Pharmacokinetics
When given orally, aminosalicylic acid and its salts are readily absorbed, and peak plasma concentrations occur after about 1 to 4 hours.

Aminosalicylate diffuses widely through body tissues and fluids, although diffusion into the CSF occurs only if the meninges are inflamed. About 15% of the sodium salt, and 50 to 70% of the acid, is bound to plasma proteins.

Aminosalicylate is metabolised in the intestine and liver primarily by acetylation. Urinary excretion is rapid, and 80% or more of a dose is excreted within 24 hours; 50% or more of the dose is excreted as the acetylated metabolite. The half-life of aminosalicylic acid is about 1 hour.

Aminosalicylate is distributed into breast milk (see under Precautions, above, for more details).

Uses and Administration
Aminosalicylic acid and its salts are second-line antimycobacterials given orally in the treatment of multidrug-resistant **tuberculosis** (p.196). They should always be given with other antituberculous drugs.

Aminosalicylic acid may be given as the acid or as the sodium salt. Sodium aminosalicylate 1.38 g is equivalent to about 1 g of aminosalicylic acid. However, a usual daily oral dose is 12 g in 3 divided doses and has been recommended for products containing the acid as well as for those containing the sodium salt.

For details of doses in infants, children, and adolescents, see below.

Aminosalicylate sodium is also given rectally in the treatment of **ulcerative colitis** in a usual dose of 2 g once daily.

Attempts have been made in formulation to overcome the bulk and exceedingly unpleasant taste of the aminosalicylates. The salts appear to be better tolerated than the free acid and solutions in iced water prepared immediately before use may be less unpleasant to take.

Administration. A small study suggested that giving aminosalicylic acid in a dose of 4 g twice daily produced adequate serum concentrations (well in excess of 1 microgram/mL, a typical MIC against *Mycobacterium tuberculosis*) for up to 12 hours after each dose.[1] The drug was taken with an acidic beverage such as fruit juice to prevent early release in the stomach. A single 4-g dose was not sufficient to maintain serum concentrations for the full 24-hour dosage interval. The authors had subsequently changed their practice to use a twice-daily regimen for aminosalicylic acid in patients with multidrug-resistant tuberculosis.

1. Peloquin CA, *et al*. Once-daily and twice-daily dosing of p-aminosalicylic acid granules. *Am J Respir Crit Care Med* 1999; **159:** 932–4.

Administration in children. For the treatment of drug-resistant tuberculosis in infants, children, and adolescents the American Academy of Pediatrics (AAP) and WHO suggest an oral dose of para-aminosalicylic acid 200 to 300 mg/kg 2 to 4 times daily, to a maximum dose of 10 g daily.

Administration in renal impairment. It has been recommended that aminosalicylic acid should be avoided in patients with renal impairment.[1] An increase in plasma clearance of aminosalicylic acid (attributed to increased hepatic metabolism) has been noted in patients with renal impairment, hence attempting to give aminosalicylate in reduced doses to such patients may lead to subtherapeutic serum concentrations.[2]

1. Appel GB, Neu HC. The nephrotoxicity of antimicrobial agents (first of three parts). *N Engl J Med* 1977; **296:** 663–70.
2. Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1984; **9:** 511–44.

Inflammatory bowel disease. Together with corticosteroids, derivatives of 5-aminosalicylic acid are one of the mainstays of the treatment of inflammatory bowel disease (p.1697). However, aminosalicylic acid (4-aminosalicylic acid) has also been investigated, and beneficial results have been reported with both enemas[1-4] and oral dose forms[5] in ulcerative colitis. Three patients who developed acute pancreatitis while taking mesalazine (5-aminosalicylic acid) for inflammatory bowel disease, later tolerated treatment with 4-aminosalicylic acid enemas.[6]

1. Campieri M, *et al*. 4-Aminosalicylic acid (4-ASA) and 5-aminosalicylic acid (5-ASA) in topical treatment of ulcerative colitis patients. *Gastroenterology* 1984; **86:** 1039.
2. Ginsberg AL, *et al*. Treatment of left-sided ulcerative colitis with 4-aminosalicylic acid enemas: a double-blind, placebo-controlled trial. *Ann Intern Med* 1988; **108:** 195–9.
3. Sharma MP, Duphare HV. 4-Aminosalicylic acid enemas for ulcerative colitis. *Lancet* 1989; **i:** 450.
4. O'Donnell LJD, *et al.* Double blind, controlled trial of 4-aminosalicylic acid and prednisolone enemas in distal ulcerative colitis. *Gut* 1992; **33:** 947–9.
5. Beeken W, *et al*. Controlled trial of 4-ASA in ulcerative colitis. *Dig Dis Sci* 1997; **42:** 354–8.
6. Daniel F, *et al*. Tolerance of 4-aminosalicylic acid enemas in patients with inflammatory bowel disease and 5-aminosalicylic-induced acute pancreatitis. *Inflamm Bowel Dis* 2004; **10:** 258–60.

