compatible with breast feeding, but caution is required in the infants mentioned above.

1. Kauffman RE, *et al.* Sulfisoxazole secretion into human milk. *J Pediatr* 1980; **97:** 839–41.
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 28/05/04)

Interactions
As for Sulfamethoxazole, p.341.

Sulfafurazole has been reported to increase the anaesthetic effect of thiopental.

Eye preparations of sulfafurazole diolamine should not be applied with preparations of silver salts.

Antimicrobial Action
As for Sulfamethoxazole, p.341.

Pharmacokinetics
Sulfafurazole is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring 1 to 4 hours after an oral dose. Acetyl sulfafurazole (the N^1-acetyl derivative) is broken down to sulfafurazole in the gastrointestinal tract before absorption, resulting in delayed and somewhat lower peak concentrations. After absorption about 85 to 90% is bound to plasma proteins. Sulfafurazole readily diffuses into extracellular fluid, but very little diffuses into cells. Concentrations in the CSF are about one-third of those in the blood. It crosses the placenta into the fetal circulation and is distributed into breast milk. About 30% of sulfafurazole in the blood and in the urine is in the form of the N^4-acetyl derivative.

Sulfafurazole is excreted rapidly in the urine, up to 97% of a single dose being eliminated in 48 hours. The half-life is reported to range from about 5 to 8 hours. Both sulfafurazole and its N^4-acetyl derivative are more soluble than many other sulfonamides in urine.

Uses and Administration
Sulfafurazole is a short-acting sulfonamide that is used similarly to sulfamethoxazole (p.341), notably in the treatment of urinary-tract infections, pneumonia due to *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), nocardiosis, and trachoma. It is also used, usually with erythromycin, in the treatment of otitis media. For details of these infections and their treatment see Choice of Antibacterial, p.162.

Sulfafurazole is usually given orally. In the treatment of susceptible infections, it has been given in an initial dose of 2 to 4 g, followed by 4 to 8 g daily in divided doses every 4 to 6 hours. For children and infants over 2 months of age, the dose has been 75 mg/kg initially, followed by 150 mg/kg daily in divided doses to a maximum of 6 g daily. Dosage modification may be necessary in patients with renal impairment. Acetyl sulfafurazole is tasteless and is used in liquid oral preparations of the drug; doses are expressed in terms of sulfafurazole. 1.16 g of acetyl sulfafurazole is equivalent to about 1 g of sulfafurazole.

Sulfafurazole diolamine has been used, as an ophthalmic ointment or solution containing the equivalent of 4% of sulfafurazole, in the topical treatment of susceptible eye infections. Sulfafurazole diolamine 1.39 g is equivalent to about 1 g of sulfafurazole.

Sulfafurazole diolamine has also been given parenterally.

Preparations
USP 31: Erythromycin Estolate and Sulfisoxazole Acetyl Oral Suspension; Erythromycin Ethylsuccinate and Sulfisoxazole Acetyl for Oral Suspension; Sulfisoxazole Acetyl Oral Suspension; Sulfisoxazole Tablets.

Proprietary Preparations (details are given in Part 3)
Turk.: Gansol; ***USA:*** Gantrisin†; ***Venez.:*** Ganticol; Soxacol†.

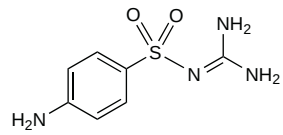
Multi-ingredient: ***Arg.:*** Pediazole†; ***Canad.:*** Pediazole; ***Chile:*** Bioquin; Pediazole†; ***Fr.:*** Pediazole; ***Gr.:*** Pediazole; ***Hong Kong:*** Pediazole†; ***Israel:*** Pediazole; ***Mex.:*** Pediazole; Urovec; ***Turk.:*** Azo Gantrisin; ***USA:*** Eryzole†; Pediazole; ***Venez.:*** Pediazole†.

Sulfaguanidine *(BAN, rINN)*

Solfaguanidina; Sulfaguanidiini; Sulfaguanidin; Sulfaguanidina; Sulfaguanidinas; Sulfaguanidinum; Sulfaguanidyna; Sulfamidinum; Sulginum; Sulphaguanidine; Szulfaguanidin. 1-Sulphanilylguanidine; *N*′-Amidinosulphanilamide.

