

Flumequine (BAN, USAN, rINN)

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

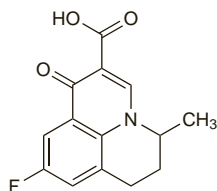
Флумехин

$C_{14}H_{12}FNO_3 = 261.2$.

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 (rINN)

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

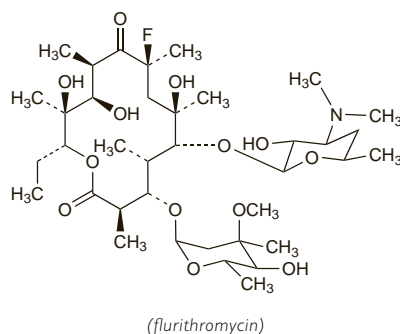
Флуритромицина Этилсукцинат

$C_{43}H_{74}FNO_{16} = 880.0$.

CAS — 82664-20-8 (flurithromycin); 82730-23-2 (flurithromycin ethyl succinate).

ATC — J01FA14.

ATC Vet — QJ01FA14.

**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; Methylene-sulfathiazole.

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. (1R,2S)-1,2-Epoxypropylphosphonic acid.

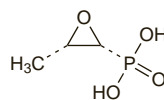
Фосфомицин

$C_3H_7O_4P = 138.1$.

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, rINN)

Calcii Fosfomycinum; Fosfomicina cálcica; Fosfomicino calcio druska; Fosfomycin vápenatá sůl monohydrát; Fosfomycine calcique; Fosfomycinkalcium; Fosfomycinum calcium; Fosfomycinum Calcium Monohydricum; Fosfomysiinikalsium; Foszfomicin-kalcium.

Кальций Фосфомицин

$C_3H_5CaO_4PH_2O = 194.1$.

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, rINN)

Fosfomicina sódica; Fosfomicino natrio druska; Fosfomycin disodná sůl; Fosfomycine sodique; Fosfomycinnatrium; Fosfomycinum Dinatrium; Fosfomycinum natrium; Fosfomysiinnatrium; 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, rINN)

Fosfomicina trometamol; Fosfomicinas trometamol; Fosfomisin Trometamol; Fosfomycin Trometamine (USAN); Fosfomycine trométamol; Fosfomycintrometamol; Fosfomycin-trometamol; Fosfomycinum Trometamol; Fosfomycinum Trometamoli; Fosfomycinum trometamolium; Fosfomycyna z trometamolem; Fosfomysiinitrometamol; Foszfomicin-trometamol; FZ-588; Z-1282.

Фосфомицин Трометамол

$C_3H_7O_4PC_4H_{11}NO_3 = 259.2$.

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 report-

ed 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, methicillin-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.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Veramin; **Austria:** Monuril; **Belg.:** Monuril; **Braz.:** Monuril; **Canad.:** Monuril; **Chile:** Monuril; **Fin.:** Monuril†; **Fr.:** Fosfocine; Monuril; Undoz; **Ger.:** InfectoFos; Monuril; **Gr.:** Monuril†; **Hong Kong:** Monuril; **Hung.:** Monuril; **Indon.:** Fosmicin; Fosmidex; Monuril; **Israel:** Monuril; **Ital.:** Afos†; Faremicin†; Foslocin; Francital†; Ipamicina†; Monuril; Ultramicina†; **Jpn.:** Fosmicin-S; **Malaysia:** Monuril; **Mex.:** Foslocil; Monuril; **Neth.:** Monuril; **Philipp.:** Monuril; **Pol.:** Monuril; **Port.:** Monuril; **Rus.:** Monuril (Моноурал); **S.Afr.:** Urizone; **Spain:** Foslocina; Monuril; Solufos; **Swed.:** Monuril†; **Switz.:** Monuril; **Thai.:** Fosmicin; **Turk.:** Monuril; **USA:** Monuril.

