NAME OF THE MEDICINE

Aztreonam

DESCRIPTION

Azactam (aztreonam) is a totally synthetic monocyclic beta lactam belonging to a new class of antibiotics, the monobactams. Chemically, aztreonam is designated as:

\[(Z)-2-(((2\text{-amino-4-thiazolyl})-(((2S,3S)-2\text{-methyl-4-oxo-1-sulfo-3-azetidinyl}) \text{carbamoyl)methylene})\text{-amino)}\text{oxy})-2\text{-methylpropionic acid.}

The structural formula is:

![Structural formula of aztreonam](image)

Aztreonam contains a sulphonic acid substituent in the 1-position of the beta-lactam nuclear ring, which activates the beta-lactam moiety. It also contains an aminothiazolyl oxime side chain in the 3-position and a methyl group in the 4-position which confer the specific anti-bacterial spectrum and beta-lactamase stability.

Azactam for Injection (Aztreonam for Injection) is a white to off-white, free flowing sterile non-pyrogenic powder blend of aztreonam and L-arginine which upon reconstitution is intended for intravenous or intramuscular administration. Azactam for Injection is sodium free and contains approximately 814mg L-arginine per gram of aztreonam. The pH of Azactam solution, depending on the type and amount of diluent used, ranges between 4.5 and 7.5.

PHARMACOLOGY

Azactam V5.0
Pharmacokinetics

Azactam is not intended for oral administration as it is not absorbed from the gastrointestinal tract. Single 30-minute intravenous infusions of 0.5, 1 and 2gm doses of Azactam in healthy volunteers produced serum levels of 54, 90 and 204mcg/mL, respectively, immediately after administration (Figure 1). Single 3-minute intravenous injections of the same doses resulted in peak serum levels of 58, 125 and 242mcg/mL. Serum levels of aztreonam 8 hours after 3 or 30 minute infusions were 1, 3 and 6mcg/mL.

Figure 1 summarises the serum concentrations of aztreonam in healthy subjects after completion of single 30 minute intravenous infusions of 0.5, 1 or 2gm, or immediately following single intramuscular injections of 0.5 or 1gm. After intramuscular administration, maximum serum aztreonam concentrations occur at about one hour. After identical single intravenous or intramuscular doses of Azactam, either 0.5 or 1gm, 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.

After single 0.5, 1 and 2gm intravenous doses of Azactam (30 minute infusion) average urine concentrations of aztreonam were approximately 1100, 3500 and 6600mcg/mL, respectively, within the first two hours. After intramuscular injection of a single 0.5 or 1gm dose of Azactam urinary levels were approximately 500 and 1200mcg/mL respectively within the first two hours, declining to 180 and 470mcg/mL in the 6 to 8 hour specimens.

The range of average concentrations for aztreonam in the 8 to 12 hour urine specimens in the above studies was 25 to 120mcg/mL. 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 subjects over 65 years of age and a mean creatinine clearance of 40 mL/minute the serum
half-life was 8.5 hours. The half-life of the metabolite of aztreonam is approximately 15-20 hours. In healthy subjects, based on a 70kg person, the serum clearance was 91 mL/minute and renal clearance was 56mL/minute; the apparent mean volume of distribution at steady-state averaged 12.6 litres, approximately equivalent to extra-cellular fluid volume.

Intravenous or intramuscular administration of a single 0.5 or 1gm 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. An average of about 6% of a 1gm intramuscular dose was excreted as a microbiologically inactive open beta-lactam ring hydrolysis product of aztreonam in the zero to 8 hour urine collection on the last day of multiple dosing.

In healthy subjects approximately 60 to 70% of the intravenous or intramuscular dose administered was recovered in the urine by 8 hours. Urinary excretion of a single parenteral dose was essentially complete by 12 hours after injection. About 12% of a single radio-labelleld dose was recovered in the faeces; both unchanged aztreonam and the inactive beta-lactam ring hydrolysis product of aztreonam were present.

