DATA SHEET

1. PRODUCT NAME

AZACTAM 1g Powder for solution for Injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 g aztreonam

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

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AZACTAM for Injection (aztreonam for Injection) is indicated for the treatment of infections caused by susceptible gram-negative microorganisms. It has been used successfully to treat:

Urinary tract infections (including pyelonephritis and cystitis (initial and recurrent) and asymptomatic bacteriuria, including those due to the pathogens resistant to the aminoglycosides, cephalosporins or penicillins); lower respiratory tract infections (including pneumonia and bronchitis); bacteraemia/septicemia; bone and joint infections; skin and skin-structure infections (including those associated with postoperative wounds, ulcers and burns); intra-abdominal infections (including peritonitis); Gynaecologic infections (including pelvic inflammatory disease, endometritis, and pelvic cellulitis); gonorrhoea (acute uncomplicated urogenital or anorectal infections due to beta-lactamase producing or non-producing strains of N.gonorrhoeae).

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 may be started empirically before results of the susceptibility testing are available (See **Concurrent Therapy**).

Concurrent Therapy:

In seriously ill patients, additional antibiotic therapy should be initiated concurrently with AZACTAM to provide broad-spectrum coverage before identification and susceptibility testing results of the causative organism(s) are known.

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

4.2 Dose and method of administration

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).

Adults

AZACTAM for Injection may be administered intravenously or by intramuscular injection.

Dosage and route of administration should be determined by susceptibility of the causative organisms, severity of infection, and the condition of the patient (See the following table for dosage guidelines).

Type of Infection	**Dose*** **(g)**	**Frequency (hr)**
Urinary tract infection	0.5 or 1	8 or 12
Moderately severe systemic infection	1 or 2	8 or 12
Severe systemic, or life-threatening infections	2	6 or 8

* Maximum recommended dose is 8 g per day.

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 and appropriate dosage modification made if necessary (See **Renal Impairment**).

The intravenous route is recommended for patients requiring single doses greater than 1 g or those with bacterial septicemia, 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.

A single dose of 1 g AZACTAM administered intra-muscularly is effective in the treatment of acute uncomplicated gonorrhoea and acute uncomplicated cystitis.

Paediatrics

The usual dosage for patients older than one week is 30mg/kg/dose every 6 or 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.

Renal impairment

Since aztreonam is mostly eliminated by the kidney it is recommended that after an initial loading dose of 1 to 2 gs, the dose of AZACTAM should be halved in patients with estimated creatinine clearance between 10 and 30 mL/min/1.73m^2.

In patients with severe renal failure creatinine clearance (<10 mL/min/1.73m^2), 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.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

Aztreonam is contraindicated in pregnancy. Aztreonam crosses the placenta and enters the foetal circulation.

4.4 Special warnings and precautions for use

As with other drugs inquiry should be made regarding a history of hypersensitivity reactions. Antibiotics should be given with caution to any patient who has had some form of allergy, particularly to structurally related compounds or to other drugs. If an allergic reaction to AZACTAM occurs, discontinue the drug. Serious hypersensitivity reactions may require epinephrine 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.

Concurrent therapy with other antimicrobial agents and AZACTAM is recommended as initial therapy in seriously ill patients who are at risk of having an infection due to pathogens that are not susceptible to aztreonam

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.

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.

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.

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.

4.5 Interaction with other medicines and other forms of interaction

Concomitant administration of probenecid or furosemide and aztreonam cause clinically insignificant increases in the serum levels of aztreonam.

Single-dose pharmacokinetic studies have not shown any significant interaction between aztreonam and gentamicin, nafcillin sodium, cephradine, clindamycin or metronidazole.

No reports of disulfiram-like reactions with alcohol ingestion have been noted. This is not unexpected since, unlike cefamandole, moxalactam and cefoperazne, aztreonam does contain a methyl-tetrazole side chain.

4.6 Fertility, pregnancy and lactation

Fertility
AZACTAM produced no adverse effects in two-generation reproduction studies in rats at doses of 150 and 600 mg/kg/day.

Pregnancy
Aztreonam crosses the placenta and enters the foetal circulation. (**see 4.3 Contraindications).**

Studies in pregnant rats and rabbits disclosed no evidence of embryotoxocity, fetotoxicity, or teratogenicity. In rats given AZACTAM during late gestation and lactation no medicine-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 the potential benefit justifies the potential risk.

Breast-feeding

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

This medicine can have an important impact on the ability to drive and use machines should encephalopathy occur (**see 4.4 Special warnings and precautions for use** and **4.9 Overdose**).

4.8 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:

Hypersensitivity
Anaphylaxis, angioedema, bronchospasm.

Dermatologic:
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.

Haematologic:

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 transminases 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). Transient increase in serum creatinine were uncommon.

Local Reactions:
Discomfort at the IV injection site and phlebitis; 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; candidiasis; hypotension; seizure; diplopia; weakness; paraesthesia; confusion; dizziness; vertigo; insomnia; ECG changes; tinnitus; headache; breast tenderness; halitosis; altered taste; muscle aches; fever; malaise; dyspnea; chest pain; sneezing and nasal congestion

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting.

