

AUSTRALIAN PRODUCT INFORMATION – AZACTAM[®] (AZTREONAM)

1 NAME OF THE MEDICINE

Aztreonam

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AZACTAM 1 g powder for injection.

AZACTAM for injection is sodium free and contains approximately 814mg L-arginine per g of aztreonam. The pH of AZACTAM solution, depending on the type and amount of diluent used, ranges between 4.5 and 7.5.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder for injection. 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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF 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 (Refer to Table 1).

Table 1: Adults Dosage Guide

TYPE OF INFECTION	DOSE (g)	FREQUENCY (hr)
Urinary tract infection	0.5 or 1	8 or 12
Moderately severe systemic infections	1 or 2	8 or 12
Severe systemic or life-threatening ⁺ infections	2	6 or 8

* Maximum recommended dose is 8 g per day.

+ 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 below).

The intravenous route is recommended for patients requiring single doses greater than 1 g or those with bacterial septicaemia, localised 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 6 or 8 hours is recommended, at least for initial therapy, in systemic infections caused by this organism. (See 5.1 Pharmacodynamic properties: Mechanism of action: *Microbiology*).

A single dose of 1 g 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 g, the dose of AZACTAM should be reduced in patients with estimated creatinine clearances as shown in the Table 2 below:

Table 2: Dosing in Renal Impairment

CREATININE CLEARANCE	DOSE AS FRACTION OF NORMAL
> 80mL/minute > 1.3mL/s	1
30-79mL/minute 0.5-1.3mL/s	½
10-29mL/minute 0.02-0.5mL/s	⅓
< 10mL/minute <0.2mL/s	¼

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.

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

Females: 0.85 x above value

In patients with severe renal failure creatinine clearance (< 0.2mL/s), such as those supported by haemodialysis, the usual dose of 0.5, 1 or 2 g 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 g 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 g of aztreonam supplied in 15mL vials should be initially constituted with at least 3mL of Water for Injection, BP provides 1 g 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 g 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[®] B and 5% Glucose
Isolyte[®] E
Isolyte[®] E with 5% Glucose
Isolyte[®] M with 5% Glucose
Normosol[®] -R
Normosol[®] R and 5% Glucose Normosol (R) M and
5% Glucose
10% Travert[®] Injection
Mannitol Injection (5%)
Mannitol Injection (10%)
Lactated Ringer's and 5% Glucose Injection
Plasma-Lyte[®] M and 5% Glucose Injection
10% Travert[®] in Electrolyte No. 1 Injection
10% Travert[®] in Electrolyte No. 2 Injection
10% Travert[®] in Electrolyte No. 3 Injection

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 non-susceptible 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.

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, beta-lactam antibiotics should be discontinued immediately and an alternative treatment should be considered.

Use in 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.

Use in renal impairment

No data available.

Use in the elderly

No data available.

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 4.2 Dose and method of 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.

Effects on laboratory tests

A positive direct or indirect Coombs test may develop during treatment with AZACTAM. See 4.8 Adverse Effects (Undesirable effects): *Haematological*.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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, cephadrine, clindamycin or metronidazole. No reports of disulfiram-like reactions with alcohol ingestion have been noted.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy:

Pregnancy Category B1

Aztreonam crosses the placenta and enters the foetal circulation.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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:

<i>Hypersensitivity:</i>	Anaphylaxis, angioedema, bronchospasm.
<i>Dermatological:</i>	Rash, pruritus, petechiae, purpura, diaphoresis, flushing, urticaria, erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and exfoliative dermatitis.
<i>Haematological:</i>	Eosinophilia, increases in prothrombin and partial thromboplastin time, thrombocytosis, thrombocytopenia, leukocytosis, neutropenia, anaemia, pancytopenia, bleeding and positive Coombs Test have occurred rarely.
<i>Hepatobiliary:</i>	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.
<i>Gastrointestinal:</i>	Diarrhoea, nausea and/or vomiting, abdominal cramps, mouth ulcer and altered taste. Abdominal distension has been noted in children. Rare cases of <i>C. Difficile</i> -associated diarrhoea, including pseudomembranous colitis, or gastro-intestinal bleeding have occurred.
<i>Renal:</i>	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 4.4 Special warnings and precautions for use)

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, dyspnoea and chest pain. Transient increase in serum creatinine were uncommon.

