Pharmacokinetics

Spectinomycin is poorly absorbed orally but is rapidly absorbed after the intramuscular injection of the hydrochloride. A 2-g dose produces peak plasma concentrations of about 100 micrograms/mL at 1 hour while a 4-g dose produces peak concentrations of about 160 micrograms/mL at 2 hours. Therapeutic plasma concentrations are maintained for up to 8 hours. Distribution into saliva is poor (which limits its value in pharyngeal gonorrhoea). It is poorly bound to plasma proteins. Spectinomycin is excreted in an active form in the urine and up to 100% of a dose has been recovered within 48 hours. A half-life of about 1 to 3 hours has been reported; it is prolonged in patients with renal impairment. Spectinomycin is partially removed by dialysis.

Uses and Administration

Spectinomycin is used as an alternative to cephalosporins or fluoroquinolones in the treatment of gonorrhoea (p.191) although poor distribution into saliva limits its usefulness in pharyngeal infections. It has also been used in the treatment of chancroid (p.191).

Spectinomycin is given as the hydrochloride but doses are expressed in terms of the base. Spectinomycin hydrochloride 1.5 g is equivalent to about 1 g of spectinomycin. In the treatment of gonorrhoea it is given by deep intramuscular injection as a single dose equivalent to 2 g of spectinomycin, although a dose of 4 g may sometimes be required, divided between two injection sites. Multiple-dose courses have been used for the treatment of disseminated infections.

Spectinomycin is not effective against syphilis or chlamydial infections and additional therapy for these infections may also be needed.

For details of doses in children, see below.

Administration in children. Parenteral spectinomycin is not recommended in neonates because of the presence of benzyl alcohol, a preservative that has been associated with fatalities in neonates due to the 'gasping syndrome' (see p.1632).

For prophylaxis in neonates born to mothers with gonorrhoea WHO recommends a single intramuscular dose of spectinomycin 25 mg/kg (maximum 75 mg) as an alternative to ceftriaxone. The CDC recommends spectinomycin as an alternative to cephalosporins in the treatment of uncomplicated gonorrhoea (p.191) in children beyond the newborn period and weighing under 45 kg; a single intramuscular dose equivalent to 40 mg/kg of spectinomycin may be given.

Preparations

USP 31: Spectinomycin for Injectable Suspension.

Proprietary Preparations (details are given in Part 3)

Arg.: Togamycin†; ***Austral.:*** Trobicin; ***Austria:*** Trobicin; ***Belg.:*** Trobicin; ***Braz.:*** Trobicin†; ***Fr.:*** Trobicine; ***Ger.:*** Stanilo; ***Hong Kong:*** Kirin; Trobicin; ***India:*** Spectin; Trobicin; ***Israel:*** Togamycin†; ***Ital.:*** Trobicin; ***Malaysia:*** Kirin†; ***Mex.:*** Trobicin; ***Port.:*** Trobicin†; ***Rus.:*** Kirin (Кирин); Trobicin (Тробицин)†; ***S.Afr.:*** Trobicin; ***Singapore:*** Trobicin; ***Spain:*** Kempi; ***Switz.:*** Trobicin; ***Thai.:*** Trobicin; Vabicin; ***Venez.:*** Trobicin†.

Spiramycin *(BAN, USAN, rINN)*

Espiramicina; IL-5902; NSC-55926; NSC-64393 (spiramycin hydrochloride); RP-5337; Spiramicin; Spiramicinas; Spiramisin; Spiramycine; Spiramycinum; Spiramysiini. A mixture comprised principally of (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,16*R*)-(11*E*,13*E*)-6-[(*O*-2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-(1→4)-(3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyl)oxy]-7-formylmethyl-4-hydroxy-5-methoxy-9,16-dimethyl-10-[(2,3,4,6-tetradeoxy-4-dimethylamino-D-*erythro*-hexopyranosyl)oxy]oxacyclohexadeca-11,13-dien-2-one (Spiramycin I).

