Revised: June 2009 (7th version)

Standard Commodity Classification No. of Japan
876122

- Aztreonam for injection, JP -

Azactam® Injection 0.5g
Azactam® Injection 1g

Prescription drug

Storage
AZACTAM should be stored at room temperature. AZACTAM should be protected from light after opening package as it is gradually colored by light.

Expiration date
AZACTAM should be used before the expiration date indicated on the package or label.

	Injection 0.5 g	Injection 1 g
Approval No.	16200MZY00336000	16200MZY00335000
Date of listing in the NHI reimbursement price	Mar 1987	Mar 1987
Date of initial marketing in Japan	Mar 1987	Mar 1987
Date of latest reexamination	Mar 1996	
Date of latest reevaluation	Sep 2004	
Date of latest approval of indications	May 1988	

Caution : Use only as directed by a physician.

CONTRAINDICATIONS (AZACTAM is contraindicated in the following patients.)
Patients with a history of shock to any ingredients of AZACTAM.

DESCRIPTION

Composition

Each vial of AZACTAM is a white or yellowish white mass or powder (freeze-dried) containing the following components.
It must to be dissolved prior to use as an injection.

Component		Content per vial	
		Injection 0.5 g	Injection 1 g
Ingredient	Aztreonam	0.5 g (potency)	1 g (potency)
Inactive ingredient	L-Arginine	0.405 g	0.81 g
Description	AZACTAM is a white or yellowish white mass or powder (freeze-dried), which must be dissolved prior to use for injection.		
pH	4.5 to 7.0 [1g (potency)/ 10 mL of water for injection, JP]		
Osmotic pressure ratio (ratio relative to isotonic sodium chloride solution)	about 1.6 [1g (potency)/ 10mL of water for injection, JP]		

INDICATIONS

[Bacterial strains which are susceptible to Aztreonam]
The following infections caused by Azactam susceptible strains of *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Escherichia coli*, *Citrobacter* sp., *Klebsiella* sp., *Enterobacter* sp., *Serratia* sp., *Proteus* sp., *Morganella morganii*, *Providencia* sp., *Pseudomonas aeruginosa*, and *Haemophilus influenzae*:
[Diseases which are susceptible to treatment]
Septicemia, pneumonia, lung abscess, secondary infections in chronic respiratory lesion, cystitis, pyelonephritis, prostatitis (in acute stage or chronic stage), urethritis, cervicitis, peritonitis, intraabdominal abscess, cholecystitis, cholangitis, bartholinitis, intrauterine infection, uterine adnexitis, parametritis, purulent meningitis, inflammation of the cornea (includes corneal ulcer), otitis media, sinusitis

DOSAGE AND ADMINISTRATION

Usually the adult dosage for intravenous injection, intravenous drip infusion or intramuscular injection use is 1 to 2 g (potency) daily in two divided doses. The usual dosage for intramuscular or intravenous injection use in patients with gonococcal infections and cervicitis is 1 to 2 g (potency) once daily.
Usually the dosage for intravenous injection or intravenous drip infusion use in children is 40 to 80 mg (potency)/kg daily in two to four divided doses.
The dosage may be adjusted depending on the patient's age and symptoms. However, for intractable or severe infections in adults, the dosage may be increased up to 4 g (potency) per day, administered in two to four divided doses. For intractable or severe infections in children, the dosage may be increased up to 150 mg (potency)/kg per day, administered in three to four divided doses.
Usually the dosage for intravenous injection or intravenous drip infusion use in prematures and neonates is 20 mg (potency)/kg twice per day within 3 days of birth, and twice or three times per day from the 4th day onwards.

<Precaution>

In order to prevent the emergence of resistant bacteria, bacterial susceptibility should be confirmed and the duration of administration of AZACTAM limited to the minimum period required for the eradication of the infection.

<Preparation methods>

1. Intravenous injection
   Dissolve one dose of AZACTAM in 5 mL or more of water for injection, JP, isotonic sodium chloride solution, JP or glucose injection, JP to prepare a total volume of 20 mL of injection per 1 g (potency) of AZACTAM.
2. Intravenous drip infusion
   Dissolve one dose of AZACTAM in an infusion fluid, such as carbohydrate solution, electrolyte solution or amino acid preparation. When preparing an intravenous drip infusion,

do not use water for injection (water for injection makes the infusion hypotonic).

