Azlocillin Sodium (BANM, rINNM)

Azlocilina sódica: Azlocilline Sodique: Azlocillinum Natricum: Azlocylina sodowa; Bay-e-6905; Natrii Azlocillinum. Sodium (6R)-6-[D-2-(2-oxoimidazolidine-I-carboxamido)-2-phenylacetamido]penicillanate

Натрий Азлоциллин

 $C_{20}H_{22}N_5NaO_6S = 483.5.$ CAS — 37091-65-9. ATC - 101 CA09. ATC Vet — QJ01CA09.

Pharmacopoeias. In Pol.

Incompatibility. Azlocillin sodium has been reported to be incompatible with aminoglycosides, ciprofloxacin, metronidazole, and tetracyclines.

Adverse Effects and Precautions

As for Carbenicillin Sodium, p.216

Prolongation of bleeding time has been less frequent and less severe with azlocillin than with carbenicillin.

Hypouricaemia. Reports of transient asymptomatic decreases in serum-uric acid concentrations during treatment with azlocil-lin. 1,2

- 1. Faris HM, Potts DW. Azlocillin and serum uric acid. Ann Intern Med 1983; 98: 414.
- Ernst JA, Sy ER. Effect of azlocillin on uric acid levels in serum. Antimicrob Agents Chemother 1983; 24: 609–10.

Sodium content. Each g of azlocillin sodium contains about 2.1 mmol of sodium. As azlocillin sodium has a lower sodium content than carbenicillin sodium, hypernatraemia and hypokalaemia are less likely to occur.

Interactions

As for Benzylpenicillin, p.214.

Antibacterials. For the effect of azlocillin on the clearance of cefotaxime, and a report of neurotoxicity, see p.228. For reference to azlocillin affecting the disposition of ciprofloxacin, see p.246.

Antimicrobial Action

Azlocillin has an antimicrobial action similar to that of piperacillin (p.315). Its activity in vitro against Enterobacteriaceae is generally less than that of mezlocillin or piperacillin, but it has comparable activity to piperacillin against Pseudomonas aeruginosa.

Pharmacokinetics

Azlocillin is not absorbed from the gastrointestinal tract to any significant extent. It has nonlinear dose-dependent pharmacokinetics. Doubling an intravenous dose results in more than double the plasma concentration. Between 20 and 46% of azlocillin in the circulation is bound to plasma proteins. The plasma half-life is usually about 1 hour, but is longer in neonates; in patients with renal impairment half-lives of 2 to 6 hours have been reported.

Azlocillin is widely distributed in body tissues and fluids. It crosses the placenta into the fetal circulation and small amounts are distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed.

Azlocillin is metabolised to a limited extent. About 50 to 70% of a dose is excreted unchanged in the urine by glomerular filtration and tubular secretion within 24 hours of a dose, resulting in high urinary concentrations. Azlocillin is partly excreted in the bile where it is also found in high concentrations

Plasma concentrations are enhanced if probenecid is given.

Azlocillin is removed by haemodialysis

Uses and Administration

Azlocillin is a ureidopenicillin and, like piperacillin (p.316), is used mainly for the treatment of infections caused by Pseudomonas aeruginosa. It has been used particularly for septicaemia, and infections of the respiratory and urinary tracts, and also for peritonitis; for details of these infections, see under Choice of Antibacterial, p.162.

Azlocillin is commonly used with an aminoglycoside; however, they should be given separately as they have been shown to be incompatible (see Incompatibility, above).

Administration and dosage. Azlocillin is given intravenously as the sodium salt. Doses are expressed in terms of the equivalent amount of azlocillin; 1.05 g of azlocillin sodium is equivalent to about 1 g of azlocillin. A 10% solution in a suitable diluent is given by slow injection for doses of 2 g or less; higher doses should be infused over 20 to 30 minutes

The usual adult dose is 5 g every 8 hours for life-threatening infections, or 2 g every 8 hours for less severe infections and urinary-tract infections.