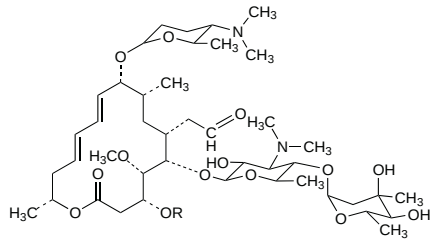
Спирамицин

$C_{43}H_{74}N_2O_{14}$ = 843.1.

CAS — 8025-81-8.

ATC — J01FA02.

ATC Vet — QJ01FA02; QJ51FA02.



Spiramycin I R = H
Spiramycin II R = $COCH_3$
Spiramycin III R = $COCH_2CH_3$

Pharmacopoeias. In *Eur.* (see p.vii). Also in *BP (Vet). Jpn* includes Acetylspiramycin.

Ph. Eur. 6.2 (Spiramycin). A macrolide antibiotic produced by the growth of certain strains of *Streptomyces ambofaciens* or obtained by any other means. The potency is not less than 4100 units/mg, calculated with reference to the dried substance. A white or slightly yellowish, slightly hygroscopic powder. Slightly soluble in water; freely soluble in alcohol, in acetone, and in methyl alcohol. A 0.5% solution in methyl alcohol and water has a pH of 8.5 to 10.5. Store in airtight containers.

Adverse Effects and Precautions

As for Erythromycin, p.270.

The most frequent adverse effects are gastrointestinal disturbances. Transient paraesthesia has been reported during parenteral use.

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p.271.

Cytochrome P450 isoenzymes. Spiramycin is reported to have little or no effect on hepatic cytochrome P450 isoenzymes and may therefore produce fewer interactions than erythromycin with other drugs metabolised by this enzyme system (see Mechanism, under Interactions of Erythromycin, p.271). The lack of interactions between spiramycin and theophylline and ciclosporin would appear to support this. Nevertheless, a report of torsade de pointes in a patient with a congenital long QT syndrome during treatment with spiramycin and *mequitazine*[1] suggests that caution is still needed.

Reduced plasma concentrations of *levodopa* have been reported when given with spiramycin (see p.807).

1. Verdun F, *et al.* Torsades de pointes sous traitement par spiramycine et méquitazine: à propos d'un cas. *Arch Mal Coeur Vaiss* 1997; **90:** 103–6.

Antimicrobial Action

As for Erythromycin, p.271, although it is somewhat less active *in vitro* against many species. It is active against *Toxoplasma gondii*.

Pharmacokinetics

Spiramycin is incompletely absorbed from the gastrointestinal tract and absorption is reduced by food. It is widely distributed into tissues, although it does not cross the blood-brain barrier. Spiramycin crosses the placenta and is distributed into breast milk. Plasma protein binding ranges from 10 to 25%. An oral dose of 6 million units produces peak blood concentrations of 3.3 micrograms/mL after 1.5 to 3 hours; the half-life is about 5 to 8 hours. High tissue concentrations are achieved and persist long after the plasma concentration has fallen to low levels.

Spiramycin is metabolised in the liver to active metabolites; substantial amounts are excreted in the bile and about 10% in the urine.

Uses and Administration

Spiramycin is a macrolide antibacterial that is used similarly to erythromycin (p.272) in the treatment of susceptible bacterial infections. It has also been used in the protozoal infections cryptosporidiosis (p.823) and toxoplasmosis (p.826).

Spiramycin is given orally as the base or intravenously as the adipate; it has also been given rectally as the adipate. The usual oral adult dose is 6 to 9 million units daily, in 2 or 3 divided doses. Doses of up to 15 million units have been given daily in divided doses for severe infections. A dose of 1.5 million units of spiramycin may be given by slow intravenous infusion every 8 hours; in severe infection the dose may be doubled.

Spiramycin is available in combination preparations with metronidazole in some countries.

Acetylspiramycin is also used.

◊ Reviews.