3. Intramuscular injection
   Dissolve one dose of AZACTAM in water for injection, JP or isotonic sodium chloride solution, JP to prepare 3 mL of injection per 1 g (potency) of AZACTAM.

<Stability of solution>

The solution obtained by dissolving AZACTAM is pale yellow to light yellow and transparent. If this solution is left standing, its color will change slightly.

Use the solution promptly after preparation. If it is not used immediately, use the prepared solution within 48 hr if it has been refrigerated, or within 24 hr if it has been stored at room temperature. If AZACTAM is dissolved in a total amino acid infusion, the solution should be used straight away and not stored.

PRECAUTIONS

1. Careful Administration (AZACTAM should be administered with care in the following patients.)

(1) Patients with a history of hypersensitivity to penicillin or cefem antibiotics
[It has been reported that a cross-allergy reaction may occur.]

(2) Patients with a personal or familial predisposition to allergic reactions such as bronchial asthma, rash or urticaria.

(3) Patients with severe renal function disorders
[Since the blood concentration remains high in these patients, the dosage of AZACTAM should be reduced or the interval between administrations increased. (See "Pharmacokinetics" section.]

(4) Elderly patients
[See "Use in the Elderly" section.]

(5) Any patient whose oral ingestion ability is poor, who is taking nutrients parenterally, or whose overall body condition is poor.
[Since vitamin K deficiency may occur, the condition of such patients should be carefully observed.]

2. Important Precautions

(1) There are no reliable methods for predicting shock or anaphylactoid symptoms due to the administration of Aztreonam. So the following precautions must be taken prior to use.

1) Patients should be carefully interviewed to assess their past medical history. Their allergic history with respect to antibiotics must be checked in particular.

2) Preparations should be made for administrating emergency measures in case of shock,etc.

3) From the beginning to the end of administration, the patient should be kept in a resting state and his or her condition carefully observed. At the start of administration, particular attention should be paid to the patient's condition.

(2) Since abnormalities in hepatic function may occur, hepatic function tests are recommended, when necessary.

3. Drug Interactions

Precautions for coadministration (AZACTAM should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Diuretics Furosemide, etc.	Aggravation of renal function disorders has been reported.	Mechanism unknown

4. Adverse Reactions

Adverse reactions were reported in 840 of 15,267 patients (5.50%). (At the end of the reevaluation period)

(1) Clinically significant adverse reactions (incidence unknown)

1) Shock
Shock may occur. Patients should be carefully observed. In the event of such symptons as unwell feeling, oral cavity discomfort, wheezing, dizziness, desire to defecate, tinnitus or diaphoresis, treatment should be discontinued and appropriate measures taken.

2) Acute renal failure
As serious renal function disorders, such as acute renal failure may occur, patients should be carefully observed through periodic examinations. If any abnormality occurs, treatment should be discontinued and appropriate measures taken.

3) Colitis
Serious colitis accompanied by bloody stool, such as pseudomembranous colitis, may occur. If abdominal pain or frequent diarrhea occurs, appropriate measures, such as discontinuation of the medication, should be taken immediately.

4) It has been reported that AZACTAM caused toxic epidermal necrolysis.

(2) Clinically significant adverse reaction (analogous compounds)
It has been reported that hemolytic anemia occurred as an adverse reaction to penicillin or cefem antibiotics. If any abnormality occurs, treatment should be discontinued and appropriate measures taken.

(3) Other adverse reactions

	5% > ≥0.1%	<0.1%	Incidence unknown
Hypersensitivity[note)]	Rash and fever	Urticaria and itching	Redness
Renal		Elevation of serum potassium, and hematuria	Proteinuria
Hematologic	Eosinophilia	Thrombocytopenia, anemia and granulocytopenia	
Hepatic	Elevation of AST (GOT), ALT (GPT), Al-P, γ-GTP, LDH and LAP, etc.		Jaundice
Gastrointestinal		Vomiting and anorexia	
Substituted microbism			Stomatitis and candidiasis
Avitaminosis			Vitamin K deficiency (hypothrombinemia and tendency to bleed, etc.)