In patients with impaired renal function the serum half-life of aztreonam is prolonged. Aztreonam is cleared from the serum by haemodialysis, approx, 38% being removed in 4 hours.

Since the liver is a minor pathway of excretion, the serum half-life of aztreonam is only slightly prolonged in patients with hepatic impairment.

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

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### Extravascular Concentrations of Aztreonam After a Single Parenteral Dose**

<table>
<thead>
<tr>
<th>Fluid/Tissue</th>
<th>Dose (g)</th>
<th>Route</th>
<th>Mean Peak Concentration (mcg/mL or mcg/g)</th>
<th>Hours Post Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bile</td>
<td>1</td>
<td>IV</td>
<td>43</td>
<td>2</td>
</tr>
<tr>
<td>blister fluid</td>
<td>1</td>
<td>IV</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>bronchial secretion</td>
<td>2</td>
<td>IV</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>pericardial fluid</td>
<td>2</td>
<td>IV</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>synovial fluid</td>
<td>2</td>
<td>IV</td>
<td>102</td>
<td>1</td>
</tr>
<tr>
<td><strong>cont'd</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fluid/Tissue</th>
<th>Dose (g)</th>
<th>Route</th>
<th>Mean Peak Concentration (mcg/mL or mcg/g)</th>
<th>Hours Post Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tissues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>arterial appendage</td>
<td>2</td>
<td>IV</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>kidney</td>
<td>2</td>
<td>IV</td>
<td>48</td>
<td>3</td>
</tr>
</tbody>
</table>

Azactam V5.0
lungs  2  IV  25  2
prostate  1  IM  8  2
skeletal muscle  2  IV  13  1

# See susceptibility testing for MIC break points.

*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 0.8 hour after a single 1 gram intravenous dose was 0.2 mcg/mL, in breast milk at 2.4 hours after a single 1 gram intravenous dose was 0.2 mcg/mL and at 6 hours after a single 1 gram intramuscular dose was 0.3 mcg/mL, and in amniotic fluid at 6 hours after a single gram intravenous dose was 2 mcg/mL.

**Pharmacokinetics (Paediatrics)**

The pharmacokinetics of Azactam in paediatric patients are dependent on age and body weight. Data obtained after single doses for various patient subgroups are listed in the following table:

<table>
<thead>
<tr>
<th>Age (weight)</th>
<th>Mean serum conc. (mcg/mL)</th>
<th>Mean urine conc. (mcg/mL)</th>
<th>Mean serum half-life (hours)</th>
<th>Serum clearance (mL/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time</td>
<td>2</td>
<td>Time</td>
<td>2</td>
</tr>
<tr>
<td>&lt; 1 week</td>
<td>Peak</td>
<td>83</td>
<td>5.7</td>
<td>0.94</td>
</tr>
<tr>
<td>(&lt; 2.5 kg)</td>
<td>5 hours</td>
<td>31.7</td>
<td>756</td>
<td>179</td>
</tr>
<tr>
<td></td>
<td>6-12 hours</td>
<td>786</td>
<td>5.7</td>
<td>0.94</td>
</tr>
<tr>
<td>&lt; 1 week</td>
<td>Peak</td>
<td>98</td>
<td>2.6</td>
<td>1.41</td>
</tr>
<tr>
<td>(&gt; 2.5 kg)</td>
<td>5 hours</td>
<td>17.5</td>
<td>656</td>
<td>358</td>
</tr>
<tr>
<td></td>
<td>6-12 hours</td>
<td>656</td>
<td>2.6</td>
<td>1.41</td>
</tr>
<tr>
<td>1 week - 1 month</td>
<td>2</td>
<td>84</td>
<td>1.68</td>
<td>1.68</td>
</tr>
<tr>
<td></td>
<td>5.8</td>
<td>993</td>
<td>1.68</td>
<td>1.68</td>
</tr>
<tr>
<td>1 month - 2 years</td>
<td>2</td>
<td>141</td>
<td>1.87</td>
<td>1.87</td>
</tr>
<tr>
<td></td>
<td>5.8</td>
<td>1,414</td>
<td>1.87</td>
<td>1.87</td>
</tr>
<tr>
<td>2-12 years</td>
<td>141</td>
<td>1,414</td>
<td>1.7</td>
<td>2.50</td>
</tr>
<tr>
<td></td>
<td>5.8</td>
<td>3,727</td>
<td>1.7</td>
<td>2.50</td>
</tr>
</tbody>
</table>