Manganese toxicity. Intravenous aminosalicylic acid, given in a course of 6 g daily for 4 days a week, for fifteen courses, produced significant benefit in a patient with parkinsonism induced by chronic occupational manganese exposure.[1] The patient remained well on prolonged follow-up. Other cases of benefit had been reported in the Chinese literature.

1. Jiang Y-M, *et al*. Effective treatment of manganese-induced occupational Parkinsonism with p-aminosalicylic acid: a case of 17-year follow-up study. *J Occup Environ Med* 2006; **48:** 644–9.

Preparations
USP 31: Aminosalicylate Sodium Tablets; Aminosalicylic Acid Tablets.

Proprietary Preparations (details are given in Part 3)
Canad.: Nemasol†; ***Chile:*** Aflogol; ***Cz.:*** Quadrasa†; ***Fr.:*** Quadrasa; ***Ger.:*** Pas-Fatol N; ***Ital.:*** Quadrasa†; Salf-Pas; ***Port.:*** Paramino-Corazida; ***Rus.:*** Pask-Akri (Паск-Акри); ***Switz.:*** Perfusion de PAS†; ***Thai.:*** PAS Sodium; ***Turk.:*** PAS; ***USA:*** Paser.

Multi-ingredient: ***India:*** Inapas.

Amoxicillin *(BAN, rINN)*

Amoksisilin; Amoksisilliini; Amoxicilina; Amoxicilline; Amoxicillinum; Amoxycillin. (6*R*)-6-[α-D-(4-Hydroxyphenyl)glycylamino]penicillanic acid.

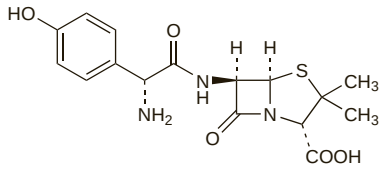
Амоксициллин

$C_{16}H_{19}N_3O_5S$ = 365.4.

CAS — 26787-78-0.

ATC — J01CA04.

ATC Vet — QG51AX01; QJ01CA04.



Amoxicillin Sodium *(BANM, USAN, rINNM)*

Amoksicilino natrio druska; Amoksisilin Sodyum; Amoksisilliininatrium; Amoksycylina sodowa; Amoxicilin sodná sůl; Amoxicilina sódica; Amoxicilline sodique; Amoxicillinnatrium; Amoxicillinátrium; Amoxicillinum natricum; Amoxycillin Sodium; BRL-2333AB-B; Natrii Amoxicillinum.

Натрий Амоксициллин

$C_{16}H_{18}N_3NaO_5S$ = 387.4.

CAS — 34642-77-8.

ATC — J01CA04.

ATC Vet — QJ01CA04.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Amoxicillin Sodium). A white or almost white, very hygroscopic powder. Very soluble in water; sparingly soluble in dehydrated alcohol; very slightly soluble in acetone. A 10% solution in water has a pH of 8.0 to 10.0. Store in airtight containers.

Amoxicillin Trihydrate *(BANM, rINNM)*

Amoksicilinas trihidratas; Amoksisilin Trihidrat; Amoksisilliinitrihydraatti; Amoksycylina trójwodna; Amoxicilin trihydrát; Amoxicilina trihidrato; Amoxicillin *(USAN)*; Amoxicilline trihydratée; Amoxicillin-trihidrát; Amoxicillintrihydrat; Amoxicillinum trihydricum; Amoxycillin Trihydrate; BRL-2333.

Амоксициллин Тригидрат

$C_{16}H_{19}N_3O_5S,3H_2O$ = 419.4.

CAS — 61336-70-7.

ATC — J01CA04.

ATC Vet — QJ01CA04.

NOTE. Compounded preparations of amoxicillin may be represented by the following names:

- Co-amoxiclav *x/y* (*BAN*)—amoxicillin (as the trihydrate or the sodium salt) and potassium clavulanate; *x* and *y* are the strengths in milligrams of amoxicillin and clavulanic acid respectively
- Co-amoxiclav (*PEN*)—amoxicillin trihydrate and potassium clavulanate.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*
Ph. Eur. 6.2 (Amoxicillin Trihydrate). A white or almost white, crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in fatty oils. It dissolves in dilute acids and in dilute solutions of alkali hydroxides. A 0.2% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.
USP 31 (Amoxicillin). A white, practically odourless crystalline powder. Slightly soluble in water and in methyl alcohol; insoluble in carbon tetrachloride, in chloroform, and in benzene. pH of a 0.2% solution in water is between 3.5 and 6.0. Store in airtight containers.