Сульфагуанидин

$C_7H_{10}N_4O_2S$ = 214.2.
CAS — 57-67-0 (anhydrous sulfaguanidine); 6190-55-2 (sulfaguanidine monohydrate).
ATC — A07AB03.
ATC Vet — QA07AB03.



Pharmacopoeias. In *Eur.* (see p.vii).
Viet. includes the monohydrate.
Ph. Eur. 6.2 (Sulfaguanidine). A white or almost white, fine crystalline powder. Very slightly soluble in water and in alcohol; slightly soluble in acetone; practically insoluble in dichloromethane. It dissolves in dilute solutions of mineral acids. Protect from light.

Profile
Sulfaguanidine is a sulfonamide with properties similar to those of sulfamethoxazole (p.340). It is absorbed to a limited extent from the gastrointestinal tract and may therefore be more likely to cause systemic effects than less well absorbed drugs such as phthalylsulfathiazole and succinylsulfathiazole. It is used, usually with other drugs, in the treatment of gastrointestinal infections, and has also been applied locally to the skin and throat.

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

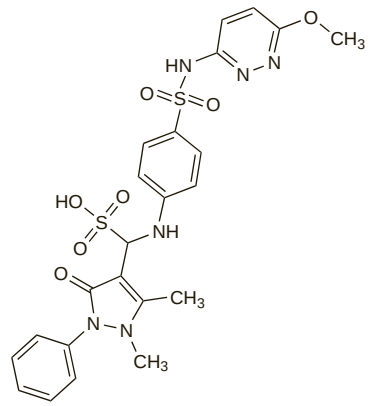
Multi-ingredient: ***Braz.:*** Sanadiar†; ***Chile:*** Carbon Sulfaguanidina; ***Mex.:*** Neopecsul; ***Thai.:*** Biodan†.

Sulfamazone Sodium *(rINNM)*

Natrii Sulfamazonum; Sulfamazona sódica; Sulfamazone Sodique; Sulfenazone; Sulphenazone. Sodium α-{*p*-[(6-methoxy-3-pyridazinyl)sulfamoyl]anilino}-2,3-dimethyl-5-oxo-1-phenyl-3-pyrazoline-4-methanesulphonate.

Натрий Сульфамазон

$C_{23}H_{24}N_6O_7S_2Na$ = 583.6.
CAS — 65761-24-2 (sulfamazone); 13061-27-3 (sulfamazone sodium).
ATC — J01ED09.



(sulfamazone)

Profile
Sulfamazone is an antibacterial with antipyretic activity that has been given as the sodium salt, orally or rectally, in infections of the upper respiratory tract.

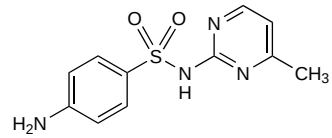
Preparations
Proprietary Preparations (details are given in Part 3)
Ital.: Marespin†.

Sulfamerazine *(BAN, rINN)*

RP-2632; Solfamerazina; Sulfamerasinum; Sulfameratsiini; Sulfamerazin; Sulfamerazina; Sulfamerazinas; Sulfamérazine; Sulfamerazinum; Sulfamethyldiazine; Sulfamethylpyrimidine; Sulphamerazine; Szulfamerazin. N^1-(4-Methylpyrimidin-2-yl)sulphanilamide.

Сульфамеразин

$C_{11}H_{12}N_4O_2S$ = 264.3.
CAS — 127-79-7.
ATC — D06BA06; J01ED07.
ATC Vet — QD06BA06.



Pharmacopoeias. In *Eur.* (see p.vii). Also in *BP(Vet)*.
Ph. Eur. 6.2 (Sulfamerazine). White, yellowish-white, or pinkish-white, crystalline powder or crystals. Very slightly soluble in water and in dichloromethane; slightly soluble in alcohol; sparingly soluble in acetone. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

Sulfamerazine Sodium *(BANM, rINN)*

Soluble Sulphamerazine; Sulfamerazina de sodio; Sulfamerazina sódica; Sulfamérazine sodique; Sulfamerazinum Natricum; Sulphamerazine Sodium.

Сульфамеразин Натрий

$C_{11}H_{11}N_4NaO_2S$ = 286.3.
CAS — 127-58-2.
ATC — D06BA06; J01ED07.
ATC Vet — QD06BA06.

Profile
Sulfamerazine is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p.340). It has usually been given with other sulfonamides, or with trimethoprim.

Preparations
USP 31: Trisulfapyrimidines Oral Suspension; Trisulfapyrimidines Tablets.