1. Peak concentrations were measured within 15 minutes after the end of the infusion; other times are relative to the end of the infusion.
2. In this age group (n=5)

In paediatric patients, during the 24 hours following administration, approximately 75% of the administered dose of Azactam is excreted unchanged in the urine and about 1 to 4% is excreted as the open beta-lactam ring hydrolysis product of aztreonam.

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

Aztreonam exhibits bactericidal activity against a number of gram-negative aerobes. The bactericidal action of aztreonam results from the inhibition of bacterial cell wall synthesis due to its binding to Penicillin Binding Protein 3 (PBP3). Aztreonam is resistant to hydrolysis by many beta-lactamases (ie penicillinases and cephalosporinases) produced by gram-negative and gram-positive pathogens. In vitro resistance to aztreonam can be induced by repeated passage through antibiotic containing media in the same manner as with other beta-lactam antibiotics.

Aztreonam, unlike the majority of beta-lactam antibiotics, is usually not an inducer of beta-lactamase activity. Aztreonam is active in vitro against most strains of the following susceptible organisms:

- Escherichia coli;
- Enterobacter species;
- Klebsiella species, including K. pneumoniae and K. oxytoca (except those producing K-1 type beta lactamase);
- Proteus mirabilis;
- Proteus vulgaris;
- Morganella morganii (formerly Proteus morganii);
- Providencia species, including P. stuartii and P. rettgeri (formerly Proteus rettgeri);
- Serratia marcescens;
- Neisseria gonorrhoeae (including penicillinase-producing strains);
- Haemophilus influenzae (including ampicillin-resistant and other penicillinase producing strains);
- Citrobacter species;
- Pseudomonas aeruginosa*.

* Pseudomonas aeruginosa strains usually are either sensitive or have intermediate sensitivity (see susceptibility testing) to aztreonam. Other Pseudomonas species are usually resistant.

Aztreonam and aminoglycosides are synergistic in vitro against many of the strains of P. aeruginosa. However, such synergy is not always predictable.

Due to the induction of beta-lactamases, certain antibiotics (eg, 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 normal flora in the body by antibiotics permit overgrowth of potential pathogens, eg Candida and Clostridium species. Unlike broad spectrum antibiotics, aztreonam produces no effects on the normal intestinal anaerobic microflora. Clostridium difficile and its cytotoxin were not found in animal models following administration of aztreonam.

**SUSCEPTIBILITY TESTING**

*Diffusion Technique*

Quantitative procedures that require measurement of zone diameters give a precise estimate of antibiotic susceptibility. One such method, recommended for use with the aztreonam 30 mcg disc, is the National Committee of Clinical Laboratory Standards (NCCLS) approved procedure.

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

<table>
<thead>
<tr>
<th>ZONE DIAMETER (MM)</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>16-21</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>&lt;15</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

Since aztreonam has been shown in vitro to be active against organisms found to be resistant when other beta-lactams discs are used, susceptibility to aztreonam should be determined only with the 30 mcg aztreonam disc.

*Dilution Technique*

Broth or agar dilution methods may be used to determine the minimal inhibitory concentration (MIC) of aztreonam.

<table>
<thead>
<tr>
<th>(MCG/ML)</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>16</td>
<td>Intermediate (I)</td>
</tr>
<tr>
<td>&gt;32</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

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" suggests that the pathogen will be susceptible to Azactam if high doses are used, or if the infection is confined to tissues and fluids (e.g., urine, bile) in which high aztreonam levels are attained. (See DOSAGE AND ADMINISTRATION).
INDICATIONS

1. Azactam is indicated for use as a single agent in the treatment of infections known or strongly suspected to be due to susceptible gram negative aerobes, such as urinary tract infection, gonorrhoea, etc.

