Florfenicol *(BAN, USAN, rINN)*

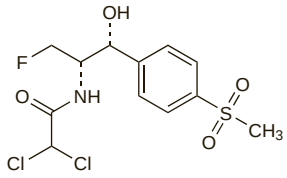
Florfénicol; Florfenicolum; Florfenikol; Florfenikoli; Sch-25298. 2,2-Dichloro-*N*-[(*αS*,*βR*)-α-(fluoromethyl)-β-hydroxy-4-methanesulfonylphenethyl]acetamide.

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.

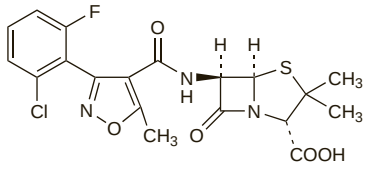
Флуклоксациллин

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

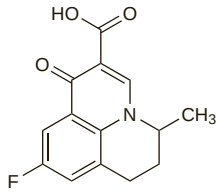
Multi-ingredient: ***Ger.:*** Flanamox; ***S.Afr.:*** Macropen; Megapen; Suprapen; ***UK:*** Magnapen.

Flumequine *(BAN, USAN, rINN)*

Flumechin; Flumekiini; Flumekin; Flumekvinas; Flumequina; Fluméquine; Flumequinum; R-802. 9-Fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid.

Флумехин

$C_{14}H_{12}FNO_3$ = 261.2.
CAS — 42835-25-6.
ATC — J01MB07.
ATC Vet — QJ01MB07.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Flumequine). A white or almost white microcrystalline powder. Practically insoluble in water; sparingly soluble in dichloromethane; very slightly soluble in methyl alcohol; freely soluble in dilute solutions of alkali hydroxides.

Profile
Flumequine is a 4-quinolone antibacterial with actions and uses similar to those of nalidixic acid (p.303). It may be more active *in vitro* against some Enterobacteriaceae. In the treatment of urinary-tract infections doses of 400 mg are given orally 3 times daily.

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

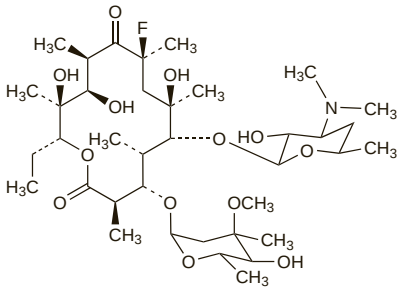
Preparations
Proprietary Preparations (details are given in Part 3)
Fr.: Apurone.

Flurithromycin Ethyl Succinate *(rINNM)*

Etilsuccinato de fluritromicina; Flurithromycin Ethylsuccinate; Flurithromycine, Éthylsuccinate de; Flurithromycini Ethylsuccinas. (8*S*)-8-Fluoroerythromycin mono(ethyl butanedioate) ester.

Флуритромицина Этилсукцинат

$C_{43}H_{74}FNO_{16}$ = 880.0.
CAS — 82664-20-8 (flurithromycin); 82730-23-2 (flurithromycin ethyl succinate).
ATC — J01FA14.
ATC Vet — QJ01FA14.



(flurithromycin)

Profile
Flurithromycin is a fluorinated macrolide antibacterial derived from erythromycin (p.269). It is given orally as the ethyl succinate but doses are expressed in terms of the base. The usual dose in the treatment of susceptible infections is the equivalent of 375 mg of flurithromycin twice daily, after meals.

◊ References.
1. Saverino D, *et al.* Antibacterial profile of flurithromycin, a new macrolide. *J Antimicrob Chemother* 1992; **30:** 261–72.

Preparations
Proprietary Preparations (details are given in Part 3)
Ital.: Flurizic; Mizar; Ritro.

Formosulfathiazole

Formaldehyde-sulphathiazole; Formosulfatiazol; Formosulphathiazole; Methylenesulfathiazole.

CAS — 13968-86-0.
ATC Vet — QA07AB90; QD06BA90.

Profile
Formosulfathiazole, a condensation product of sulfathiazole with formaldehyde, has properties similar to those of sulfamethoxazole (p.340). It is poorly absorbed and has been given for its antibacterial action in the gastrointestinal tract, often with other antibacterials.

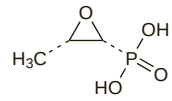
Preparations
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Pol.:*** Sterovag; ***Spain:*** Sulfintestin Neomicina.