The following doses may be used for children: premature infants, 50 mg/kg twice daily; neonates less than 7 days old, 100 mg/kg twice daily; infants between 7 days and 1 year, 100 mg/kg three times daily; children up to 14 years, 75 mg/kg three times daily.

Dosage of azlocillin may need to be adjusted in patients with hepatic or renal impairment (see below).

Administration in hepatic or renal impairment. The interval between doses of azlocillin may need to be increased to every 12 hours in moderate to severe renal impairment (creatinine clearance less than 30 mL/minute); additional dosage reductions may be needed in patients with both severe renal and hepatic impairment.

Aztreonam (BAN, USAN, rINN)

Atstreonami: Azthreonam: Aztréonam: Aztreonamum: SO-26776. (Z)-2-{2-Aminothiazol-4-yl-[(2S,3S)-2-methyl-4-oxo-Isulphoazetidin-3-ylcarbamoyl]methyleneamino-oxy}-2-methylpropionic acid.

Азтреонам

 $C_{13}H_{17}N_5O_8S_2 = 435.4.$ CAS - 78110-38-0. ATC — JOIDFOI. ATC Vet - QIOIDFOI.

Pharmacopoeias. In Jpn and US, which allows the anhydrous or hydrated forms.

USP 31 (Aztreonam). A white, odourless crystalline powder. Very slightly soluble in dehydrated alcohol; practically insoluble in chloroform, in ethyl acetate, and in toluene; soluble in dimethylformamide and in dimethyl sulfoxide; slightly soluble in methyl alcohol. Store in airtight containers.

Incompatibility and stability. Aztreonam has been reported to be incompatible with cefradine, metronidazole, nafcillin, and vancomycin.

References.

- Bell RG, et al. Stability of intravenous admixtures of aztreonam and cefoxitin, gentamicin, metronidazole, or tobramycin. Am J Hosp Pharm 1986; 43: 1444–53.
- Riley CM, Lipford LC. Interaction of aztreonam with nafcillin in intravenous admixtures. Am J Hosp Pharm 1986; 43: 2221–4.
- Belliveau PP, et al. Stability of aztreonam and ampicillin sodi-um-sulbactam sodium in 0.9% sodium chloride injection. Am J Hosp Pharm 1994; 51: 901-4
- 4. Trissel LA, Martinez JF. Compatibility of aztreonam with selected drugs during simulated Y-site administration. Am J Health-Syst Pharm 1995; 52: 1086–90.
- Trissel LA, et al. Compatibility and stability of aztreonam and vancomycin hydrochloride. Am J Health-Syst Pharm 1995; 52: 2560–4.

Adverse Effects

The adverse effects of aztreonam are similar to those of other beta lactams (see Benzylpenicillin, p.213, and Cefalotin, p.219). Hypersensitivity reactions, including skin rashes, urticaria, angioedema, exfoliative dermatitis, eosinophilia, bronchospasm, and rarely anaphylaxis and toxic epidermal necrolysis, may occur in patients receiving aztreonam, although it has been reported to be only weakly immunogenic. Gastrointestinal effects include diarrhoea, nausea, vomiting, mouth ulcer, and an abnormal taste.

Phlebitis or thrombophlebitis has been reported after the intravenous use of aztreonam, and pain or swelling after intramuscular injection.

Use of aztreonam may result in the overgrowth of nonsusceptible organisms, including Gram-positive cocci. Pseudomembranous colitis or gastrointestinal bleeding may develop.

Other adverse effects that have been reported with aztreonam include jaundice and hepatitis, increases in liver enzymes, and prolongation of prothrombin and partial thromboplastin times.

Effects on the skin. References.

1. McDonald BJ, et al. Toxic epidermal necrolysis possibly linked to aztreonam in bone marrow transplant patients. Ann Pharmacother 1992: 26: 34-5

Precautions

Aztreonam should not be given to patients who are hypersensitive to it and should be used with caution in those known to be hypersensitive to other beta lactams, although the incidence of cross-sensitivity appears to be low (but see below).

