of diabetes mellitus. Periodic monitoring of blood glucose, thyroid function, and visual function is desirable.

Ethionamide is teratogenic in *animals*.

Porphyria. Ethionamide is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Interactions

The adverse effects of other antimycobacterials may be increased when ethionamide is used (see Effects on the Liver, above, and under Cycloserine, Interactions, p.260).

Alcohol. A psychotic reaction has been reported in a patient receiving ethionamide after excessive intake of alcohol.[1]

1. Lansdown FS, *et al.* Psychotoxic reaction during ethionamide therapy. *Am Rev Respir Dis* 1967; **95:** 1053–5.

Antimicrobial Action

Ethionamide is active only against mycobacteria including *Mycobacterium tuberculosis*, *M. kansasii*, *M. leprae*, and some strains of *M. avium* complex.

Resistance develops rapidly if used alone and there is complete cross-resistance between ethionamide and protionamide. Cross-resistance has been reported *in vitro* with isoniazid or with thioacetazone.

Pharmacokinetics

Ethionamide has been given as a sugar-coated tablet or more recently as a more stable film-coated tablet. Both formulations are readily absorbed from the gastrointestinal tract: after an oral dose of 250 mg, sugar-coated tablets produce a peak plasma concentration of about 1.5 micrograms/mL after 1.5 hours, while film-coated tablets give a peak plasma concentration of 2.16 micrograms/mL after about 1 hour. Distribution of ethionamide from the film-coated tablet into body tissues and fluids has not been studied, but is expected to be similar to that of the sugar-coated tablets. Ethionamide from sugar-coated tablets is widely distributed throughout body tissues and fluids. It crosses the placenta and penetrates the uninflamed meninges, appearing in the CSF in concentrations equivalent to those in serum. It is about 30% bound to plasma proteins. The half-life for the sugar-coated tablet is reported to be 2 to 3 hours and 1.92 hours for the film-coated tablet. Ethionamide is extensively metabolised, probably in the liver, to the active sulfoxide and other inactive metabolites and less than 1% of a dose appears in the urine as unchanged drug.

Distribution. After single oral doses of ethionamide 15 or 20 mg/kg in children with tuberculous meningitis, the peak spinal fluid concentration was reached in 1⁄ to 2⁄ hours.[1] A wide range of concentrations was reported but doses of 20 mg/kg were more likely to produce spinal fluid concentrations above 2.5 micrograms/mL, the concentration considered by the authors to be essential for therapeutic success.

1. Donald PR, Seifart HI. Cerebrospinal fluid concentrations of ethionamide in children with tuberculous meningitis. *J Pediatr* 1989; **115:** 483–6.

Uses and Administration

Ethionamide is a thioamide derivative considered to be interchangeable with protionamide. It is used with other antituberculous drugs for the treatment of tuberculosis (p.196) when resistance to primary drugs has developed. It has also been used, as a substitute for clofazimine, in regimens for the treatment of leprosy (p.176) but less toxic alternatives are now preferred.

In the treatment of resistant tuberculosis, adults may be given 15 to 20 mg/kg daily (maximum 1 g daily) orally. Ethionamide may be given in divided doses with meals, or as a single daily dose after the evening meal, or at bedtime, to minimise gastrointestinal adverse effects. For details of doses in infants, children, and adolescents, see below.

Similar doses were used for the treatment of leprosy.

Ethionamide has also been used as rectal suppositories; the hydrochloride has been given intravenously.

Administration in children. For the treatment of drug-resistant tuberculosis in infants, children, and adolescents the American Academy of Pediatrics suggests an oral dose of ethionamide 15 to 20 mg/kg (to a maximum of 1 g) daily, given in 2 to 3 divided doses.

Preparations

USP 31: Ethionamide Tablets.

Proprietary Preparations (details are given in Part 3)

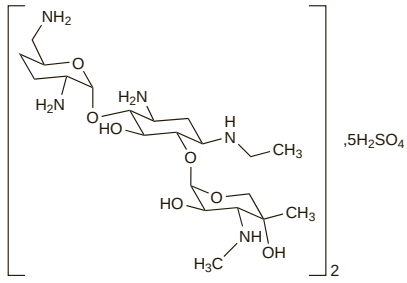
Gr.: Trecator; ***India:*** Ethide; Myobid; ***S.Afr.:*** Ethatyl; ***Thai.:*** Eton; ***Turk.:*** Etyomid; ***USA:*** Trecator.