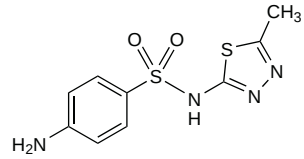
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ger.:*** Berlocombin†; ***Indon.:*** Trisulfa; ***Thai.:*** Sulfatril.

Sulfamethizole *(BAN, rINN)*

Sulfaméthizol; Sulfamethizol; Sulfamethizolum; Sulfametitsoli; Sulfametizol; Sulfametizolas; Sulphamethizole; Szulfametizol. N^1-(5-Methyl-1,3,4-thiadiazol-2-yl)sulphanilamide.

Сульфаметизол

$C_9H_{10}N_4O_2S_2$ = 270.3.
CAS — 144-82-1.
ATC — B05CA04; D06BA04; J01EB02; S01AB01.
ATC Vet — QB05CA04; QD06BA04; QJ01EQ02; QS01AB01.



Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Sulfamethizole). White or yellowish-white crystalline powder or crystals. Very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.
USP 31 (Sulfamethizole). Practically odourless, white crystals or powder. Soluble 1 in 2000 of water, 1 in 38 of alcohol, 1 in 13 of acetone, and 1 in 1900 of chloroform and of ether; freely soluble in solutions of ammonium, potassium, and sodium hydroxides; soluble in dilute mineral acids; practically insoluble in benzene. Protect from light.

Adverse Effects, Treatment, and Precautions
As for Sulfamethoxazole, p.340.

Sulfamethizole and its acetyl derivative are relatively soluble in urine, and the risk of crystalluria is quite low, but an adequate fluid intake should generally be maintained.

Interactions
As for Sulfamethoxazole, p.341.

Antimicrobial Action
As for Sulfamethoxazole, p.341.

Pharmacokinetics
Sulfamethizole is readily absorbed from the gastrointestinal tract; about 90% has been reported to be bound to plasma proteins. Its half-life has been reported to range from about 1.5 to 3 hours. It is only slightly acetylated in the body and is rapidly excreted, about 60% of a dose being eliminated in the urine in 5 hours and around 90% within 10 hours. Sulfamethizole and its acetyl derivative are readily soluble in urine over a wide pH range. Only low concentrations are achieved in blood and tissues because of its rapid excretion.

Uses and Administration
Sulfamethizole is a short-acting sulfonamide that is given orally in the treatment of infections of the urinary tract, sometimes with other antibacterials; it is unsuitable for the treatment of systemic infection since only relatively low concentrations of drug are achieved in the blood and tissues.

It is given in adult doses of 1.5 to 4 g daily in 3 or 4 divided doses. A usual dose for children is 30 to 45 mg/kg daily in 4 divided doses.

Sulfamethizole monoethanolamine has also been used.

Preparations
USP 31: Sulfamethizole Oral Suspension; Sulfamethizole Tablets.

Proprietary Preparations (details are given in Part 3)
Denm.: Lucosil; ***Fr.:*** Rufol; ***Norw.:*** Lucosil†; ***Thai.:*** Luco-Oph†.

Multi-ingredient: ***Spain:*** Micturol Sedante; ***USA:*** Urobiotic-250; ***Venez.:*** Bacteval.

Sulfamethoxazole *(BAN, USAN, rINN)*

Ro-4-2130; Sulfamethoxazol; Sulfaméthoxazole; Sulfamethoxazolum; Sulfametoksatsoli; Sulfametoksazol; Sulfametoksazolas; Sulfametoxazol; Sulfisomezole; Sulphamethoxazole; Szulfametoxazol. N^1-(5-Methylisoxazol-3-yl)sulphanilamide.

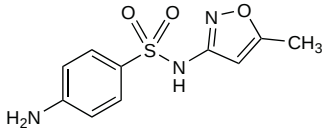
Сульфаметоксазол

$C_{10}H_{11}N_3O_3S$ = 253.3.

CAS — 723-46-6.

ATC — J01EC01.

ATC Vet — QJ01EQ11.



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

- Co-trimoxazole (*BAN*)—sulfamethoxazole 5 parts and trimethoprim 1 part (see p.258)
- Co-trimoxazole (*PEN*)—sulfamethoxazole and trimethoprim.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 6.2 (Sulfamethoxazole). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone. It dissolves in dilute solutions of sodium hydroxide and in dilute acids. Protect from light.