Aztreonam should be used with caution in patients with renal or hepatic impairment.

Breast feeding. In a study in 12 healthy women given aztreonam, peak concentrations in breast milk were found to be less than 1% of those in serum and this was considered suggestive of a low risk of adverse effects in breast-fed infants.1 Academy of Pediatrics states that no adverse effects have been seen in breast-fed infants whose mothers received aztreonam and considers it to be usually compatible with breast feeding,2 although UK licensed product information recommends that mothers should refrain from breast feeding while receiving aztre-

- 1. Fleiss PM, et al. Aztreonam in human serum and breast milk. Br
- J Clin Pharmacol 1985; 19: 509–11.

 2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. Pediatrics 2001; 108: 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Hypersensitivity. Aztreonam is said to show little cross-reactivity with other beta lactams, 1,2 but there have been isolated reports of immediate hypersensitivity to aztreonam in patients with a history of hypersensitivity to penicillin.3,4

- 1. Saxon A, et al. Lack of cross-reactivity between aztreonam, a monobactam antibiotic, and penicillin in penicillin-allergic subjects. *J Infect Dis* 1984; **149:** 16–22.
- Adkinson NF. Immunogenicity and cross-allergenicity of aztre-onam. Am J Med 1990; 88 (suppl 3C): 12S–15S.
- 3. Alvarez JS, et al. Immediate hypersensitivity to aztreonam. Lancet 1990; 335: 1094.
- Hantson P, et al. Immediate hypersensitivity to aztreonam and imipenem. BMJ 1991; 302: 294–5.

Interactions

Caution is recommended in patients receiving aztreonam and oral anticoagulants because of the possibility of increased prothrombin time.

Antimicrobial Action

Aztreonam is bactericidal and acts similarly to the penicillins by inhibiting synthesis of the bacterial cell wall; it has a high affinity for the penicillin-binding protein 3 (PBP-3) of Gram-negative bacteria. The activity of aztreonam is restricted to Gram-negative aerobic organisms, including beta-lactamase-producing strains, with poor or no activity against Gram-positive aerobes or anaerobic organisms. It is active against most Enterobacteriaceae including Escherichia coli, Klebsiella, Proteus, Providencia, Salmonella, Serratia, Shigella, and Yersinia spp. Some strains of Enterobacter and Citrobacter spp. are resistant. Aztreonam has some activity against Pseudomonas aeruginosa, although most strains of other Pseudomonas spp. are insensitive. Aztreonam has good activity against Haemophilus influenzae and Neisseria spp.

Synergy has been reported in vitro between aztreonam and aminoglycosides against Ps. aeruginosa and some

Aztreonam is stable to hydrolysis by many beta-lactamases and appears to be a poor inducer of beta-lactamase production. Acquired resistance has occasionally been reported.

Pharmacokinetics

Aztreonam is poorly absorbed from the gastrointestinal tract and is therefore given parenterally. Absorption after intramuscular injection is good; peak plasma concentrations of about 46 micrograms/mL have been achieved within 1 hour of a 1-g dose. Aztreonam has a plasma half-life of about 1.7 hours. The half-life may be prolonged in neonates, in the elderly, in patients with renal impairment, and to some extent in those with hepatic impairment. Aztreonam is about 56% bound to plasma proteins. It is widely distributed in body tissues and fluids, including bile. Diffusion into the CSF is poor unless the meninges are inflamed. It crosses the placenta and enters the fetal circulation; small amounts are distributed into breast milk.

Aztreonam is not extensively metabolised. The principal metabolite, SQ-26992, is inactive and is formed by opening of the beta-lactam ring; it has a much longer half-life than the parent compound. Aztreonam is excreted mainly in the urine, by renal tubular secretion and glomerular filtration; about 60 to 70% of a dose appears within 8 hours as unchanged drug with only small quantities of metabolites. Only small amounts of unchanged drug and metabolites are excreted in the faeces.

Aztreonam is removed by haemodialysis and to a lesser extent by peritoneal dialysis.

