IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0002/052/001
Case No: 2049681

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Bristol-Myers Squibb Pharmaceuticals Ltd

Swords, **Co. Dublin**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Azactam 500 mg Powder for Solution for Injection or Infusion, vial

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **11/08/2008** until **04/03/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Azactam 500 mg Powder for Solution for Injection or Infusion, vial

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg aztreonam.

For excipients, see 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 viscous 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

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:

Type of Infection	Dosage (g)	Frequency (hr)	Route
Urinary tract	0.5-1	8-12	IM or IV
Gonorrhoea / cystitis	1	single dose	IM
Cystic Fibrosis	2	6-8	IV
Severe or life-threatening infections			
either	1	8	IM or IV
or	2	12	IV

The intravenous route is recommended for patients requiring single doses greater than 1g, 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.

Children:
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 total daily dose should not exceed 8 g. Dosage information is not yet available for new-borns less than 1 week old.

Elderly:
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).
Estimated creatinine clearance should be used to determine appropriate dosage, since serum creatinine is not an accurate measurement of renal function in these patients.

Renal Impairment:
In patients with impaired renal function the normal recommended initial dose should be given. This should be followed by maintenance doses as shown in the following table:

Estimated Creatinine Clearance	Maintenance Dose
10-30	Half the initial dose
Less than 10	One quarter of the initial dose

The normal dose interval should not be altered.

In patients on haemodialysis, a supplementary one-eighth of the initial dose should be given after each dialysis.

Reconstitution:
Azactam for Injection 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 1.0 g	1.5 ml 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.

4.3 Contraindications

Patients with a known hypersensitivity to aztreonam or L-arginine.
Aztreonam is contraindicated in pregnancy. Aztreonam crosses the placenta and enters the foetal circulation.

4.4 Special warnings and precautions for use

Precautions
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).

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.

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

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. It is recommended that prothrombin times should be monitored if the patient is on concomitant anticoagulant therapy.

Prolonged use of the antibiotic may result in superinfection by organisms resistant to the drug.

4.5 Interaction with other medicinal products and other forms of interaction

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 Pregnancy and lactation

Aztreonam is contraindicated in pregnancy. 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

Not applicable.

4.8 Undesirable effects

The following side effects have been reported from Azactam therapy:

Azactam is generally well-tolerated.

Dermatological: Rash; pruritus, urticaria, erythema, petechiae, exfoliative dermatitis, flushing; very rarely, toxic

epidermal necrolysis.

Haematological: Eosinophilia; increases in prothrombin and partial thromboplastin time have occurred. There have been isolated reports of thrombocytopenia, neutropenia, anaemia, bleeding and pancytopenia.

Hepatobiliary: Jaundice and hepatitis; transient elevations of hepatic transaminases and alkaline phosphatase (without overt signs or symptoms of hepatobiliary dysfunction).

Hypersensitivity: Anaphylaxis, angioedema, bronchospasm.

Gastrointestinal: Diarrhoea; very rarely pseudomembranous colitis or gastrointestinal bleeding, nausea and/or vomiting, abdominal cramps, mouth ulcer and altered taste.

Local reactions: Phlebitis and discomfort at the i.v. injection site; discomfort at the i.m. injection site.

Rare instances of the following events have been reported: Vaginitis, candidosis, seizures, dyspnoea, bronchospasm, hypotension, weakness, confusion, dizziness, vertigo, sweating, headache, breast tenderness, halitosis, muscle aches, fever malaise, sneezing and nasal congestion; transient increases in serum creatinine.

4.9 Overdose

There have been no reported cases of overdosage. If necessary, aztreonam can be removed from the body by haemodialysis and/or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 include 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)

6.2 Incompatibilities

Azactam should not be physically mixed with any other drug, antibiotic or diluent except those listed in the dosage and administration section under reconstitution for intravenous infusion.

6.3 Shelf Life

(a) Product unopened: 3 years.
(b) Reconstituted product: See Section 4.2 Reconstitution.

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^{o}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 8ºC unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

a) Storage before reconstitution:
Do not store above 25^{o}C.

b) Storage after reconstitution:
See Sections 4.2 and 6.3.

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: pack of 5 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 content of product remaining after use should be discarded.
For detailed instructions on the reconstitution of the product, see Section 4.2.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharmaceuticals Limited
Swords
Co. Dublin

8 MARKETING AUTHORISATION NUMBER

PA 2/52/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 March 1985

Date of last renewal: 05 March 2005

10 DATE OF REVISION OF THE TEXT

July 2005