Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Azactam 2 g Powder for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2g aztreonam.

Excipients with known effect

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion
A sterile white to off-white, sodium-free powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of the following infections caused by susceptible aerobic Gram-negative micro-organisms:

Urinary tract infections: Including pyelonephritis and cystitis (initial and recurrent) and asymptomatic bacteriuria, including those due to pathogens resistant to the aminoglycosides, cephalosporins or penicillins.

Gonorrhoea: Acute uncomplicated urogenital or anorectal infections including infections due to beta-lactamase producing or non-producing strains of *N. gonorrhoeae*.

Lower respiratory tract infections: Including pneumonia, bronchitis and lung infections in patients with cystic fibrosis.

Bacteraemia / septicaemia.

Meningitis caused by *Haemophilus influenzae* or *Neisseria meningitidis*. Since Azactam provides only Gram negative cover, it should not be given alone as initial blind therapy, but may be used with an antibiotic active against Gram positive organisms until the results of sensitivity tests are known.

Bone and joint infections.

Skin and soft tissue infections: Including those associated with postoperative wounds, ulcers and burns.

Intra-abdominal infections: Peritonitis.

Gynaecological infections: Pelvic inflammatory disease, endometritis, and pelvic cellulitis.

Azactam is indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscus perforations, cutaneous infections and infections of serous surfaces.

Bacteriological studies to determine the causative organism(s) and their sensitivity to aztreonam should be performed. Therapy may be instituted prior to receiving the results of sensitivity tests.

In patients at risk of infections due to non-susceptible pathogens, 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. Based on these results, appropriate antibiotic therapy should be continued.

Some patients with serious *Pseudomonas* infections may benefit from concurrent use of Azactam and an aminoglycoside because of their synergistic action. If such concurrent therapy is considered in these patients, susceptibility tests should be performed *in vitro* to determine the activity in combination. The usual monitoring of serum levels and renal function during aminoglycoside therapy applies.

4.2 Posology and method of administration

Posology

Intramuscular or intravenous injection or intravenous infusion.

Adults:

The dose range of Azactam is 1 to 8 g daily in equally divided doses. The usual dose is 3 to 4 g daily. The maximum recommended dose is 8 g daily. The dosage and route of administration should be determined by the susceptibility of the causative organisms, severity of infection, and the condition of the patient.

Dosage Guide: Adults

Type of Infection		**Dosage**	**Frequency (hours)**	**Route**
Urinary tract infections		500 mg or 1 g	8 or 12	IM or IV
Gonorrhoea / cystitis		1 g	single dose	IM
Cystic Fibrosis		2 g	6 - 8	IV
Moderately severe systemic infections		1 g or 2 g	8 or 12	IM or IV
Severe systemic or life-threatening infections		2 g	6 or 8	IM or IV
Other infections	either	1 g	8	IM or IV
	or	2 g	12	IV

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, meningitis or other severe systemic or life-threatening infections. Because of the serious nature of infections due to *Ps. aeruginosa*, a dosage of 2 g every 6 to 8 hours is recommended, at least for initial therapy in systemic infections caused by this organism.

Paediatric population:

The usual dosage for patients older than one week is 30 mg/kg/dose every 6 or 8 hours. For severe infections in patients 2 years of age or older, 50 mg/kg/dose every 6 to 8 hours is recommended.

The maximum daily paediatric dose should not exceed the maximum recommended dose for adults.

Dosage information is not yet available for new-borns less than 1 week old.

Elderly:

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

Elderly patients with a creatinine clearance in excess of 30 mL/min should receive the normal recommended dose. If renal function is below this level, the dosage schedule should be adjusted (see Renal Impairment).

Renal Impairment:

Prolonged serum levels of aztreonam may occur in patients with transient or persistent renal insufficiency. Therefore, after an initial usual dose, the dosage of aztreonam should be halved in patients with estimated creatinine clearances between 10 and 30 mL/min/1.73 m^2.

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

Hepatic impairment:

A dose reduction of 20-25% is recommended for long-term treatment of patients with chronic liver disease with cirrhosis, especially in cases of alcoholic cirrhosis and when renal function is also impaired.