Etimicin Sulfate

Antibiotic 89-07; E-402. 1-*N*-Ethyl gentamicin C_{1a} sulfate.

$(C_{21}H_{43}N_5O_7)_2,5H_2SO_4$ = 1445.6.

CAS — 59711-96-5 (etimicin); 362045-44-1 (etimicin sulfate).



Pharmacopoeias. In *Chin.*

Profile

Etimicin, a derivative of gentamicin C_{1a}, is an aminoglycoside antibacterial with actions similar to those of gentamicin (p.282). It is given intravenously as the sulfate.

◊ References.

1. Zhao C, *et al.* A randomized controlled clinical trial on etimicin, a new aminoglycoside antibiotic, versus netilmicin in the treatment of bacterial infections. *Chin Med J (Engl)* 2000; **113:** 1026–30.

Faropenem Sodium *(rINNM)*

ALP-201; Faropenem sódico; Faropénem Sodique; Fropenem Sodium; Furopenem; Natrii Faropenemum; SUN-5555; SY-5555; Wy-49605; YM-044. Sodium (+)-(5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-7-oxo-3-[(2*R*)-tetrahydro-2-furyl]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

Натрий Фаропенем

$C_{12}H_{14}NaNO_5S$ = 307.3.

CAS — 106560-14-9 (faropenem); 141702-36-5 (faropenem medoxomil); 122547-49-3 (faropenem sodium).

Pharmacopoeias. *Jpn* includes the hemipentahydrate.

Profile

Faropenem is a penem antibacterial that is given orally as the sodium salt for the treatment of susceptible infections.

Faropenem medoxomil (*USAN*) (Bay-56-6854) is being investigated for the treatment of respiratory-tract infections and uncomplicated skin and skin structure infections. NOTE. Faropenem medoxomil has also been referred to as faropenem daloxate although such use of the term daloxate is not in keeping with *INN* nomenclature conventions.

◊ References.

1. Critchley IA, *et al.* Activities of faropenem, an oral β-lactam, against recent US isolates of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. *Antimicrob Agents Chemother* 2002; **46:** 550–5.
2. von Eiff C, *et al.* Comparative in vitro activity of faropenem against staphylococci. *J Antimicrob Chemother* 2002; **50:** 277–80.
3. Milatovic D, *et al.* In vitro activity of faropenem against 5460 clinical bacterial isolates from Europe. *J Antimicrob Chemother* 2002; **50:** 293–9.
4. Wexler HM, *et al.* In vitro activities of faropenem against 579 strains of anaerobic bacteria. *Antimicrob Agents Chemother* 2002; **46:** 3669–75.
5. Jones ME, *et al.* Activity of faropenem, a new furanem, against European respiratory pathogens collected during 2000-2001: a comparison with other beta-lactam agents. *J Antimicrob Chemother* 2003; **51:** 196–9.
6. Gettig JP, *et al.* Faropenem medoxomil. *Ann Pharmacother* 2008; **42:** 80–90.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Farom.

Fleroxacin *(BAN, USAN, rINN)*

AM-833; Fleroksasiini; Fléroxacine; Fleroxacino; Fleroxacinum; Ro-23-6240; Ro-23-6240/000. 6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid.

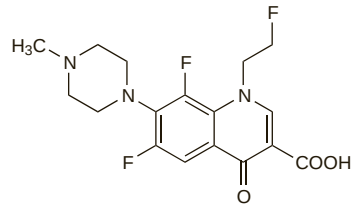
Флероксацин

$C_{17}H_{18}F_3N_3O_3$ = 369.3.

CAS — 79660-72-3.

ATC — J01MA08.

ATC Vet — QJ01MA08.



Pharmacopoeias. In *Chin.*

Profile

Fleroxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p.243), but is reported to have greater systemic bioavailability and a longer half-life. It is given orally for the treatment of susceptible infections in usual doses of 200 to 300 mg once daily. It has also been given by intravenous infusion.

The incidence of adverse effects associated with fleroxacin has been relatively high.

◊ General references.

1. Balfour JA, *et al.* Fleroxacin: a review of its pharmacology and therapeutic efficacy in various infections. *Drugs* 1995; **49:** 794–850.

Adverse effects. References to adverse effects associated with fleroxacin.