Fosfomycin *(BAN, USAN, rINN)*

Fosfomicina; Fosfomycine; Fosfomycinum; Fosfomysiini; MK-955; Phosphomycin; Phosphonomycin. (1*R*,2*S*)-1,2-Epoxypropylphosphonic acid.

Фосфомицин

$C_3H_7O_4P$ = 138.1.
CAS — 23155-02-4.
ATC — J01XX01.
ATC Vet — QJ01XX01.



Description. Fosfomycin is an antibacterial isolated from *Streptomyces fradiae* and other *Streptomyces* spp. or produced synthetically.

Fosfomycin Calcium *(BANM, rINNM)*

Calcii Fosfomycinum; Fosfomicina cálcica; Fosfomicino kalcio druska; Fosfomycin vápenatá sůl monohydrát; Fosfomycine calcique; Fosfomycinkalcium; Fosfomycinum calcicum; Fosfomycinum Calcicum Monohydricum; Fosfomysiinikalsium; Foszfomicin-kalcium.

Кальций Фосфомицин

$C_3H_5CaO_4P,H_2O$ = 194.1.
CAS — 26016-98-8.
ATC — J01XX01.
ATC Vet — QJ01XX01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn*.
Ph. Eur. 6.2 (Fosfomycin Calcium). A white or almost white powder. Slightly soluble in water; practically insoluble in acetone, in dichloromethane, and in methyl alcohol. A 0.1% solution in water has a pH of 8.1 to 9.6. Store in airtight containers. Protect from light.

Fosfomycin Sodium *(BANM, rINNM)*

Fosfomicina sódica; Fosfomicino natrio druska; Fosfomycin disodná sůl; Fosfomycine sodique; Fosfomycinnatrium; Fosfomycinum Dinatricum; Fosfomycinum natricum; Fosfomysiininatrium; Foszfomicin-nátrium; Natrii Fosfomycinum.

Натрий Фосфомицин

$C_3H_5Na_2O_4P$ = 182.0.
CAS — 26016-99-9.
ATC — J01XX01.
ATC Vet — QJ01XX01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn*.
Ph. Eur. 6.2 (Fosfomycin Sodium). A white or almost white, very hygroscopic powder. Very soluble in water; practically insoluble in dehydrated alcohol and in dichloromethane; sparingly soluble in methyl alcohol. A 5% solution in water has a pH of 9.0 to 10.5. Store in airtight containers. Protect from light.

Fosfomycin Trometamol *(BANM, rINNM)*

Fosfomicina trometamol; Fosfomicinas trometamolis; Fosfomisin Trometamol; Fosfomycin Tromethamine *(USAN)*; Fosfomycine trométamol; Fosfomycintrometamol; Fosfomycin-trometamol; Fosfomycinum Trometamol; Fosfomycinum Trometamoli; Fosfomycinum trometamolum; Fosfomycyna z trometamolem; Fosfomysiinitrometamoli; Foszfomicin-trometamol; FZ-588; Z-1282.

Фосфомицин Трометамол

$C_3H_7O_4P,C_4H_{11}NO_3$ = 259.2.
CAS — 78964-85-9.
ATC — J01XX01.
ATC Vet — QJ01XX01.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Fosfomycin Trometamol). A white or almost white, hygroscopic powder. Very soluble in water; slightly soluble in alcohol and in methyl alcohol; practically insoluble in acetone. A 5% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

Adverse Effects and Precautions
Gastrointestinal disturbances including nausea and diarrhoea, transient increases in serum concentrations of aminotransferases, headache, visual disturbances, and skin rashes have been reported after use of fosfomycin. Eosinophilia and, rarely, angioedema, aplastic anaemia, exacerbation of asthma, cholestatic jaundice, hepatic necrosis, and toxic megacolon, have also occurred.

Antimicrobial Action
Fosfomycin is a bactericidal antibacterial. After active uptake into the cell it is reported to interfere with the first step in the synthesis of bacterial cell walls. It is active *in vitro* against a range of Gram-positive and Gram-negative bacteria including *Staphylococcus aureus*, some streptococci, most Enterobacteriaceae, *Haemophilus influenzae*, *Neisseria* spp., and some strains of *Pseudomonas aeruginosa* although some are resistant. *Bacteroides* spp. are not sensitive.

Bacterial resistance to fosfomycin has been reported and can be chromosomal or, in some organisms, transferred by plasmids encoding multiple resistance (for example in *Serratia marcescens*). However, there appears to be little cross-resistance with other antibacterials.