Framycetin Sulfate (rINN)

Framicetino sulfatas; Framicetin-szulfát; Framycetin Sulphate (BANM); Framycétine, sulfate de; Framycetini sulfas; Framycetinsulfat; Framycetin-sulfát; Framysetiniisulfaatti; Neomycin B Sulfate; Sulfato de framicitina. 2-Deoxy-4-O-(2,6-diamino-2,6-dideoxy- α -D-glucopyranosyl)-5-O-[3-O-(2,6-diamino-2,6-dideoxy- β -L-idopyranosyl)- β -D-ribofuranosyl]streptamine sulphate.

Фрамицетина Сульфат

C₂₃H₄₆N₆O₁₃·xH₂SO₄.

CAS — 119-04-0 (framycetin); 4146-30-9 (framycetin sulfate).

ATC — D09AA01; R01AX08; S01AA07.

ATC Vet — QD09AA01; QR01AX08; QS01AA07.

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

Ph. Eur. 6.2 (Framycetin Sulphate). A substance produced by growth of selected strains of *Streptomyces fradiae* or *S. decaris* or obtained by any other means. It contains not more than 3% of neomycin C (p.305) and loses not more than 8% of its weight on drying. A white or yellowish-white, hygroscopic powder. The potency is not less than 630 units of neomycin B per mg, calculated with reference to the dried substance. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 6.0 to 7.0. Store in airtight containers. Protect from light.

Profile

Framycetin is an aminoglycoside antibiotic which forms the major component of neomycin (p.305) and has similar actions and uses. Framycetin sulfate is used topically in usual concentrations of 1% for the treatment of infections of the skin, and in concentrations of 0.5% for infections of the eye and ear. It is often used with other antibacterials and corticosteroids in topical preparations.

Framycetin sulfate is poorly absorbed from the gastrointestinal tract and has been given orally for the treatment of gastrointestinal infections and pre-operatively for bowel preparation. It has sometimes been given prophylactically as part of regimens for the selective decontamination of the digestive tract in patients in intensive care.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Sofra-Tulle; Soframycin; **Austria:** Sofra-Tull; **Belg.:** Soframycine; **Canad.:** Sofra-Tulle; Soframycin; **Fin.:** Sofra-Tulle†; **Ger.:** Leukase N; Sofra-Tulle†; **Hong Kong:** Sofra-Tulle†; **India:** Sofra-Tulle; Soframycin; **Indon.:** Daryant-Leuk; Sofra-Tulle; **Irl.:** Soframycin; **Israel:** Sofra-Tulle†; **Malaysia:** Sofra-Tulle†; **Norw.:** Sofra-Tulle; **NZ:** Soframycin; **Rus.:** Isofra (Visoopa); **S.Afr.:** Sofra-Tulle; Soframycin; **Singapore:** Sofra-Tulle†; **Switz.:** Fraktacine†; Sofra-Tulle†; Soframycin; **Thai.:** Sofra-Tulle; **UK:** Sofra-Tulle; Soframycin†.

Multi-ingredient: **Arg.:** Biotaer Nasal; **Austral.:** Otodex; Sofradex; Soframycin; **Austria:** Leukase; Leukase-Kegel; **Belg.:** Frakidex; Sofraline; Sofrasolone; **Braz.:** Fonerin; **Canad.:** Opticort; Proctol; Proctomyxin HC; Proctosedyl; ratio-Proctosone; Sofracort; Soframycin; **Cz.:** Pulpomixine; Septomixine; Sofradex†; **Denm.:** Proctosedyl; Sofradex; **Fin.:** Proctosedyl; Sofradex; **Fr.:** Corticetine; Frakidex; Framyxone; Novomyxine†; Polyfra; **Ger.:** Leukase N; **Hong Kong:** Frakidex; Frazoline; Proctosedyl†; Sofradex; **India:** Proctosedyl; Sofracort; Sofradex; Sofradex-F; **Indon.:** Sofradex; **Irl.:** Proctosedyl; Sofradex; Soframycin†; **Malaysia:** Proctosedyl; Sofradex; **Neth.:** Proctosedyl; Sofradex; **Norw.:** Proctosedyl; Sofradex; **NZ:** Sofradex; Soframycin; **Philipp.:** Proctosedyl; **Pol.:** Carident; Dexadent; **Port.:** Frakidex; **S.Afr.:** Proctosedyl; Sofradex; **Singapore:** Frakidex†; Proctosedyl; Sofradex; **Spain:** Abrasone; Aldo Otico†; Aldoderma; Nesfare; Otomidrin; **Swed.:** Proctosedyl†; **Switz.:** Corticetine†; Dexalocal-F; Frakidex; Septomixine; Sofradex; **Thai.:** Proctosedyl; Sofradex; Topifram; **UK:** Sofradex.