◊ Reviews

1. Mattie H. Clinical pharmacokinetics of aztreonam: an update. Clin Pharmacokinet 1994; 26: 99–106.

Uses and Administration

Aztreonam is a monobactam or monocyclic betalactam antibacterial used parenterally as an alternative to aminoglycosides or third-generation cephalosporins for the treatment of infections caused by susceptible Gram-negative aerobic organisms. These have included bone and joint infections, gonorrhoea, intra-abdominal and pelvic infections, lower respiratory-tract infections including pseudomonal infections in patients with cystic fibrosis, meningitis, septicaemia, skin and soft-tissue infections, and urinary-tract infections. For details of these infections and their treatment, see under Choice of Antibacterial, p.162. To broaden the spectrum of activity for empirical treatment of infections, aztreonam should be used with other antibacterials. Use with an aminoglycoside may be of benefit in serious Pseudomonas aeruginosa infections.

Aztreonam is usually given parenterally by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intravenous infusion over 20 to 60 minutes. It is given to adults, in usual doses ranging from 1 to 8 g daily, in divided doses every 6 to 12 hours, according to the severity of the infection. Single doses over 1 g should be given by the intravenous route.

UK licensed product information recommends that infants older than one week and children be given aztreonam 30 mg/kg every 6 or 8 hours. For severe infections, children of 2 years or older may be given 50 mg/kg every 6 or 8 hours up to a maximum total daily dose of 8 g. Although not licensed in the UK for neonates less than one week old, the *BNFC* suggests a dose of 30 mg/kg every 12 hours. In the USA the dose for children from 9 months of age is 30 mg/kg every 8 hours for mild to moderate infection, or every 6 to 8 hours in moderate to severe infection up to a maximum total daily dose of 120 mg/kg.

For details of dosage in patients with renal impairment, see below.

A single intramuscular dose of 1 g has been recommended for the treatment of gonorrhoea or cystitis.

Aztreonam lysine is under investigation for inhalational use in respiratory-tract infections.

♦ General references.

- Brogden RN, Heel RC. Aztreonam: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1986; 31: 96–130.
- Neu HC. ed. Aztreonam's role in the treatment of Gram-negative infections. Am J Med 1990; 88 (suppl 3C): 1S–43S.
- Hellinger WC, Brewer NS. Carbapenems and monobactams: imipenem, meropenem, and aztreonam. Mayo Clin Proc 1999; 74: 420–34.

Administration. References to the use of aztreonam (as aztreonam lysine) by inhalation in the treatment of airway infections in patients with cystic fibrosis. ^{1,2}

- Gibson RL, et al. Microbiology, safety, and pharmacokinetics of aztreonam lysinate for inhalation in patients with cystic fibrosis. Pediatr Pulmonol 2006; 41: 656-65.
- Retsch-Bogart GZ, et al. A phase 2 study of aztreonam lysine for inhalation to treat patients with cystic fibrosis and Pseudomonas aeruginosa infection. Pediatr Pulmonol 2008; 43: 47–58.

Administration in renal impairment. Dosage of aztreonam should be reduced in moderate to severe renal impairment. Patients with renal impairment may be given a usual initial dose followed by a maintenance dose adjusted according to creatinine clearance (CC):

- \bullet CC 10 to 30 mL/minute: half the initial dose
- CC less than 10 mL/minute: one-quarter of the initial dose
- haemodialysis patients: a supplementary dose of one-eighth of the initial dose may be given after each dialysis session

Preparations

USP 31: Aztreonam for Injection; Aztreonam Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Azactam; Austral: Azactam; Austria: Azactam; Austria: Azactam; Austria: Azactam; Austria: Azactam; Austria: Azactam; Belg.: Azactam; Braz.: Azactam; Cr.: Azactam; Cr.: Azactam; Cr.: Azactam; Azac

Bacampicillin Hydrochloride (BANM, USAN, rINNM)

Ampicillin Ethoxycarbonyloxyethyl Hydrochloride; Bacampicilline, chlorhydrate de; Bacampicillini hydrochloridum; Bakampicillin-hydrochlorid; Bakampicillino hidrochloridas; Bakampicillin-hidroklorid; Bakampicillinihydroklorid; Bakampisillini Hidroklorid; Bakampisillinihydrokloridi; Carampicillin; EPC-272; Hidrocloruro de bacampicillina. 1-(Ethoxycarbonyloxy)ethyl (6R)-6-(α -D-phenylgycylamino)penicillanate hydrochloride.