	5% > ≥0.1%	<0.1%	Incidence unknown
			and vitamin B group deficiency (glossitis, stomatitis, anorexia and neuritis, etc.)
Others		Chest pain, hypoaesthesia, headache, peripheral edema and palpitation	

Note) In the event of such symptoms, treatment should be discontinued.

5. Use in the Elderly

AZACTAM should be administered with care to the elderly while observing their condition. Close attention should be paid to the dosage, administration intervals and the following points.

(1) AZACTAM is excreted mainly through the kidney.
Renal function is often lower in the elderly and a tendency for the blood concentration to remain high has been observed in a pharmacokinetic study on such patients.

(2) The elderly may have a tendency to bleed due to vitamin K deficiency.

6. Use during Pregnancy, Delivery or Lactation

(1) AZACTAM should only be used to pregnant women or women suspected of being pregnant, if the expected therapeutic benefits are evaluated to outweight the possible risk of treatment.
[The safety of AZACTAM in pregnant women has not been established.]

(2) Since AZACTAM is excreted in human milk, nursing mothers should discontinue breast feeding during treatment.

7. Precautions concerning Use

(1) Cautions in administration

1) Intravenous injection
High intravenous doses may cause vascular pain, phlebitis or burning pain. To avoid such complications, caution should be exercised in preparing the injection, selecting the injection site and method. The rate of injection should be as slow as possible.

2) Intramuscular injection
Caution should be excercised regarding the following points.

a) Intramuscular injection should be employed only when absolutely necessary. The duration of intramuscular administration should be kept to the absolute minimum.
Avoid repeated injections at the same site.

b) Do not administer AZACTAM to low birth weight infants, neonates, nursing infants, infants or children by intramuscular injection.

c) Do not inject the agent in densely innervated sites.

d) If insertion of the injection needle induces intense pain, or if blood flows back into the syringe, withdraw the needle immediately and inject at a different site.

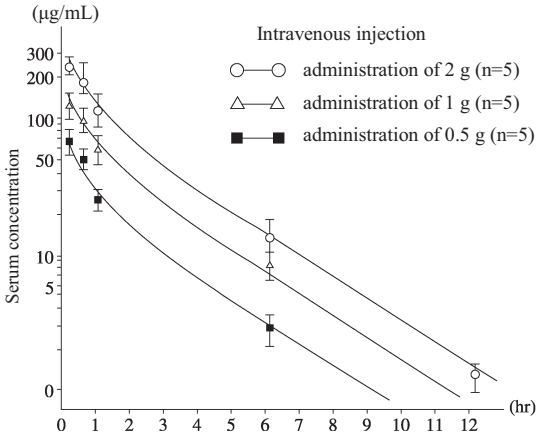
e) Intramuscular administration may cause pain or induration at the injection site.

(2) Method of preparation
Use promptly after reconstitution. In particular, if AZACTAM is dissolved in a total amino acid infusion, and the fluid is stored after dissolution, drug potency may decrease. It should therefore be dissolved in a total amino acid infusion only immediately before use.

PHARMACOKINETICS

1. Blood concentrations

(1) Intravenous injection
When 1 g (potency) of AZACTAM was administered intravenously to 5 healthy adult volunteers in a single dose, the average serum concentration at 5 min after administration was a high as 130.6 μg/mL, and the half-life was 1.85 hr. Also, when 0.5 and 2 g (potency) of AZACTAM were administered intravenously to 3 to 5 healthy adult volunteers in a single dose, the average serum concentrations at 5 min after administration were 70.7 and 256.0 μg/mL, respectively. These values were roughly proportional to the dosages.[1)]