For instructions on dilution of the product before administration, see section 6.6.

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

Allergic reactions
Antibiotics, like other drugs, should be given with caution to any patients with a history of allergic reaction to structurally related compounds. If an allergic reactions occurs, discontinue the drug and institute supportive treatments as appropriate. Serious hypersensitivity reactions may require epinephrine and other emergency measures.

Renal/hepatic impairment
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.

The biological half-life is prolonged in patients with renal insufficiency or creatinine clearance of less than 30 mL/min. Dosage adjustments should be based on creatinine clearance.

In so far as the elderly may have a significant degree of renal dysfunction, dosage of the drug should be undertaken with particular care (See section on dosage and administration in the elderly.)

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

Serious blood/skin disorders
Serious blood disorders (incl. pancytopenia) and skin disorders (incl. toxic epidermal necrolysis) have been reported with the use of aztreonam. In case of serious hemogram and skin changes, it is recommended to stop aztreonam.

Convulsions
Convulsions have rarely been reported during treatment with beta-lactams, including aztreonam (see section 4.8).

***Clostridium difficile* associated diarrhoea**
Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including Azactam, and may range in severity from mild diarrhoea to fatal colitis. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Medication that inhibits intestinal peristalsis should not be given.

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

Specific studies have not shown significant cross-reactivity between aztreonam and either penicillins or cephalosporins. The incidence of hypersensitivity to Azactam in clinical trials has been very low but caution should be exercised in patients with a history of hypersensitivity until further experience is gained.

Overgrowth of non-susceptible organisms
Therapy with Azactam may result in overgrowth of non-susceptible organisms, including gram-positive organisms and fungi. Should superinfection occur during therapy, appropriate measures should be taken.

Prolongation of prothrombin time / increased activity of oral anticoagulants
Prolongation of prothrombin time has been reported rarely in patients receiving aztreonam. Additionally, numerous cases of increased activity of oral anticoagulants have been reported in patients receiving antibiotics, including beta-lactams. Severe infection or inflammation, and the age and general condition of the patient appear to be risk factors. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

Concomitant use with aminoglycosides
If an aminoglycoside is used concurrently with aztreonam, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics.

Paediatric population
Data on safety and effectiveness in neonates younger than one week are limited; use in this population needs to be carefully assessed.

Arginine
Aztreonam for injection contains arginine. Studies in low birth weight infants have demonstrated that arginine administered in the aztreonam 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.

Interference with serological testing
A positive direct or indirect Coombs test may develop during treatment with aztreonam.

4.5 Interaction with other medicinal products and other forms of interaction

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

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.

Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.4 and 4.8).

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

No disulfiram-like reactions with alcohol ingestion have been reported.

4.6 Fertility, pregnancy and lactation

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

There are no adequate and well-controlled studies in pregnant women. Studies in pregnant rats and rabbits, with daily doses up to 15 and 5 times the maximum recommended human dose respectively, revealed no evidence of embryo- or fetotoxicity or teratogenicity. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed.

Breastfeeding
Aztreonam is excreted in breast milk in concentrations that are less than 1% of those in simultaneously obtained maternal serum. Lactating mothers should refrain from breast feeding during the course of therapy.

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 special precautions for use and 4.9 Overdose).

4.8 Undesirable effects

The list of undesirable effects shown below is presented by system organ class, MedDRA preferred term, and frequency.