2. In combination with other suitable antibiotics to treat serious infections due to problem organisms known or likely to be susceptible to aztreonam.*

3. Meningitis caused by Haemophilus influenzae or Neisseria meningitidis. Azactam should not be used alone, but only in combination with other suitable antibiotics, in cases where meningitis is known or presumed to be due to the above organisms. Appropriate therapy should be instituted when results of sensitivity tests are known.

* Some patients with serious Pseudomonas infections may benefit from concurrent use of Azactam and an aminoglycoside because of synergistic action. However, this enhanced activity is not predictable. If such concurrent therapy is considered in patients with serious infections, susceptibility tests should be performed in vitro to determine the activity of the drugs in combination. Because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics, renal function should be monitored according to the aminoglycoside manufacturer's prescribing information, especially if high dosages of the aminoglycoside are to be used or if therapy is prolonged.

Before instituting treatment with Azactam, appropriate specimens should be obtained for isolation of the causative organism(s) and for determination of susceptibility to aztreonam.

Treatment with Azactam should normally be initiated on the basis of susceptibility tests, but it may be initiated in the above situations before the results of identification and sensitivity testing of the causative organism become available.

CONTRAINDICATIONS

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

PRECAUTIONS

As with other drugs inquiry should be made regarding a history of hypersensitivity reactions.

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. Serious hypersensitivity reactions may require adrenaline and other emergency measures.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics.
including Azactam. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibiotic agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Azactam is not indicated for the treatment of gynaecological infections or for other sites where aerobic gram negative organisms are not the common infective agents, but may be used if the infection can be shown to be due to susceptible gram negative organisms only.

Experience with patients with impaired hepatic function is limited. Appropriate monitoring of liver function in such patients is recommended during therapy.

Therapy with Azactam may result in overgrowth of nonsusceptible organisms which may require therapy.

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.

**Hepatic impairment**

A dose reduction is recommended for long-term treatment of patients with alcoholic cirrhosis, especially in cases when renal function is also impaired.

**INTERACTIONS WITH OTHER MEDICINES**

Concomitant administration of probenecid or frusemide 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.

**USE IN PREGNANCY:** Pregnancy Category B1

Aztreonam crosses the placenta and enters the fetal circulation.

Azactam produced no mutagenic changes in several standard laboratory models.

Studies in pregnant rats and rabbits disclosed no clear evidence of embryo toxicity, fetotoxicity, or teratogenicity. In rats given Azactam during late gestation and lactation no drug-induced changes were seen in any of the maternal, fetal, or neonatal parameters that were monitored.
Since studies in pregnant women have not been done, Azactam should be used during pregnancy only if clearly needed.

USE IN LACTATION

Studies in lactating women have shown that aztreonam is excreted in breast 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 during treatment with Azactam.

CARCINOGENESIS

Carcinogenicity studies in animals have not been performed.

PAEDIATRIC 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 EFFECTS

Azactam is generally well tolerated.

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

- **Hypersensitivity:** Anaphylaxis, angioedema, bronchospasm.

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

- **Haematological:** Eosinophilia, increases in prothrombin and partial thromboplastin time, thrombocytosis, thrombocytopenia, leukocytosis, neutropenia, anaemia, pancytopenia, bleeding and positive Coombs Test have occurred rarely.

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

_Gastrointestinal:_ Diarrhoea, nausea and/or vomiting, abdominal cramps, mouth ulcer and altered taste. Abdominal distension has been noted in children. Rare cases of _C. Difficile_-associated diarrhoea, including pseudomembranous colitis, or gastro-intestinal bleeding have occurred.

_Renal:_ Aztreonam was not associated with changes in renal function in healthy subjects. Renal function was monitored using standard tests (serum creatinine, creatinine clearance, BUN, urinalysis and total urinary protein excretion) as well as special tests (excretion of N-acetyl-B-glucosaminidase, alanine aminopeptidase and B2-microglobulin).