Adverse Effects and Precautions
As for Ampicillin, p.204.

The incidence of diarrhoea is less with amoxicillin than ampicillin.

Hepatitis and cholestatic jaundice have been reported with amoxicillin plus clavulanic acid; the clavulanic acid component has been implicated. Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and exfoliative dermatitis have also been attributed occasionally to the use of amoxicillin with clavulanic acid.

Breast feeding. Although amoxicillin is excreted in breast milk in small amounts,[1] the American Academy of Pediatrics considers that it is usually compatible with breast feeding.[2]

1. Kafetzis DA, *et al.* Passage of cephalosporins and amoxicillin into the breast milk. *Acta Paediatr Scand* 1981; **70:** 285–8.
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 24/05/04)

Effects on the liver. Hepatitis and cholestatic jaundice associated with the combination amoxicillin with clavulanic acid (co-amoxiclav) have been reported[1-4] and by 1993 the UK CSM had received 138 reports of hepatobiliary disorders, 3 of which were fatal.[5] It warned that, although usually reversible, the reaction often occurred after stopping therapy with a delay of up to 6 weeks. It appeared that the clavulanic acid was probably responsible. Retrospective analysis of cases reported in Australia[6] and a cohort study in the UK[7] found increasing age and prolonged treatment to be major risk factors for jaundice after co-amoxiclav; male sex is also a risk factor. By 1997 the CSM considered that cholestatic jaundice occurred with a frequency of about 1 in 6000 adult patients and that the risk of acute liver injury was about 6 times greater with co-amoxiclav than with amoxicillin alone. Therefore it recommended that co-amoxiclav should be reserved for bacterial infections likely to be caused by amoxicillin-resistant strains, and that treatment should not usually exceed 14 days.[8]

1. Stricker BHC, *et al.* Cholestatic hepatitis due to antibacterial combination of amoxicillin and clavulanic acid (Augmentin). *Dig Dis Sci* 1989; **34:** 1576–80.
2. Wong FS, *et al.* Augmentin-induced jaundice. *Med J Aust* 1991; **154:** 698–701.
3. Larrey D, *et al.* Hepatitis associated with amoxycillin-clavulanic acid combination report of 15 cases. *Gut* 1992; **33:** 368–71.
4. Hebbard GS, *et al.* Augmentin-induced jaundice with a fatal outcome. *Med J Aust* 1992; **156:** 285–6.
5. Committee on Safety of Medicines/Medicines Control Agency. Cholestatic jaundice with co-amoxiclav. *Current Problems* 1993; **19:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024454&RevisionSelectionMethod=LatestReleased (accessed 28/07/08)
6. Thomson JA, *et al.* Risk factors for the development of amoxycillin-clavulanic acid associated jaundice. *Med J Aust* 1995; **162:** 638–40.
7. Rodríguez LAG, *et al.* Risk of acute liver injury associated with the combination of amoxicillin and clavulanic acid. *Arch Intern Med* 1996; **156:** 1327–32.
8. Committee on Safety of Medicines/Medicines Control Agency. Revised indications for co-amoxiclav (Augmentin). *Current Problems* 1997; **23:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 11/07/06)

Effects on the teeth. A report of tooth discoloration in 3 children associated with the use of amoxicillin with clavulanic acid.[1]

1. Garcia-López M, *et al.* Amoxycillin-clavulanic acid-related tooth discoloration in children. *Pediatrics* 2001; **108:** 819–20.

Sodium content. Each g of amoxicillin sodium contains about 2.6 mmol of sodium.

Interactions
As for Ampicillin, p.204.

Antimicrobial Action
As for Ampicillin, p.204.

Amoxicillin has been reported to be more active *in vitro* than ampicillin against *Enterococcus faecalis, Helicobacter pylori,* and *Salmonella* spp., but less active against *Shigella* spp.

Amoxicillin is inactivated by beta lactamases and complete cross-resistance has been reported between amoxicillin and ampicillin. The spectrum of activity of amoxicillin may be extended by use with a beta-lactamase inhibitor such as clavulanic acid (p.250). As well as reversing resistance to amoxicillin in beta-lactamase-producing strains of species otherwise sensitive, clavulanic acid has also been reported to enhance the activity of amoxicillin against several species not generally considered sensitive. These have included *Bacteroides, Legionella,* and *Nocardia* spp., *Haemo-*