1. Bowie WR, *et al.* Adverse reactions in a dose-ranging study with a new long-acting fluoroquinolone, fleroxacin. *Antimicrob Agents Chemother* 1989; **33:** 1778–82.
2. Geddes AM. Safety of fleroxacin in clinical trials. *Am J Med* 1993; **94** (suppl 3A): 201S–203S.
3. Kimura M, *et al.* Photosensitivity induced by fleroxacin. *Clin Exp Dermatol* 1996; **21:** 46–7.

Breast feeding. The American Academy of Pediatrics[1] states that fleroxacin is usually compatible with breast feeding. However, in a study,[2] in which women were given a single 400-mg dose and breast feeding was withheld for 48 hours, it was concluded that although a breast-fed infant would only receive a moderate amount (maximum 10 mg daily), fleroxacin should not be used in breast-feeding mothers due to the potential for adverse effects such as arthropathy in the infant.

1. 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 26/05/04)
2. Dan M, *et al.* Penetration of fleroxacin into breast milk and pharmacokinetics in lactating women. *Antimicrob Agents Chemother* 1993; **37:** 293–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Quinodis†; ***Jpn:*** Megalocin.

Flomoxef Sodium *(rINNM)*

Flomoxef sódico; Flomoxef Sodique; Natrii Flomoxefum; 6315-S. 7*R*-7-[2-(Difluoromethylthio)acetamido]-3-[1-(2-hydroxyethyl)-1*H*-tetrazol-5-ylthiomethyl]-7-methoxy-1-oxa-3-cephem-4-carboxylic acid sodium.

Натрий Фломоксеф

$C_{15}H_{17}F_2N_6NaO_7S_2$ = 518.4.

CAS — 99665-00-6 (flomoxef); 92823-03-5 (flomoxef sodium).

Pharmacopoeias. In *Jpn.*

Profile

Flomoxef is an oxacephalosporin or oxacephem antibacterial with properties similar to latamoxef (p.292). It is given intravenously as the sodium salt and doses are expressed in terms of flomoxef; 1.04 g of flomoxef sodium is equivalent to about 1 g of flomoxef. The usual dose is 1 to 2 g daily in two divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Flumarin.

Florfenicol *(BAN, USAN, rINN)*

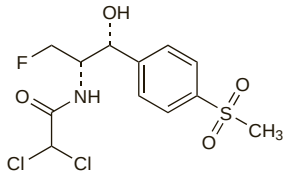
Florfénicol; Florfenicolum; Florfenikol; Florfenikoli; Sch-25298. 2,2-Dichloro-*N*-[(*αS*,*βR*)-α-(fluoromethyl)-β-hydroxy-4-methanesulfonylphenethyl]acetamide.

Флорфеникол

$C_{12}H_{14}Cl_2FNO_4S$ = 358.2.

CAS — 76639-94-6.

ATC Vet — QJ01BA90; QJ51BA90.



Profile

Florfenicol, a fluorinated analogue of chloramphenicol, is an antibacterial used in veterinary medicine.

Flucloxacillin *(BAN, rINN)*

BRL-2039; Floxacillin *(USAN)*; Flucloxacilina; Flucloxacilline; Flucloxacillinum; Flukloksasilin; Flukloksasilliini; Flukloxacillin. (6*R*)-6-[3-(2-Chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxamido]penicillanic acid.

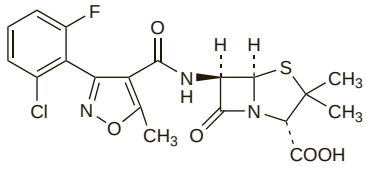
Флуклоксациллин

$C_{19}H_{17}ClFN_3O_5S$ = 453.9.

CAS — 5250-39-5.

ATC — J01CF05.

ATC Vet — QJ01CF05; QJ51CF05.



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

- Co-fluampicil (*BAN*)—flucloxacillin 1 part and ampicillin 1 part (w/w).

Flucloxacillin Magnesium *(BANM, rINNM)*

Flucloxacilina magnésica; Flucloxacilline Magnesique; Flucloxacilline-magnésium; Flucloxacillinum magnesicum; Magnesii Flucloxacillinum.

Магния Флуклоксациллин

$(C_{19}H_{16}ClFN_3O_5S)_2Mg,8H_2O$ = 1074.2.

CAS — 58486-36-5.