_Local Reactions:_ Discomfort at the IV injection site and phlebitis/thrombophlebitis; mild discomfort was noted at 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, paraesthesia, confusion, dizziness, vertigo, insomnia, ECG changes, tinnitus, headache, breast tenderness, halitosis, altered taste, muscle aches, fever, malaise, sneezing and nasal congestion, wheezing, dyspnea and chest pain. Transient increase in serum creatinine were uncommon.

**DOSAGE AND ADMINISTRATION**

Azactam for Injection may be administered intravenously or by intra-muscular injection.

Dosage and route of administration should be determined by susceptibility of the causative organisms, severity of infection, and the condition of the patient.

<table>
<thead>
<tr>
<th>ADULTS DOSAGE GUIDE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TYPE OF INFECTION</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Moderately severe systemic infections</td>
</tr>
<tr>
<td>Severe systemic or life-threatening* infections</td>
</tr>
</tbody>
</table>

* Maximum recommended dose is 8 grams per day.

Azactam V5.0
For meningitis, appropriate therapy should be instituted when results of sensitivity tests are known. Duration of Azactam therapy should be as follows:

- N. meningitidis duration of therapy should be 7-10 days;
- H. influenzae duration of therapy should be 10-14 days.

In the elderly, renal status is the major determinant of dosage. Estimated creatinine clearance should be used to determine appropriate dosage since serum creatinine is not an accurate measurement of renal function in these patients. (See RENAL IMPAIRMENT).

The intravenous route is recommended for patients requiring single doses greater than 1 gram or those with bacterial septicaemia, localised parenchymal abscess (eg 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 grams every 6 or 8 hours is recommended, at least for initial therapy, in systemic infections caused by this organism. (See MICROBIOLOGY).

A single dose of 1 gram Azactam administered intramuscularly is effective in the treatment of acute uncomplicated gonorrhoea and acute uncomplicated cystitis.

**Renal Impairment**

Since aztreonam is mostly eliminated by the kidney it is recommended that after an initial loading dose of 1 to 2 grams, the dose of Azactam should be reduced in patients with estimated creatinine clearances as shown in the table below:

<table>
<thead>
<tr>
<th>CREATININE CLEARANCE</th>
<th>DOSE AS FRACTION OF NORMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80mL/minute &gt; 1.3mL/s</td>
<td>1</td>
</tr>
<tr>
<td>30-79mL/minute 0.5-1.3mL/s</td>
<td>½</td>
</tr>
<tr>
<td>10-29mL/minute 0.02-0.5mL/s</td>
<td>¼</td>
</tr>
<tr>
<td>&lt; 10mL/minute &lt;0.2mL/s</td>
<td>⅛</td>
</tr>
</tbody>
</table>

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. The serum creatinine should represent a steady state of renal function.

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

**Females:** $0.85 \times$ above value

In patients with severe renal failure creatinine clearance ($< 0.2\text{mL/s}$), such as those supported by Azactam V5.0
haemodialysis, the usual dose of 0.5, 1 or 2 grams should be given initially. The maintenance dose should be one-fourth of the usual initial dose given at fixed intervals of 6, 8 or 12 hours. For serious infections, in addition to the latter maintenance doses, one-eighth of the initial dose should be given after each haemodialysis.

**Paediatric Patients**
The usual dosage for patients older than one week is 30mg/kg/dose every 8 hours. For severe infections in patients 2 years of age or older, 50mg/kg/dose every 6 or 8 hours is recommended. Total maximum daily dose should not exceed recommended dose for adults. Dosage information is not yet available for newborns less than one week old.

**Constitution and Stability**
Depending upon the concentration of aztreonam and diluent used, constituted Azactam for Injection yields a colourless to light straw yellow solution which may develop a slight pink tint on standing. The pH of Azactam solutions, depending on the type and amount of diluent used, ranges between 4.5 and 7.5.