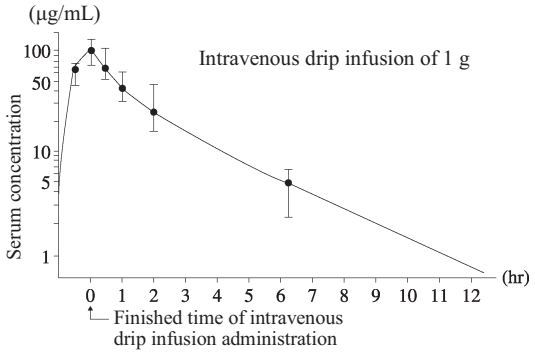


The average serum concentration after intravenous administration at a single dose of 0.5 to 2 g of AZACTAM

Pharmacokinetic parameters after intravenous administration at a single dose of 0.5 to 2 g of AZACTAM

Parameter \ Dosage	0.5 g (n = 3)	1 g (n = 5)	2 g (n = 5)
$t_{1/2}$ (hr)	1.76	1.85	1.63
AUC (μg · hr/mL)	99.0	222	389
Vd (L)	15.9	13.1	13.6

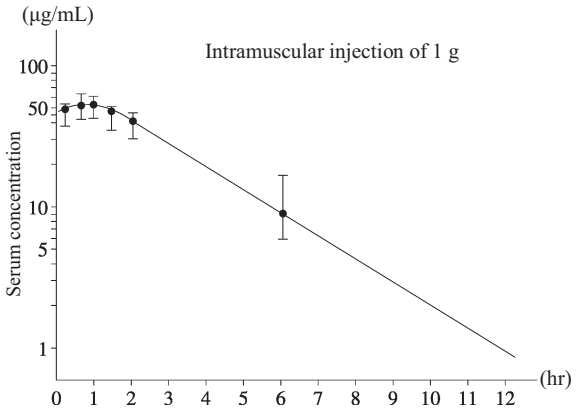
(2) Intravenous drip infusion
When 1 g (potency) of AZACTAM was drip-infused intravenously over 1 hr to 5 healthy adult volunteers in a single dose, the average serum concentration immediately after completing the infusion peaked at 93.4 μg/mL. The time course of serum concentration was the same as that for intravenous injection.[1)]



The average serum concentration after drip-infused intravenous administration at a single dose of 1 g of AZACTAM

(3) Intramuscular injection

When 1 g (potency) of AZACTAM was administered intramuscularly to 5 healthy adult volunteers in a single dose, the average serum concentration at 40 min after administration peaked at 66.3 μg/mL, and the half-life was 2.01 hr.[1)]



The average serum concentration after intramuscular administration at a single dose of 1 g of AZACTAM

(4) Consecutive administration

When 1 g (potency) of AZACTAM was intravenously administered to 6 healthy adult volunteers 9 Consecutive times (in 5 days) at 12 hr intervals over 5 days, no evidence of accumulation was observed from the serum concentration and urinary excretion determined.[1)]

2. Distribution

AZACTAM is well transported to body fluids such as sputum, bile, intra-abdominal exudate, cerebrospinal fluid, pelvic dead space exudate and aqueous humor, as well as into gallbladder tissue, prostatic tissue, the tissues of the uterus/uterine appendages and middle ear membrane.[2-9)]

3. Metabolism and excretion

AZACTAM is almost totally non-metabolized, and is excreted mainly into the urine. The urinary excretion rates up to 24 hr after the administration to healthy adult volunteers by intravenous injection and intramuscular injection were 57% and 81%, respectively. Most of AZACTAM was excreted within 8 hr after the administration.[1)]

4. Blood concentration and urinary excretion in patients with renal function disorders

1 g (potency) of AZACTAM was administered intravenously to 8 adult patients with renal function disorders in a single dose. Their blood concentrations rose to high levels at the same time as the creatinine clearance (Ccr) decreased and the half-life of AZACTAM extended. The urinary excretion rate thus decreased in pace with the decrease in the Ccr. Therefore, when AZACTAM is administered to the patients with renal function disorders, the dosage and administration intervals must be properly controlled.[10)]

5. Blood concentration after intravenous administration to children

When 10, 20 and 50 mg (potency)/kg of AZACTAM were administered intravenously to children in a single dose, the average blood concentrations at 15 min after the administration were a high 50.1, 160.4 and 179.2 μg/mL, respectively. The half-life was 1.35 to 1.56 hr, slightly shorter than that for healthy adult volunteers.[5)]