USP 31 (Sulfamethoxazole). A white to off-white, practically odourless, crystalline powder. Soluble 1 in 3400 of water, 1 in 50 of alcohol, and 1 in 1000 of chloroform and of ether; slowly and usually incompletely soluble 1 in 2 of carbon disulfide; freely soluble in acetone and in dilute solutions of sodium hydroxide. Protect from light.

Adverse Effects and Treatment
Nausea, vomiting, anorexia, and diarrhoea are relatively common after use of sulfamethoxazole and other sulfonamides.

Hypersensitivity reactions to sulfonamides have proved a problem. Fever is relatively common, and reactions involving the skin may include rashes, pruritus, photosensitivity reactions, exfoliative dermatitis, and erythema nodosum. Severe, potentially fatal, skin reactions including toxic epidermal necrolysis and the Stevens-Johnson syndrome have occurred in patients treated with sulfonamides. Dermatitis may also occur from contact of sulfonamides with the skin. SLE, particularly exacerbation of pre-existing disease, has also been reported.

Nephrotoxic reactions including interstitial nephritis and tubular necrosis, which may result in renal failure, have been attributed to hypersensitivity to sulfamethoxazole. Lumbar pain, haematuria, oliguria, and anuria may also occur due to crystallisation in the urine of sulfamethoxazole or its less soluble acetylated metabolite. The risk of crystalluria can be reduced by giving fluids to maintain a high urine output. If necessary, alkalinisation of the urine with sodium bicarbonate may increase solubility and aid the elimination of sulfonamides.

Blood disorders have occasionally occurred during treatment with the sulfonamides including sulfamethoxazole, and include agranulocytosis, aplastic anaemia, thrombocytopenia, leucopenia, hypoprothrombinaemia, and eosinophilia. Many of these effects on the blood may result from hypersensitivity reactions. Sulfonamides may rarely cause cyanosis due to methaemoglobinaemia. Acute haemolytic anaemia is a rare complication which may be associated with G6PD deficiency.

Other adverse effects that may be manifestations of a generalised hypersensitivity reaction to sulfonamides include a syndrome resembling serum sickness, hepatic necrosis, hepatomegaly and jaundice, myocarditis, pulmonary eosinophilia and fibrosing alveolitis, and vasculitis including polyarteritis nodosa. Anaphylaxis has been reported only very rarely.

Other adverse reactions reported after sulfamethoxazole or other sulfonamides include hypoglycaemia, hypothyroidism, neurological reactions including aseptic meningitis, ataxia, benign intracranial hypertension, convulsions, dizziness, drowsiness, fatigue, headache, insomnia, mental depression, peripheral or optic neuropathies, psychoses, tinnitus, vertigo, and pancreatitis.

Sulfonamides may displace serum-bound bilirubin, resulting in kernicterus in premature neonates.

As with other antimicrobials, sulfamethoxazole may cause alterations of the bacterial flora in the gastrointestinal tract. There is, therefore, the possibility, although it appears to be small, that pseudomembranous colitis may occur.

Slow acetylators of sulfamethoxazole may be at greater risk of adverse reactions than fast acetylators.

For further information on the adverse effects of sulfamethoxazole when used with trimethoprim, see Co-trimoxazole, p.258.

Precautions
In patients given sulfamethoxazole, adequate fluid intake is necessary to reduce the risk of crystalluria; the daily urine output should be 1200 mL or more. Compounds that render the urine acidic may increase the risk of crystalluria; the risk may be reduced with alkaline urine.

Treatment with sulfonamides should be stopped immediately a rash appears because of the danger of severe allergic reactions such as the Stevens-Johnson syndrome.

Sulfamethoxazole should be given with care to patients with renal or hepatic impairment and is contra-indicated in patients with severe impairment or with blood disorders. Dosage reduction may be necessary in renal impairment. Complete blood counts and urinalyses with microscopic examination should be carried out particularly during prolonged therapy. Sulfamethoxazole should not be given to patients with a history of hypersensitivity to sulfonamides as cross-sensitivity may occur between drugs of this group. Care is generally advisable in patients with a history of allergy or asthma. Caution is also needed in the elderly, who may be more likely to have other risk factors for reactions. Some consider sulfamethoxazole to be contra-indicated in lupus erythematosus as it may exacerbate the condition. Patients with glucose 6-phosphate dehydrogenase deficiency may be at risk of haemolytic reactions.