System Organ Class	Frequency	MedDRA Term
Blood and lymphatic system disorders	Rare	Pancytopenia[a], thrombocytopenia, thrombocythaemias, leukocytosis, neutropenia, eosinophilia, anaemia, prothrombin time prolonged, activated partial thromboplastin time prolonged, Coombs test positive[a]
Ear and labyrinth disorders	Rare	Vertigo, tinnitus
Eye disorders	Rare	Diplopia
Gastrointestinal disorders	Rare	Gastro intestinal haemorrhage, pseudomembranous colitis[a], breath odour
	Not known	Abdominal pains, mouth ulceration, nausea, vomiting, diarrhoea, altered taste
General disorders and administration site conditions	Rare	Chest pain, pyrexia, asthenia, malaise
	Not known	Injection site discomfort, weakness, sweating, muscle aches, fever, transient increases in serum creatinine
Hepato-biliary disorders	Rare	Hepatitis, jaundice
	Not known	Transaminases increased*, blood alkaline phosphatase increased*
Infections and infestations	Rare	Vaginitis, vaginal candidiasis
Immune system disorders	Not known	Anaphylactic reaction
Investigations	Rare	Electrocardiogram change
Musculoskeletal, connective tissue and bone disorders	Rare	Myalgia
Nervous system disorders	Rare	Convulsions[a], paresthesia, dizziness, headache
	Not known	Dysgeusia, Encephalopathy (confusional state, altered state of consciousness, epilepsy, movement disorder)
Psychiatric disorders	Rare	Confusional state, insomnia
Renal and urinary disorders	Uncommon	Blood creatinine increased
Reproductive system and breast disorders	Rare	Breast tenderness
Respiratory, thoracic and mediastinal disorders	Rare	Wheezing, dyspnoea, sneezing, nasal congestion

	Not known	Bronchospasm
Skin and subcutaneous tissue disorders	Not known	Toxic epidermal necrolysis[a], angioedema, erythema multiforme, dermatitis exfoliative, hyperhidrosis, petechiae, purpura, urticaria, rash, pruritus
Vascular disorders	Rare	Hypotension, haemorrhage
	Not known	Phlebitis, thrombophlebitis, flushing

*Usually reversing during therapy and without overt signs or symptoms of hepatobiliary dysfunction.
[a]See section 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via:
HPRA Pharmacovigilance
Earlsfort Terrace
IRL-Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

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.

There have been no reported cases of overdosage. If necessary, aztreonam can be removed from the body by haemodialysis and/or peritoneal dialysis. Aztreonam has been shown to be cleared from the serum by continuous arteriovenous hemofiltration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Aztreonam is a monocyclic beta-lactam (monobactam) anti-infective with bactericidal activity against a spectrum of most Gram-negative aerobic pathogens, including *Pseudomonas aeruginosa*.

Aztreonam is active *in vitro* against most strains of the following Gram-negative micro-organisms:

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

Aztreonam does not induce beta–lactamase activity and it is highly resistant to hydrolysis by the beta-lactamases produced by most pathogens.

Certain antibiotics (e.g. cefoxitin, imipenem) may induce high levels of beta-lactamase *in vitro* in some gram-negative aerobes such as *Enterobacter* and *Pseudomonas* species, resulting in antagonism to aztreonam.

5.2 Pharmacokinetic properties

Aztreonam is the first member of a new class of antibiotics, the monobactams. It has been synthesised as a monocyclic beta-lactam antibiotic in which the sulphonic acid substituent in the 1-position of the nuclear ring activates the beta-lactam moiety.

While the drug may undergo some metabolism in the liver, it is excreted mostly unchanged through bile and appears to undergo much of its biotransformation in the gut lumen. Excretion depends principally on renal pathways.

Single 30-minute i.v. infusions of 0.5 g, 1.0 g, and 2.0 g in healthy volunteers produced immediate serum levels of 54, 90 and 240 mg/l, and single 3-minute i.v. injections of the same doses produced peak levels of 58, 125 and 242 mg/l. Peak levels of aztreonam are achieved at about one hour after i.m. administration. After identical single i.m. or i.v. doses, the serum concentrations are comparable at 1 hour (1.5 hours from the start of i.v. infusion), with similar slopes of serum concentrations thereafter.

The serum half-life of aztreonam averaged 1.7 hours in subjects with normal renal function, independent of the dose and route. In healthy subjects 60-70% of a single i.m. or i.v. dose was recovered in the urine by 8 hours, and urinary excretion was essentially complete by 12 hours. In renal dysfunction, these times may be considerably prolonged.

As with other antibiotics, in the treatment of acute pulmonary exacerbations in patients with cystic fibrosis, while clinical improvement is usually noted, lasting bacterial eradications may not be achieved.