CLINICAL STUDIES

Clinical efficacy

1. Open labeled clinical trials

The table below summarizes the results of open labeled clinical trials involving 2,459 patients.[2,3,6,9,11-16)]

Diagnosis		Nunbaer of patients	Efficacy rate (%)
Septicemia		16/26	61.5
Respiratory tract infections	pneumonia, lung abscess, secondary infections in chronic respiratory lesion	187/257 8/15 148/223	72.8 53.3 66.4
Urinary tract infections	cystitis, pyelonephritis, prostatitis (in acute stage or chronic stage), urethritis	224/363 169/240 13/18 294/319	61.7 70.4 72.2 92.2
Intraperitoneal infections	peritonitis, intraabdominal abscess	90/109 2/2	82.6 100
Biliary tract infections	cholecystitis, cholangitis	71/79 28/45	89.9 62.2
Gynecological infections	bartholinitis, cervicitis, intrauterine infection, uterine adnexitis, parametritis	21/23 41/41 66/76 39/45 23/28	91.3 100 86.8 86.7 82.1
Purulent meningitis		12/12	100
Opthalmical infections	inflammation of the cornea (include corneal ulcer)	4/4	100
Otorhinological infections	otitis media, sinusitis	37/57 18/35	64.9 51.4

Note) In a clinical trial involving 12 cases of purulent meningitis, the daily doses were 134 to 400 mg/kg. (Dosage and administration are unapproved.) [16)]

2. Comparative clinical trials

The usefulness of AZACTAM has been demonstrated through comparative clinical trials involving respiratory tract infections and complicated urinary tract infections caused by gram-negative bacteria.[17, 18)]

PHARMACOLOGY

1. Excellent antibacterial activity against gram-negative bacteria including *Pseudomonas aeruginosa*

Aztreonam has a strong antibacterial effect against *Escherichia coli*, *Cytolobacter* sp., *Klebsiella* sp., *Proteus* sp., *Morganella morganii*, *Providencia* sp., *Hemophilus influenzae*, *Neisseria gonorrhoeae* and *Neisseria meninigtidis*. It is very effective against *Pseudomonas aeruginosa*, *Serratia* sp. and *Enterobacter* sp. which are resistant to many b-lactam-type antibiotics. [19-23)]

2. Stability against β-lactamase and induction of β-lactamase production

Aztreonam is stable against the β-lactamase produced by various bacteria, and has a very powerful antibacterial action against β-lactamase producing gram-negative bacteria. Almost no induction of β-lactamase production has been observed. [19-21, 23)]

3. Mechanisms of action

Aztreonam has a particularly high bonding affinity for the penicillin bonded protein (PBP) 3, one of the PBPs of sensitive bacteria, and its strong bactericidal action is achieved by interfering with cell wall synthesis.

Aztreonam also shows good permeability through the external membranes of gram-negative bacteria. [20, 22, 24)]

PHYSICOCHEMISTRY

Nonproprietary name: Aztreonam (JAN, INN)

Chemical name:

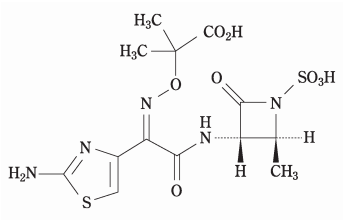
2-{(*Z*)-(2-Aminothiazol-4-yl)-[(2*S*, 3*S*)-2-methyl-4-oxo-1-sulfoazetidin-3-ylcarbamoyl] methyleneamino oxy}-2-methyl-1-propanoic acid

Abbreviation: AZT

Molecular formula: $C_{13}H_{17}N_5O_8S_2$

Molecular weight: 435.43

Structural formula:



Description:

Aztreonam occurs as a white or yellowish white crystalline powder. It is freely soluble in dimethyl sulfoxide, slightly soluble in water and in methanol, very slightly soluble in ethanol (95).

PACKAGING

Aztreonam For Injection, JP

AZACTAM Injection 0.5 g: Boxes of 10 vials

AZACTAM Injection 1 g: Boxes of 10 vials

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