Sulfamethoxazole and other sulfonamides are not usually given to infants within 1 to 2 months of birth because of the risk of producing kernicterus; for the same reason, they are generally contra-indicated in women prior to delivery (see below).

Patients with AIDS may be particularly prone to adverse reactions, especially when sulfamethoxazole is given with trimethoprim as co-trimoxazole.

Sulfonamides have been reported to interfere with some diagnostic tests, including those for urea, creatinine, and urinary glucose and urobilinogen.

Breast feeding. Sulfonamides are excreted into breast milk in low concentrations and, although they are generally contra-indicated in the USA in breast-feeding women because of the risk of kernicterus, they are usually thought to pose a negligible risk to healthy neonates. However, sulfonamides should be used with caution in breast-feeding mothers of ill, stressed, or premature infants and of infants with jaundice, hyperbilirubinaemia or G6PD deficiency.

The American Academy of Pediatrics considers sulfamethoxazole, when given with trimethoprim, to be compatible with breast feeding.[1]

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 28/05/04)

Immunocompromised patients. Sulfamethoxazole is mainly conjugated in the liver to the N^4-acetyl derivative, but is also oxidised, to a limited extent, to the hydroxylamine metabolite.[1-5] Although this metabolite was originally implicated[6] in the development of adverse reactions to sulfonamides, recent work[7] has cast some doubt on this hypothesis. The metabolite appears to be produced through cytochrome P450 oxidative metabolism, and it has been suggested that slow acetylators of sulfamethoxazole exhibit increased oxidation compared with other metabolic routes.[1] AIDS patients also exhibit increased oxidation, since they may be depleted of substrates such as acetylcoenzyme A or glutathione necessary for acetylation or detoxification, and this may explain their susceptibility to sulfamethoxazole toxicity.[2,3]

There have been attempts to inhibit the formation of the hydroxylamine metabolite by competitive inhibition of cytochrome P450 enzymes, notably with fluconazole and ketoconazole.[4,5] Encouraging results have been obtained with fluconazole in healthy subjects, but the potential for clinical benefit in AIDS patients requires further study.[5]

However, one successful method of overcoming adverse effects in AIDS patients has been **desensitisation**. Desensitisation by use of initial doses of 4 mg of sulfamethoxazole or 5 mg of sulfadiazine every 6 hours, doubled at 24-hour intervals until the desired dose was reached, was uneventful in 9 of 13 patients with AIDS requiring sulfonamide treatment for opportunistic infections.[8] The remaining 4 had cutaneous reactions with fever, but in 2 of these the reactions were successfully managed with an antihistamine. Although there is a risk of anaphylaxis, patients with AIDS can be successfully treated with sulfonamides after desensitisation.

See also Immunocompromised Patients under Precautions of Co-trimoxazole, p.258.

1. Cribb AE, Spielberg SP. Sulfamethoxazole is metabolized to the hydroxylamine in humans. *Clin Pharmacol Ther* 1992; **51:** 522–6.
2. Lee BL, *et al.* The hydroxylamine of sulfamethoxazole and adverse reactions in patients with acquired immunodeficiency syndrome. *Clin Pharmacol Ther* 1994; **56:** 184–9.
3. van der Ven AJA, *et al.* Urinary recovery and kinetics of sulphamethoxazole and its metabolites in HIV-seropositive patients and healthy volunteers after a single oral dose of sulphamethoxazole. *Br J Clin Pharmacol* 1995; **39:** 621–5.
4. Mitra AK, *et al.* Inhibition of sulfamethoxazole hydroxylamine formation by fluconazole in human liver microsomes and healthy volunteers. *Clin Pharmacol Ther* 1996; **59:** 332–40.
5. Gill HJ, *et al.* The effect of fluconazole and ketoconazole on the metabolism of sulphamethoxazole. *Br J Clin Pharmacol* 1996; **42:** 347–53.
6. van der Ven AJAM, *et al.* Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338:** 431–3.
7. ter Hofstede HJM, *et al.* Drug reactions to cotrimoxazole in HIV infection: possibly not due to the hydroxylamine metabolites of sulphamethoxazole. *Br J Clin Pharmacol* 1999; **47:** 571–3.
8. Torgovnick J, Arsura E. Desensitization to sulfonamides in patients with HIV infection. *Am J Med* 1990; **88:** 548–9.

Porphyria. Sulfonamides have been associated with acute attacks of porphyria and are considered unsafe in porphyric patients.