ATC — J01CF05.

ATC Vet — QJ01CF05.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Flucloxacillin Magnesium Octahydrate). A white or almost white, crystalline powder. Slightly soluble in water; freely soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.5 to 6.5.

Flucloxacillin Sodium *(BANM, rINNM)*

Flucloxacilina sódica; Flucloxacilline sodique; Flucloxacillinum natricum; Flucloxacillinum Natricum Monohydricum; Flukloksacilino natrio druska; Flukloksasilin Sodyum; Flukloksasilliininatrium; Flukloxacilin sodná sůl monohydrát; Flukloxacillinnatrium; Flukloxacillin-nátrium; Natrii Flucloxacillinum.

Натрий Флуклоксациллин

$C_{19}H_{16}ClFN_3NaO_5S,H_2O$ = 493.9.

CAS — 1847-24-1.

ATC — J01CF05.

ATC Vet — QJ01CF05.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Flucloxacillin Sodium). A white or almost white, crystalline hygroscopic, powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 5.0 to 7.0. Store at a temperature not exceeding 25° in airtight containers.

Incompatibility. As with other penicillins, flucloxacillin sodium is incompatible with aminoglycosides.

Adverse Effects and Precautions

As for Benzylpenicillin p.213.

Hepatitis and cholestatic jaundice have been reported occasionally with flucloxacillin and may be delayed in onset for up to 2 months after treatment has been stopped; older patients and those receiving flucloxacillin for more than 2 weeks are at greater risk. Fatalities have occurred, usually in patients with serious underlying hepatic disease. There have been rare reports of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis associated with flucloxacillin. Agranulocytosis and neutropenia have been associated rarely with isoxazolyl penicillins such as flucloxacillin. Phlebitis has followed intravenous infusion.

Effects on the liver. In October 2004, the UK CSM issued a reminder[1] that flucloxacillin is associated rarely with an increased risk of hepatitis and cholestatic jaundice. In some patients, almost always those with serious underlying hepatic disease, fatalities have occurred. The onset of hepatic adverse effects may be delayed for up to 2 months after stopping treatment, and is not related to the dose or to the route. Older patients and those receiving flucloxacillin for more than 2 weeks are at increased risk. Flucloxacillin should not be used in patients with a history of hepatic dysfunction related to its use, and should be used only with caution in patients with evidence of other hepatic impairment. Careful enquiry should be made concerning previous hypersensitivity to beta lactams. A cohort study[2] using UK prescription data found that the risk of developing cholestatic liver disease in the 45 days after starting flucloxacillin was 8.5 per 100 000. In contrast to other countries, flucloxacillin continued to be seen as a first-line drug in the UK.

1. Committee on Safety of Medicines. Reminder: flucloxacillin and serious hepatic disorders. *Current Problems* 2004; **30:** 9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 11/07/06)
2. Russmann S, *et al.* Risk of cholestatic liver disease associated with flucloxacillin and flucloxacillin prescribing habits in the UK: cohort study using data from the UK General Practice Research Database. *Br J Clin Pharmacol* 2005; **60:** 76–82.

Porphyria. Flucloxacillin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Sodium content. Each g of flucloxacillin sodium contains about 2 mmol of sodium.

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

Flucloxacillin is bactericidal with a mode of action similar to that of benzylpenicillin, but is resistant to staphylococcal penicillinase. It is active therefore against penicillinase-producing and non-penicillinase-producing staphylococci. Its activity against streptococci such as *Streptococcus pneumoniae* and *Str. pyogenes* is less than that of benzylpenicillin, but sufficient to be useful when these organisms are present with penicillin-resistant staphylococci. Flucloxacillin is virtually ineffective against *Enterococcus faecalis*.

Resistance. The resistance of staphylococci to flucloxacillin and other penicillinase-resistant penicillins is described under meticillin (p.299).

Pharmacokinetics

Flucloxacillin is better absorbed from the gastrointestinal tract than cloxacillin, but absorption is reduced by the presence of food in the stomach. After an oral dose of 0.25 to 1 g, in fasting subjects, peak plasma concentrations in about 1 hour are usually in the range of 5 to 15 micrograms/mL. Plasma concentrations after intramuscular injection of flucloxacillin sodium are similar, but peak concentrations are achieved in about 30 minutes. Doubling the dose can double the plasma concentration. About 95% of flucloxacillin in the circulation is bound to plasma proteins. Flucloxacillin has been reported to have a plasma half-life of approximately 1 hour. The half-life is prolonged in neonates.