Ftivazide (rINN)

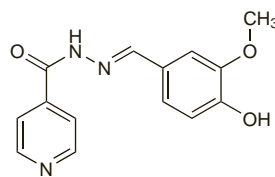
Ftivazida; Ftivazidum; Phthivazid; Phthivazidum. 2'-Vanillylideneisonicotinohydrazide monohydrate.

ФТИВАЗИД

C₁₄H₁₃N₃O₃·H₂O = 289.3.

CAS — 149-17-7 (anhydrous ftivazide).

The symbol † denotes a preparation no longer actively marketed



(anhydrous ftivazide)

Pharmacopoeias. In Chin. and Int.

Profile

Ftivazide is an antimycobacterial given orally in the treatment of tuberculosis. It is a derivative of isoniazid.

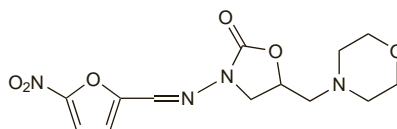
Furaltadone Hydrochloride (BANM, rINN)

Furaltadone, Chlorhydrate de; Furaltadoni Hydrochloridum; Hidrocloruro de furaltadona. (±)-5-Morpholinomethyl-3-(5-nitrofurfurylideneamino)oxazolidin-2-one hydrochloride.

Фуральтадона Гидрохлорид

C₁₃H₁₆N₄O₆·HCl = 360.8.

CAS — 139-91-3 (furaltadone); 59302-14-6 (±-furaltadone).



(furaltadone)

Pharmacopoeias. Fr. includes Furaltadone for veterinary use.

Profile

Furaltadone was formerly given orally as an antibacterial but was later withdrawn owing to its toxic effects. Furaltadone hydrochloride is still used topically in preparations for ear disorders.

Furaltadone has been used in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: **Indon.:** Otozambon; **Thai.:** Otosamthong.

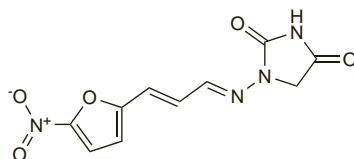
Furazidin

Akritoïn; Furagin; Furazidine. 1-[(3-(5-Nitro-2-furyl)allylidene)amino]hydantoin.

Фуразидин

C₁₀H₈N₄O₅ = 264.2.

CAS — 1672-88-4.



Profile

Furazidin is a nitrofuran antibacterial with properties similar to those of nitrofurantoin. It is used in the treatment of urinary-tract infections. A usual oral dose is 100 mg given four times daily for one day followed by 100 mg given three times daily for 7 to 8 days.

Preparations

Proprietary Preparations (details are given in Part 3)

Pol.: Furaginum.

Fusafungine (BAN, rINN)

Fusafungin; Fusafungina; Fusafunginum.

Фузафунгин

CAS — 1393-87-9.

ATC — R02AB03.

ATC Vet — QR02AB03.

Profile

Fusafungine is a depsipeptide antibacterial produced by *Fusarium lateritium* strain 437. It is active against some Gram-positive and Gram-negative organisms, *Candida albicans*, and *Mycoplasma pneumoniae*. It has also been stated to possess anti-inflammatory activity.