Fosfomycin has been reported to show antimicrobial synergy with a wide range of antibacterials against organisms such as enterococci, meticillin-resistant *Staph. aureus*, and the enterobacteria. Such synergistic effects have been reported particularly with the beta lactams, but also with aminoglycosides, macrolides, tetracyclines, chloramphenicol, rifamycin, and lincomycin. Antimicrobial antagonism with a beta lactam has also been reported.

There is some suggestion that use of fosfomycin with an aminoglycoside may also reduce the nephrotoxicity of the latter *in vivo*.

◊ References.
1. Barry AL, Brown SD. Antibacterial spectrum of fosfomycin trometamol. *J Antimicrob Chemother* 1995; **35:** 228–30.

Pharmacokinetics
Fosfomycin or fosfomycin calcium are poorly absorbed from the gastrointestinal tract. Peak plasma concentrations 4 hours after a 1-g dose of fosfomycin calcium are about 7 micrograms/mL, and bioavailability has been calculated at about 30 to 40%. Similar bioavailability has been reported for the trometamol salt, and plasma concentrations of about 22 to 32 micrograms/mL have been reported 2 hours after an oral dose equivalent to 3 g fosfomycin. Fosfomycin disodium is given intramuscularly or intravenously: intravenous infusion of a 4-g dose results in peak plasma concentrations of around 120 micrograms/mL. The plasma half-life is about 2 hours. Fosfomycin does not appear to be bound to plasma proteins. It crosses the placenta and is widely distributed in body fluids including the CSF; small amounts have been found in breast milk and bile. The majority of a parenteral dose is excreted unchanged in the urine, by glomerular filtration, within 24 hours.

Urinary concentrations of up to 3 mg/mL have been reported within 2 to 4 hours of an oral dose of fosfomycin trometamol equivalent to 3 g of fosfomycin; therapeutic concentrations of 200 to 300 micrograms/mL remained in urine after 48 hours.

◊ References.
1. Bergan T, *et al.* Pharmacokinetic profile of fosfomycin trometamol. *Chemotherapy* 1993; **39:** 297–301.

Uses and Administration
Fosfomycin is a phosphonic acid antibacterial given orally as the trometamol or calcium salt and intramuscularly or intravenously as the disodium salt in the treatment of a variety of bacterial infections due to susceptible organisms. Doses are expressed in terms of the base; fosfomycin calcium 1.4 g, fosfomycin sodium 1.3 g, and fosfomycin trometamol 1.9 g are each equivalent to about 1 g of fosfomycin.

In the treatment of acute uncomplicated infections of the urinary tract (p.199), fosfomycin trometamol is given as a single dose equivalent to 3 g of fosfomycin. Fosfomycin trometamol has also been used for the prophylaxis of infection in transurethral surgical procedures. For a discussion of surgical infections and their prophylaxis and treatment, see p.195.

The usual oral dose of fosfomycin calcium is the equivalent of 0.5 to 1 g of fosfomycin every 6 to 8 hours. Higher doses have been given parenterally as the sodium salt, with up to 20 g daily having been given intravenously in severe infection.

Fosfomycin has also been used with beta lactam antibacterials.

◊ References.
1. Reeves DS. Fosfomycin trometamol. *J Antimicrob Chemother* 1994; **34:** 853–8.
2. Patel SS, *et al.* Fosfomycin tromethamine: a review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy as a single-dose oral treatment for acute uncomplicated lower urinary tract infections. *Drugs* 1997; **53:** 637–56.
3. Stein GE. Single-dose treatment of acute cystitis with fosfomycin tromethamine. *Ann Pharmacother* 1998; **32:** 215–19.
4. Schito GC. Why fosfomycin trometamol as first line therapy for uncomplicated UTI? *Int J Antimicrob Agents* 2003; **22** (suppl 2): 79–83.
5. Rudenko N, Dorofeyev A. Prevention of recurrent lower urinary tract infections by long-term administration of fosfomycin trometamol: double blind, randomized, parallel group, placebo controlled study. *Arzneimittelforschung* 2005; **55:** 420–7.
6. Sádaba-Díaz de Rada B, *et al.* Fosfomicina trometamol: dosis múltiples como pauta larga en el tratamiento de las infecciones urinarias bajas. *Enferm Infecc Microbiol Clin* 2006; **24:** 546–50.
7. Pullukcu H, *et al.* Fosfomycin in the treatment of extended spectrum beta-lactamase-producing Escherichia coli-related lower urinary tract infections. *Int J Antimicrob Agents* 2007; **29:** 62–5.