The distribution of flucloxacillin into body tissues and fluids is similar to that of cloxacillin (p.256).

Flucloxacillin is metabolised to a limited extent and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. About 66% of an oral dose and 76% of a parenteral dose is excreted in the urine within 8 hours. Only small amounts are excreted in the bile. Flucloxacillin is not removed by haemodialysis or peritoneal dialysis.

Plasma concentrations are enhanced by probenecid.

Uses and Administration

Flucloxacillin is an isoxazolyl penicillin used primarily for the treatment of infections due to staphylococci resistant to benzylpenicillin. These include bone and joint infections, endocarditis, pneumonia, skin infections (including soft-tissue infections), and toxic shock syndrome. For discussions of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Flucloxacillin is given parenterally and orally as the sodium or magnesium salt. All doses are expressed as flucloxacillin; 1.18 g of flucloxacillin magnesium and 1.09 g of flucloxacillin sodium are each equivalent to about 1 g of flucloxacillin. Oral doses should be taken at least 30 minutes before meals as the presence of food in the stomach reduces absorption. In severe renal impairment a reduction in dosage may be necessary.

The usual adult dose orally or by intramuscular injection is 250 mg four times daily. It is given intravenously in a dose of 0.25 to 1 g four times daily by slow injection over 3 to 4 minutes or by intravenous infusion. All systemic doses may be doubled in severe infections. Up to 8 g daily in 3 or 4 divided doses may be given for osteomyelitis; in endocarditis a dose of 8 g daily in 4 divided doses may be given to patients weighing up to 85 kg, and 12 g daily in 6 divided doses may be used in those weighing more.

Flucloxacillin has been given by other routes in conjunction with systemic therapy. It has been given in a dose of 250 to 500 mg daily by intra-articular injection, dissolved if necessary in a 0.5% solution of lidocaine hydrochloride, or by intrapleural injection in a dose of 250 mg daily. Using powder for injection, 125 to 250 mg has been dissolved in 3 mL of sterile water and inhaled by nebuliser 4 times daily.

Children up to 2 years of age may be given one-quarter the adult dose and those aged 2 to 10 years one-half the adult dose.

Flucloxacillin may be used with other antibacterials, including ampicillin (known as co-fluampicil), to produce a wider spectrum of activity. If flucloxacillin is given with an aminoglycoside the two drugs should not be mixed.

Preparations

BP 2008: Co-fluampicil Capsules; Co-fluampicil Oral Suspension; Flucloxacillin Capsules; Flucloxacillin Injection; Flucloxacillin Oral Solution; Flucloxacillin Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Austral.: Flopen; Floxapen; Floxsig; Flubiclox; Flucil; Staphylex; ***Austria:*** Floxapen; ***Belg.:*** Floxapen; Staphycid; ***Chile:*** Fluxacina; Vitalpen; ***Denm.:*** Heracillin; ***Ger.:*** Fluclox; Flucloxa†; Staphylex; ***Hong Kong:*** Flucloxil; ***India:*** Floxapen†; ***Indon.:*** Floxapen; ***Irl.:*** Floxapen; Flucillin; Fluclon; Geriflox; ***Ital.:*** Betabiotic; Cloxillin; Evercid; Faifloc; Fareclox; Flucacid; Flucef; Flucinal; Fluclox; Fluxacil; Fluzerit; Liderclox; Nepenic; Pantaflux; Recaflux; ***Malaysia:*** Staphlex; ***Mex.:*** Floxapen; ***Neth.:*** Floxapen; Stafoxil†; ***NZ:*** Floxapen; Flucloxin; Staphlex; ***Philipp.:*** Stafloxin; ***Port.:*** Floxapen; Floxil†; ***S.Afr.:*** Floxapen; ***Singapore:*** Staphlex; ***Swed.:*** Heracillin; ***Switz.:*** Floxapen; ***Thai.:*** Staphycid; ***Turk.:*** Flix; Floksin; ***UK:*** Floxapen; Fluclomix; Ladropen; ***Venez.:*** Floxapen.

Multi-ingredient: ***Ger.:*** Flanamox; ***S.Afr.:*** Macropen; Megapen; Suprapen; ***UK:*** Magnapen.