such as phlebitis/thrombophlebitis following intravenous administration, and discomfort/swelling at the injection site following intramuscular 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:
  - Hyperosensitivity—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, hallucosis
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%).

Pediatric Use
AZACTAM® (aztreonam for injection, USP) is not recommended for initial therapy of serious infections in infants younger than 2 months of age.

Due to the high incidence of pseudomembranous colitis (Clostridium difficile) and the potential for serious complications, verify that the diagnosis is correct before initiating therapy.

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

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

Dosage in Pediatric Patients
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*

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Frequency (hours)</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate infections</td>
<td>8 or 12</td>
<td>30 mg/kg</td>
</tr>
<tr>
<td>Severe to moderate infections</td>
<td>8 or 12</td>
<td>30 mg/kg</td>
</tr>
</tbody>
</table>

* 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.

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 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.

Admixtures with Other Antibiotics
Intravenous infusion solutions of AZACTAM 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-clavulanate sodium and aztreonam-vancocin hydrochloride admixtures are stable in Dineal 137 (Peritoneal Dialysis Solution) with 4.25% Dextrose for up to 24 hours at room temperature.
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Aztreonam is incompatible with nafcillin sodium, cephradine, and metronidazole. Other admixtures are not recommended since compatibility data are not available.

Intravenous Solutions

For Bolus Injection: The contents of an AZACTAM 15 mL capacity vial should be constituted with 6 to 10 mL Sterile Water for Injection, USP.

For Infusion: If the contents of a 15 mL capacity 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%
- Lactated Ringer’s Injection, USP
- Sodium Chloride Injection, USP, 0.9%
- Sodium Lactate Injection, USP (M/6 Sodium Lactate)
- I Orion® 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
- Pharma-Lyte M and 5% Dextrose

Intramuscular Solutions

The contents of an AZACTAM 15 mL capacity vial should be constituted with at least 3 mL of an appropriate diluent per gram aztreonam. The following diluents may be used:

- Sterile Water for Injection, 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 Intravenous and Intramuscular Solutions

AZACTAM solutions for intravenous infusion at concentrations not exceeding 2% w/v must be used within 48 hours following constitution if kept at controlled room temperature (59°F–86°F/15°C–30°C) or within 7 days if refrigerated (36°F–46°F/2°C–8°C).

AZACTAM 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 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 (see Preparation of Parenteral Solutions: Intravenous 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

AZACTAM® (aztreonam for injection, USP)

Single-dose 15 mL capacity vials:

- 1 g/vial: Packages of 10
  NDC 0003-2560-16

- 2 g/vial: Packages of 10
  NDC 0003-2570-16

Storage

Store original packages at room temperature; avoid excessive heat.

AZACTAM® (aztreonam injection) in GALAXY plastic container (PL 2040) 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

REFERENCES


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

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