Unlike broad spectrum antibiotics, aztreonam produces no effects on the normal anaerobic intestinal flora.

5.3 Preclinical safety data

Aztreonam was well tolerated in a comprehensive series of preclinical toxicity and safety studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine 780 mg per g of aztreonam
L-arginine 1.54 g per 2 g of aztreonam

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

(a) Product unopened: 3 years.

(b) Reconstituted product:
Stability after dilution in infusion fluids: It is good practice to reconstitute immediately before use. If this is not possible, Azactam is stable for 24 hours (8 hours for glucose intravenous infusion) if stored in a refrigerator (2-8°C) when reconstituted with the recommended infusion solutions to a final concentration not exceeding 2% w/v.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C unless reconstitution/dilution etc. has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

(a) Storage before reconstitution:
Do not store above 25°C.

(b) Storage after reconstitution:
See Sections 6.3. and 6.6.

6.5 Nature and contents of container

Type III Ph. Eur. clear glass vial, closed with siliconed grey butyl rubber closure, sealed with aluminium seal and plastic flip off button: pack of 1 x 15mL.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Reconstitution:
Azactam Powder for solution for injection or infusion is supplied in 15 mL vials. Upon the addition of the diluent the contents should be shaken immediately and vigorously. Vials of reconstituted Azactam are not intended for multi-dose use, and any unused solution from a single dose must be discarded.

Depending on the type and amount of diluent, the pH ranges from 4.5 to 7.5, and the colour may vary from colourless to light straw-yellow, which may develop a slight pink tint on standing; however this does not affect the potency.

For intramuscular injection: For each gram of aztreonam add at least 3 mL of Water for Injections Ph Eur or 0.9% Sodium Chloride Injection BP and shake well.

Single-Dose Vial Size	Volume of Diluent to be added
0.5 g	1.5 mL
1.0 g	3.0 mL

Azactam is given by deep injection into a large muscle mass, such as the upper outer quadrant of the gluteus maximus or the lateral part of the thigh.

For intravenous injection: To the contents of the vial add 6 to 10 mL of Water for Injections Ph Eur, and shake well. Slowly inject directly into the vein over a period of 3 to 5 minutes.

For intravenous infusion: Each gram of drug should be reconstituted initially with at least 3 mL of Water for Injections. This solution should then be diluted in the appropriate infusion solution to a concentration not exceeding 1 g of drug per 50 mL of solution. The infusion should be administered over 20-60 minutes. Appropriate infusion solutions include:

0.9% Sodium Chloride Injection BP;
5% Glucose Intravenous Infusion BP;
5%, 10% Mannitol Intravenous Infusion BP;
Sodium Lactate Intravenous Infusion BP;
0.9%, 0.45% or 0.2% Sodium Chloride and 5% Glucose Intravenous Infusion BP;
Compound Sodium Chloride Injection BPC 1959 (Ringer's Solution for Injection);
Compound Sodium Lactate Intravenous Infusion BP (Hartmann's Solution for Injection).

A volume control administration set may be used to deliver the initial solution of Azactam 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.

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. Except for the antibiotics described below, the drugs should not be delivered simultaneously.

Intravenous infusion solutions of Azactam for Injection prepared with 0.9% Sodium Chloride Injection BP or 5% Glucose Intravenous Infusion BP, to which clindamycin phosphate, gentamicin sulphate, tobramycin sulphate, or cephazolin sodium have been added at concentrations usually used clinically, are stable for up to 24 hours in a refrigerator (2-8°C). Ampicillin sodium admixtures with aztreonam in 0.9% Sodium Chloride Injection BP are stable for 24 hours in a refrigerator (2-8°C); stability in 5% Glucose Intravenous Infusion BP is eight hours under refrigeration.

If aztreonam and metronidazole are to be used together, they should be administered separately as a cherry red colour has been observed after storage of solutions containing combinations of the two products.

7 MARKETING AUTHORISATION HOLDER

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Dublin 4
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8 MARKETING AUTHORISATION NUMBER

PA1418/021/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 March 1985

Date of last renewal: 05 March 2010

10 DATE OF REVISION OF THE TEXT

January 2026