It is used in the form of an aerosol spray in the treatment of infections of the upper respiratory tract, inhaled in usual doses of 500 micrograms every 4 hours into each nostril or via the mouth. These routes may be used simultaneously if necessary.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Locabiosol; **Belg.:** Locabiotol; **Braz.:** Locabiotol; **Chile:** Locabiosol†; **Cz.:** Bioparox; **Ger.:** Locabiosol; **Gr.:** Locabiotol; **Hong Kong:** Locabiotol†; **Hung.:** Bioparox; **Irl.:** Locabiotol; **Ital.:** Locabiotol; **Malaysia:** Locabiotol; **Philipp.:** Locabiotol; **Pol.:** Bioparox; **Port.:** Locabiosol; **Rus.:** Bioparox (Биопарокс); **S.Afr.:** Locabiotol; **Spain:** Fusaloyos; **Switz.:** Locabiotol; **Turk.:** Locabiotol; **UK:** Locabiotol†.

Fusidic Acid (BAN, USAN, rINN)

Acide fusidique; Ácido fusídico; Acidum fusidicum; Acidum Fusidicum Hemihydricum; Fucidinsyra; Fusidiinihappo; Fusidik Asit; Fusidinsyra; Fuzidinsav; Fuzido rügštis; Kyselina fusidová hemihydrát; SQ-16603. ent-16 α -Acetoxy-3 β -dihydroxy-4 β ,8 β ,14 α -trimethyl-18-nor-5 β ,10 α -cholesta-(17Z)-17(20),24-dien-21-oic acid hemihydrate.

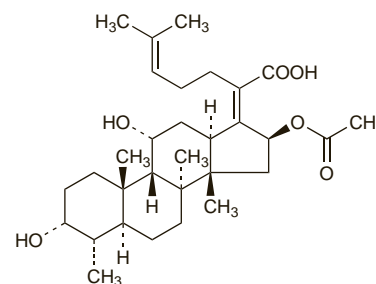
Фэузидовая Кислота

C₃₁H₄₈O₆·H₂O = 525.7.

CAS — 6990-06-3 (anhydrous fusidic acid).

ATC — D06AX01; D09AA02; J01XC01; S01AA13.

ATC Vet — QD06AX01; QD09AA02; QJ01XC01; QS01AA13.



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

Ph. Eur. 6.2 (Fusidic Acid). An antimicrobial substance produced by the growth of certain strains of *Fusidium coccineum* or by any other means. A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol. Store at a temperature of 2° to 8°. Protect from light.

Sodium Fusidate (BANM, rINN)

Fusidate de Sodium; Fusidate Sodium (USAN); Fusidato sódico; Natrii fusidas; Natrio fuzidatas; Natriumfusidaatti; Natriumfusidat; Natrium-fusidát; Nátrium-fuzidát; Sodium, fusidate de; Sodyum Fusidat; SQ-16360.

Натрий Фузидат

C₃₁H₄₇NaO₆ = 538.7.

CAS — 751-94-0.

ATC — D06AX01; D09AA02; J01XC01; S01AA13.

ATC Vet — QD06AX01; QD09AA02; QJ01XC01; QS01AA13.

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

Ph. Eur. 6.2 (Sodium Fusidate). A white or almost white, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol. A 1.25% solution in water has a pH of 7.5 to 9.0. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

Incompatibility. UK licensed product information states that reconstituted sodium fusidate injection is incompatible with infusion solutions containing glucose 20% or more, lipid infusions, and peritoneal dialysis fluids; precipitation may occur in solutions with a pH of less than 7.4.

Adverse Effects and Precautions

Apart from mild gastrointestinal upsets, fusidic acid or sodium fusidate appear to be well tolerated when given orally. Treatment with fusidates, orally or especially by the intravenous route, has been associated with jaundice and changes in liver function; normal liver function is usually restored when treatment is stopped. Therefore, fusidates should be given with caution to patients with hepatic impairment, and periodic monitoring of hepatic function is recommended in these patients and in those receiving high or prolonged oral doses. Caution is also required in biliary disease or biliary obstruction.