4.9 Overdose

There have been no reported cases of overdosage. If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis. Aztreonam has been shown to be cleared from the serum by continuous 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-infectives for systemic use, ATC code: J01DF01

Aztreonam is the first member of a new class of antibiotics, the monobactams. It is a totally synthetic monocyclic beta-lactam antibiotic with bactericidal activity against a wide spectrum of gram-negative aerobic pathogens. Aztreonam has a high degree of resistance to beta lactamases and unlike the majority of beta-lactam antibiotics, does not induce beta-lactamase activity.

5.2 Pharmacokinetic properties

Peak serum levels following single I.V. bolus of 500 mg, 1g or 2g were 58, 125 and 242µg /mL respectively. Peak levels occur 1 hour after I.M. injection. Levels 1 hour after single I.V. or I.M. injection are comparable. The serum half-life is approximately 1.7 hours in subjects with normal renal function. In patients with impaired renal function, the serum half-life of aztreonam is prolonged. The main route of excretion is urinary, and 60-70% of a dose is recovered in urine after 8 hours Aztreonam is approximately 60% bound to serum proteins.

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.

The pharmacokinetics of aztreonam in paediatric patients vary with age and body weight. Peak serum levels in paediatric patients following a 30-minute infusion of 30mg/kg in 1 week to 2 year olds, and 50mg/kg in 2-12 year olds, were 82 and 186 µg/mL respectively.

Paediatric patients
In paediatric patients, during the 24 hours following administration, approximately 3/4 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 660µg/mL, did not displace bilirubin from albumin, either in purified bilirubin albumin solution or in hyperbilirubinemic neonatal serum.

5.3 Preclinical safety data

Carcinogenesis

Carcinogenecity studies in animals have not been performed.

Aztreonam produced no mutagenic changes in several standard laboratory models and no adverse effects in two-generation reproduction studies in rats at doses of 150 and 600 mg/kg/day.

Aztreonam exhibits potent and specific activity in vitro against a wide spectrum of gram-negative aerobic pathogens including Pseudomonas aeruginosa.

The bactericidal action of aztreonam results from the inhibition of bacterial cell wall synthesis due to 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 is active in vitro and in laboratory animal models, and in clinical infections against most strains of Escherichia coli, Enterobacter spp., Klebsiella spp., Proteus mirabilis and vulgaris, Morganella morganii, Providencia spp., Pseudomonas spp., Serratia marcescens, Neisseria gonorrhoeae, Haemophilus influenzae, Citrobacter spp., some strains Acinetobacter calcoaceticus.

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.

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.

Aztreonam and aminoglycosides have been shown to be synergistic in vitro against most strains of P. aeruginosa, many strains of Enterobacteriaceae, and other gram-negative aerobic bacilli. Due to the induction of beta-lactamases, certain antibiotics (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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine (approximately 750 mg per g of aztreonam).

6.2 Incompatibilities

AZACTAM should not be physically mixed with any other medicine, antibiotic or diluent except those listed in the in section 6.6. Special precautions for disposal

6.3 Shelf life

Product unopened: 36 months

6.4 Special precautions for storage

Storage before reconstitution: Store below 30°C.

Reconstitution
AZACTAM for Injection 1 g Vial are supplied in 15 mL vials

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

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 medicines or antibiotics

For intramuscular Administration:

Aztreonam for Injection should be constituted with at least 3 mL of diluent per g of aztreonam.

AZACTAM may be diluted with Water for Injection or sodium chloride injection, or the corresponding bacteriostatic preparations containing either benzyl alcohol (see section 4.4 Special warnings and precautions for use) or parabens as preservatives.

Solutions prepared for intramuscular injection must be used within 48 hours if stored at 15-30^{0}C, or within 7 days if refrigerated (2-8^{0}C).

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.

For intravenous Administration:

For bolus injection: The selected dose should be constituted with 6 to 10 mL of 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 15 mL vials should be initially constituted with at least 3 mL of Water for Injection, BP to provide 1 g of aztreonam in a total volume of approximately 4mL. The resulting initial solution should be diluted with an appropriate infusion solution to a final concentration not exceeding 2% w/v (at least 50 mL solution per g aztreonam).

Solutions prepared for intravenous infusion (50 to 100 ml per g of aztreonam) must be used within 48 hours if kept at 15-30^{0}C or within 7 days if refrigerated (2-8^{0}C).

The AZACTAM infusion should be administered over a 20-60 minute period

With intermittent infusion of AZACTAM and another medicine via a common delivery tube, the tube should be flushed before and after delivery of AZACTAM with any appropriate infusion solution compatible with both medicine solutions. The medicines 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.

A number of intravenous solutions may be used as diluents for the administration of AZACTAM by intravenous infusion. These include sodium chloride injection, dextrose and mixed injections of sodium chloride and dextrose, Ringers and Lactated Ringers Injection, Water for Injection, Electrolyte Replacement Injections and Mannitol Injection.

Solutions more concentrated than 2% w/v should be used promptly after constitution, except where the infusion fluid is Water for Injection BP, or Sodium Chloride Injection BP. For these latter two diluents, solutions may be used within 48 hours if stored at room temperature or within 7 days if refrigerated.

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

6.5 Nature and contents of container

1g glass vials in packs of 10

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Arrotex Pharmaceuticals (NZ) Limited:
Address: C/o Quigg Partners
Level 7, The Bayleys Building
36 Brandon Street,
Wellington 6011, New Zealand

9. DATE OF FIRST APPROVAL

13 March 1986

10.DATE OF REVISION OF THE TEXT

3rd November 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Change in sponsor/sponsor details