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

Upon the addition of the diluent the contents should be shaken immediately and vigorously. Vials of constituted Azactam for Injection are not intended for multiple-dose use. Should the entire volume in the container not be used for a single dose, the unused solution must be discarded. Azactam should not be admixed with any other drugs or antibiotics. Only those diluents listed below should be used.

**Intramuscular Administration**
Azactam for Injection should be constituted with at least 3mL of diluent per gram of aztreonam. Azactam is 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). Since Azactam is well tolerated no local anaesthetic agent is required; therefore, compatibility studies have not been performed.

Azactam may be diluted with Water for Injection or Sodium Chloride Injection, or the corresponding bacteriostatic preparations containing either benzyl alcohol* or parabens as preservatives.

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

**Intravenous Administration**
For bolus injection: The selected dose should be constituted with 6 to 10mL Water for Injection, BP, and the resulting solution slowly injected directly into the vein over a period of 3 to 5
minutes.

For infusion: Each gram of aztreonam supplied in 15mL vials should be initially constituted with at least 3mL of Water for Injection, BP provides 1 gram of aztreonam in a total volume of approximately 4 mL. The resulting initial solution should be diluted with an appropriate infusion solution to a final concentration not exceeding 2% w/v (at least 50mL solution per gram aztreonam).

The Azactam infusion should be administered over a 30 minute period.

With intermittent infusion of Azactam and another drug via a common delivery tube, the tube should be flushed before and after delivery of Azactam with any appropriate infusion solution compatible with both drug solutions. The drugs should not be delivered simultaneously.

A volume control administration set may be used to deliver the initial solution of Azactam for Injection into a compatible infusion solution being administered. With use of a Y-tube administration set, careful attention should be given to the calculated volume of Azactam solution required so that the entire dose will be infused.

The following intravenous solutions may be used as diluents for the administration of Azactam for Injection by intravenous infusion.

- Water for Injection
- Sodium Chloride Injection
- Ringer's Injection
- Lactated Ringer's Injection
- Glucose Injection (5%)
- Glucose Injection (10%)
- Glucose (5%) with Sodium Chloride (0.9%) Injection
- Glucose (5%) with Sodium Chloride (0.45%) Injection
- Glucose (5%) with Sodium Chloride (0.2%) Injection
- Sodium Lactate (M/6 Sodium Lactate)
- Ionosol (R) B and 5% Glucose
- Isolyte (R) E
- Isolyte (R) E with 5% Glucose
- Isolyte (R) M with 5% Glucose
- Normosol (R) -R
- Normosol (R) R and 5% Glucose
- Normosol (R) M and 5% Glucose
- 10% Travert (R) Injection
- Mannitol Injection (5%)
- Mannitol Injection (10%)
- Lactated Ringer's and 5% Glucose Injection
- Plasma-Lyte (R) M and 5% Glucose Injection
- 10% Travert (R) in Electrolyte No. 1 Injection
- 10% Travert (R) in Electrolyte No. 2 Injection
OVERDOSAGE

In case of overdose, immediately contact the Poisons Information Centre on 13 11 26 for advice.

If necessary, aztreonam may be cleared from the serum by haemodialysis and/or peritoneal dialysis. Aztreonam has been shown to be cleared from the serum by continuous arteriovenous 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.

PRESENTATION AND STORAGE CONDITIONS

Glass vials containing 1g in packs of 5.

Powder for injection. Store below 30°C.

Solutions prepared for intramuscular injection must be used within 48 hours if kept below 25°C.

Solutions prepared for IV use should be used immediately.

NAME AND ADDRESS OF THE SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
4 Nexus Court, Mulgrave,
Victoria 3170, Australia.

POISON SCHEDULE OF THE MEDICINE

SCHEDULE 4 - Prescription Only Medicine

DATE OF FIRST INCLUSION ON THE ARTG


DATE OF MOST RECENT AMENDMENT

28 September 2017

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Azactam V5.0