Reporting suspected adverse events

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 (i.e. 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 (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 normal flora in the body by antibiotics permit overgrowth of potential pathogens, e.g. *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 in Table 3 of laboratory tests using 30 mcg aztreonam discs should be interpreted using the following criteria:

Table 3: Susceptibility Testing Results and Interpretation

ZONE DIAMETER (MM)	INTERPRETATION
22	Susceptible (S)
16-21	Intermediate (I)
<15	Resistant (R)

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. Refer to Table 4.

Table 4: Dilution Technique Results and Interpretation

(MCG/ML)	INTERPRETATION
8	Susceptible (S)
16	Intermediate (I)
>32	Resistant (R)

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 4.2 Dose and method of administration).

Clinical trials

5.2 PHARMACOKINETIC PROPERTIES

Adsorption

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 2g 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: AZACTAM Serum Concentration vs Time

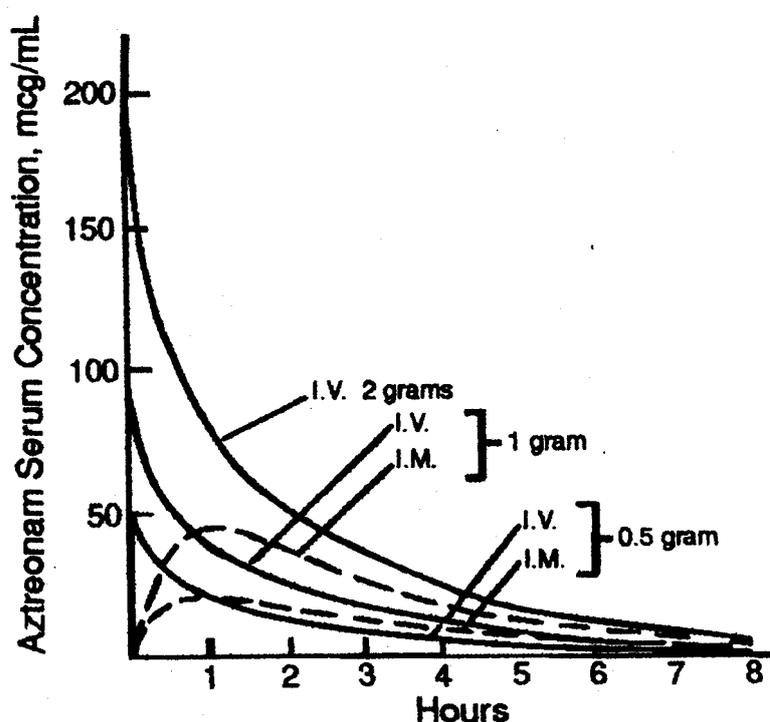


Figure 1 summarises the serum concentrations of aztreonam in healthy subjects after completion of single 30 minute intravenous infusions of 0.5, 1 or 2g, or immediately following single intramuscular injections of 0.5 or 1g. After intramuscular administration, maximum serum aztreonam concentrations occur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

0.5 or 1g, 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.