Бакампициллина Гидрохлорид

 $C_{21}H_{27}N_3O_7S$,HCI = 502.0.

CAS 50972-17-3 (bacampicillin); 37661-08-8 (bacampicillin hydrochloride).

ATC — 101 CA06.

ATC Vet — QJ01CA06.

(bacampicillin)

Pharmacopoeias. In Eur. (see p.vii), Jpn, and US.

Ph. Eur. 6.2 (Bacampicillin Hydrochloride). A white or almost white hygroscopic powder or granules. Soluble in water and in dichloromethane; freely soluble in alcohol. A 2% solution in water has a pH of 3.0 to 4.5. Store in airtight containers.

USP 31 (Bacampicillin Hydrochloride). A white or practically white, hygroscopic, powder. Soluble in water and in dichloromethane; freely soluble in alcohol and in chloroform; very slightly soluble in ether. pH of a 2% solution in water is between 3.0 and 4.5. Store in airtight containers.

Adverse Effects and Precautions

As for Ampicillin, p.204. Diarrhoea has been reported to occur less frequently with bacampicillin.

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

Bacampicillin has the antimicrobial action of ampicillin *in vivo* (p.204). It possesses no intrinsic activity and needs to be hydrolysed to ampicillin.

Pharmacokinetics

Bacampicillin is more rapidly and completely absorbed from the gastrointestinal tract than ampicillin, to which it is hydrolysed in the intestinal wall and plasma. Peak plasma-ampicillin concentations occur about 30 to 60 minutes after oral doses, and are about 2 to 3 times those after an equivalent dose of ampicillin. The absorption of bacampicillin from tablets does not appear to be affected by the presence of food in the stomach. About 75% of a dose is excreted in the urine as ampicillin within 8 hours.

Uses and Administration

Bacampicillin has actions and uses similar to those of ampicillin (p.205) to which it is rapidly hydrolysed in the body. It is given orally as the hydrochloride in adult doses of 0.8 to 2.4 g daily, in 2 divided doses; children over 5 years of age have been given 25 to 50 mg/kg daily in 2 divided doses.

In uncomplicated gonorrhoea a single dose of bacampicillin hydrochloride 1.6 g with probenecid 1 g may be given in areas where gonococci remain sensitive.

Preparations

USP 31: Bacampicillin Hydrochloride for Oral Suspension; Bacampicillin Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Proprietary Preparations (details are given in Part 3)
Austria: Penglobe; Beig.: Bacampicini; Canad.: Penglobe†; Cz.: Penglobe†; Fr.: Bacampicine†; Penglobe†; Ger.: Ambacamp†; Hong Kong: Penglobe†; Hung.: Penglobe†; India: Penglobe†; Bacaqi; Bacasint; Bacattiv†; Bacillin; Bakam; Campixen†; Penglobe†; Polibiotic†; Rebacil; Winnipeg; Molaysia: Penbaccin†; Penglobe†; Mex.: Penglobe†; Penglobe†; Pillipp.: Penglobe†; Port.: Bacampicin†; Popin: Ambaxino†; Penglobe†; Swed.: Penglobe†; Thai.: Penglobe†; Turk.: Bakamsilin; Penbak

Bacitracin (BAN, rINN)

Bacitracina; Bacitracinas; Bacitracine; Bacitracinum; Bacytracyna; Basitrasiini: Basitrasin

Бацитрацин

CAS — 1405-87-4.

ATC — D06AX05; R02AB04.

ATC Vet — QA07AA93; QD06AX05; QR02AB04.

