

Data Sheet

Name of Medicine

Azactam

Aztreonam for Injection

(Prescription Medicine)

Presentation

Azactam is available in 1g vials for bolus I.V. or I.M. injection. Azactam is supplied as a white to off-white, free flowing sterile non pyrogenic powder blend of **aztreonam** and L-arginine.

Uses

Actions

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.

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

Pharmacokinetics

Peak serum levels following single I.V. bolus of 500 mg, 1g or 2g were 58, 125 and 242 mcg/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. 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.

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 mcg/mL respectively.

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 660mcg/mL, did not displace bilirubin from albumin, either in purified bilirubin albumin solution or in hyperbilirubinemic neonatal serum.

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 bacilli. However, this enhanced activity is not predictable.

Dosage And Administration

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 infections	1 or 2	8 or 12
Severe systemic, or life-threatening infections	2	6 or 8

* Maximum recommended dose is 8 grams 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. (See **Renal Impairment**).

The intravenous route is recommended for patients requiring single doses greater than 1 gram 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 grams every 6 or 8 hours is recommended, at least for initial therapy, in systemic infections caused by this organism.

A single dose of 1 gram 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. 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 grams, the dose of **Azactam** should be halved in patients with estimated creatinine clearance between 10 and 30 mL/min.

In patients with severe renal failure creatinine clearance (<10 mL/min), such as those supported by 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.

Intramuscular Administration

Aztreonam for Injection should be constituted with at least 3 mL 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.

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

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 gram of **aztreonam** supplied in 15 mL vials should be initially constituted with at least 3 mL of Water for Injection, BP. 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 gram **aztreonam**).

The **Azactam** infusion should be administered over a 20-60 minute period. 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.

Contraindications

Azactam is contraindicated in patients with known allergy to the drug.

Warnings And Precautions

As with other drugs inquiry should be made regarding a history of hypersensitivity reactions. Preliminary evidence indicates that patients with documented penicillin allergy do not react to **Azactam**. However, until more experience is gained, patients having had immediate hypersensitivity reactions (anaphylactic or urticarial) to penicillins or cephalosporins should be treated with **Azactam** only if the potential benefit outweighs the potential risk of a severe allergic reaction. Antibiotics should be given with caution to any patient who has had some form of allergy, particularly to 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.

Mutagenicity And Reproduction

Azactam 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.

Use In Pregnancy

Aztreonam crosses the placenta and enters the fetal circulation.

Studies in pregnant rats and rabbits disclosed no evidence of embryotoxicity, 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 the potential benefit justifies the potential risk.

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.

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.

Dermatologic:

Rash; pruritus; petechiae; purpura; diaphoresis; flushing; urticaria; erythema multiforme; toxic epidermal necrolysis 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 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 gastrointestinal 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; mild discomfort was noted at IM injection site.

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; sneezing and nasal congestion. Transient increase in serum creatinine was reported rarely.

Interactions

Concomitant administration of probenecid or furosemide and **Azactam** cause clinically insignificant increases in the serum levels of **aztreonam**. Single dose pharmacokinetic studies have not shown any significant interaction between **aztreonam** and gentamicin, nafcillin sodium, cephadrine, clindamycin or metronidazole. No reports of disulfiram-like reactions with alcohol ingestion have been noted. This is not unexpected since, unlike cefamandole, moxalactam and cefoperazone, **aztreonam** does contain a methyl-tetrazole side chain.

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.

Pharmaceutical Precautions

Dry powder - Store below 30°C.

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

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.

Medicine Classification

Prescription Medicine.

Package Quantities

Powder for injection:
1g glass vials in packs of 5.

Further Information

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.

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.

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