Distribution

Aztreonam achieves measurable concentrations in the following body fluids and tissues (Table 5):

Table 5: Extravascular Concentration of AZATCAM After a Single Parental Dose

Fluid/Tissue	Dose (g)	Route	Mean Peak Concentration (mcg/mL or mcg/g)	Hours Post Injection
<u>Fluids</u>				
bile	1	IV	43	2
blister fluid	1	IV	23	2
bronchial secretion	2	IV	5	3
pericardial fluid	2	IV	28	1
synovial fluid	2	IV	102	1
<u>Tissues</u>				
arterial appendage	2	IV	17	2
kidney	2	IV	48	3
lung	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 g intravenous dose was 0.2 mcg/mL, in breast milk at 2.4 hours after a single 1 g intravenous dose was 0.2 mcg/mL and at 6 hours after a single 1 g intramuscular dose was 0.3 mcg/mL, and in amniotic fluid at 6 hours after a single gram intravenous dose was 2 mcg/mL.

Metabolism

Serum protein binding averaged 56% and was independent of dose. An average of about 6% of a 1g 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.

Excretion

After single 0.5, 1 and 2g 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 1g 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.

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-labelled 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.

Intravenous or intramuscular administration of a single 0.5 or 1g dose of AZACTAM every 8 hours for 7 days to healthy subjects produced no apparent accumulation of aztreonam or modification of its disposition characteristics. 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.

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

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 Table 6:

Table 6: Pharmacokinetic Parameters for Paediatric Patients (n=6) after a 3 minute intravenous infusion of aztreonam 30mg/kg.

Age (weight)	Mean serum conc. (mcg/mL)		Mean urine conc. (mcg/mL)		Mean serum half-life (hours)	Serum clearance (mL/min/kg)
	Time ¹		Time ¹			
	Peak	6 hours	0-3 hours	6-12 hours		
<1 week (<2.5kg)	83	31.7	789	179	5.7	0.94
<1 week (>2.5kg)	98	17.6	656	358	2.6	1.41
1 week- 1 month ²	84	14.1	993	167	2.4	1.68
1 month- 2 years	116	11.8	1,414	127	1.7	1.87
2 – 12 years	141	5.8	3,727	506	1.7	2.50

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Aztreonam produced no mutagenic changes in several standard laboratory models.

Studies in pregnant rats and rabbits disclosed no clear evidence of embryo toxicity, foetotoxicity, or teratogenicity. In rats given aztreonam during late gestation and lactation no drug-induced changes were seen in any of the maternal, foetal, or neonatal parameters that were monitored.

Carcinogenicity

Carcinogenicity studies in animals have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to section 2 – Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

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.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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.

6.5 NATURE AND CONTENTS OF CONTAINER

Glass vials containing 1g in packs of 10.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

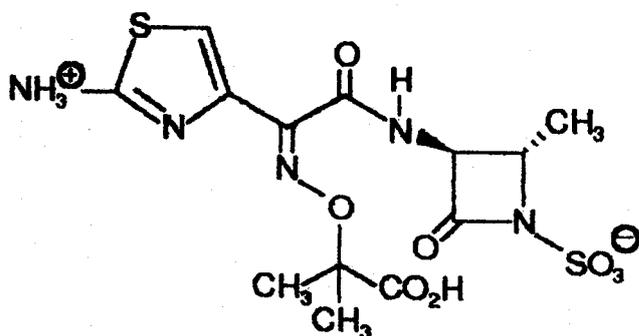
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

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-amino-4-thiazolyl)-((2S,3S)-2-methyl-4-oxo-1-sulfo-3-azetidinyloxy)-2-methylpropionyl)amino)methyl)-2-amino)oxy)-2-methylpropionic acid.



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.

CAS number

78110-38-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

8 SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
4 Nexus Court, Mulgrave,
Victoria 3170, Australia.
Toll free number: 1800 067 567
Email: MedInfo.Australia@bms.com

9 DATE OF FIRST APPROVAL (ARTG ENTRY)

5 September 1991

10 DATE OF REVISION OF THE TEXT

14 June 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	New narrative: <i>Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, beta-lactam antibiotics should be discontinued immediately and an alternative treatment should be considered.</i>
4.8	Revised narrative: <i>Dermatological: Rash, pruritus, petechiae, purpura, diaphoresis, flushing, urticaria, erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and exfoliative dermatitis.</i>

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