(bacitracin A)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn*, and *US.* **Ph. Eur.** 6.2 (Bacttracin). Mixture of antimicrobial polypeptides produced by certain strains of *Bacillus licheniformis* or *B. subtilis.* The potency is not less than 60 units/mg, calculated with reference to the dried substance. A white or almost white hygroscopic powder. Freely soluble in water and in alcohol. A 1% solution in water has a pH of 6.0 to 7.0. Store at a temperature of 8° to 15° in airtight containers.

USP 31 (Bacitracin). A mixture of polypeptides produced by the growth of an organism of the *licheniformis* group of *Bacillus subtilis* (Bacillaceae). The main components are bacitracins A, B1, B2, and B3. It has a potency of not less than 65 units/mg, calculated with reference to the dried substance. It is a white to pale buff, hygroscopic powder, odourless or having a slight odour. Freely soluble in water; soluble in alcohol, in glacial acetic acid, and in methyl alcohol, the solution in the organic solvents usually showing some insoluble residue; insoluble in acetone, in chloroform, and in ether. Its solutions deteriorate rapidly at room temperature. It is precipitated from its solutions and is inactivated by salts of many of the heavy metals. pH of a solution in water containing 10 000 units/mL is between 5.5 and 7.5. Store in airtight containers at a temperature of 8° to 15°.

Bacitracin Zinc (BANM, rINNM)

Bacitracin zinečnatý komplex; Bacitracina zinc; Bacitracin-cink; Bacitracine Zincique; Bacitracine-zinc; Bacitracino cinko kompleksas; Bacitracins Zinc Complex; Bacitracinum Zincicum; Bacitracinum zincum; Bacytracyna cynkowa; Sinkkibasitrasiini; Zinc Bacitraci; Zinci Bacitracinum; Zinkbacitracin.

Цинка Бацитрацин

CAS — 1405-89-6.

ATC — D06AX05; R02AB04.

ATC Vet — QD06AX05; QR02AB04.

Pharmacopoeias. In Eur. (see p.vii), Int., and US.

Ph. Eur. 6.2 (Bacitracin Zinc). The zinc complex of bacitracin. The potency is not less than 60 units/mg, calculated with reference to the dried substance. A white or light-yellowish-grey hygroscopic powder. Slightly soluble in water and in alcohol. The filtrate of a saturated solution has a pH of 6.0 to 7.5. Store in airtight containers.

USP 31 (Bacitracin Zinc). The zinc complex of bacitracin, which consists of a mixture of antimicrobial polypeptides, the main components being bacitracins A, B1, B2, and B3. It has a potency of not less than 65 units/mg, calculated with reference to the dried substance. It contains not less than 4% and not more than 6% of zinc, calculated with reference to the dried substance. A white or pale tan, hygroscopic powder, odourless or having a slight odour. Sparingly soluble in water. PH of a saturated solution in water is between 6.0 and 7.5. Store in airtight containers at a temperature of 8° to 15°.

Incompatibility. Bacitracin was slowly inactivated in bases containing stearyl alcohol, cholesterol, polyoxyethylene derivatives, and sodium laurilsulfate, and was rapidly inactivated in bases containing water, macrogols, propylene glycol, glycerol, cetylpyridinium chloride, benzalkonium chloride, ichthammol, phenol, and tannic acid.¹

 Plaxco JM, Husa WJ. The effect of various substances on the antibacterial activity of bacitracin in ointments. J Am Pharm Assoc (Sci) 1956; 45: 141–5.

Stability. Bacitracin zinc was more stable than bacitracin and could be stored for 18 months at temperatures up to 40° without appreciable loss of activity. Lozenges of bacitracin zinc and ointments and tablets containing bacitracin zinc with neomycin were more stable than the corresponding bacitracin preparations. Bacitracin zinc was less bitter than bacitracin and the taste was more readily disguised.¹

 Gross HM, et al. Zinc bacitracin in pharmaceutical preparations Drug Cosmet Ind 1954; 75: 612–13.