1. Rubinstein E, Keller N. Spiramycin renaissance. *J Antimicrob Chemother* 1998; **42:** 572–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Rovamycine; ***Austria:*** Rovamycin; ***Belg.:*** Rovamycine; ***Braz.:*** Rovamicina; ***Canad.:*** Rovamycine†; ***Cz.:*** Rovamycine; ***Fr.:*** Rovamycine; ***Ger.:*** Rovamycine; Selectomycin; ***Gr.:*** Rovamycine; ***Hong Kong:*** Rovamycine; ***Hung.:*** Rovamycine; ***India:*** Rovamycin; ***Indon.:*** Ethirov; Hypermycin; Ismacrol; Medirov; Osmycin; Provamed; Rofacin; Rovadin; Rovamycine; Sorov; Spirabiotic; Spiradan; Spiranter; Spirasin; Varoc; Vipram; ***Israel:*** Rovamycine; ***Ital.:*** Rovamicina; Spiromix; ***Malaysia:*** Rovamycine; ***Mex.:*** Provamicina; ***Neth.:*** Rovamycine; ***Norw.:*** Rovamycin; ***Pol.:*** Rovamycine; ***Port.:*** Rovamycine; ***Rus.:*** Rovamycine (Ровамицин); ***Singapore:*** Rovamycine; ***Spain:*** Dicorvin; Rovamycine; ***Switz.:*** Rovamycine; ***Thai.:*** Rovamycin; Spiracin; ***Turk.:*** Rovamycine; ***Venez.:*** Provamicina.

Multi-ingredient: ***Arg.:*** Estilomicin; ***Braz.:*** Periodontil; ***Cz.:*** Rodogyl†; ***Fr.:*** Birodogyl; Missilor; Rodogyl; ***Malaysia:*** Rodogyl; ***Mex.:*** Rodogyl; ***Spain:*** Rhodogil.

Streptomycin *(BAN, rINN)*

Estreptomicina; Streptomisin; Streptomycine; Streptomycinum; Streptomysiini. *O*-2-Deoxy-2-methylamino-α-L-glucopyranosyl-(1→2)-*O*-5-deoxy-3-*C*-formyl-α-L-lyxofuranosyl-(1→4)-*N*^{3},*N*^{3}-diamidino-D-streptamine.

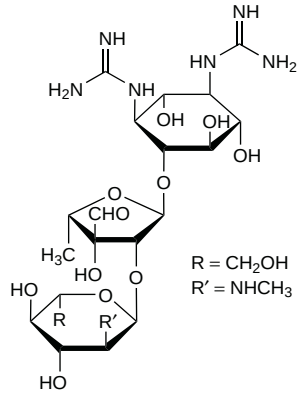
Стрептомицин

$C_{21}H_{39}N_7O_{12}$ = 581.6.

CAS — 57-92-1.

ATC — A07AA04; J01GA01.

ATC Vet — QA07AA04; QJ01GA01.



Description. An antimicrobial organic base produced by the growth of certain strains of *Streptomyces griseus*, or by any other means.

Streptomycin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de estreptomicina; Streptomycine, Chlorhydrate de; Streptomycini Hydrochloridum.

Стрептомицина Гидрохлорид

$C_{21}H_{39}N_7O_{12}$,3HCl = 691.0.

CAS — 6160-32-3.

ATC — A07AA04; J01GA01.

ATC Vet — QA07AA04; QJ01GA01.

Streptomycin Sulfate *(rINNM)*

Streptomicino sulfatas; Streptomycin Sesquisulphate; Streptomycin sulfát; Streptomycin Sulphate *(BANM)*; Streptomycine, sulfate de; Streptomycini sulfas; Streptomycinsulfat; Streptomycyny siarczan; Streptomysiinisulfaatti; Sulfato de estreptomicina; Sztreptomicin-szulfát.

Стрептомицина Сульфат

$(C_{21}H_{39}N_7O_{12})_2$,$3H_2SO_4$ = 1457.4.

CAS — 3810-74-0.

ATC — A07AA04; J01GA01.

ATC Vet — QA07AA04; QJ01GA01.

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

Ph. Eur. 6.2 (Streptomycin Sulphate). A white or almost white, hygroscopic powder. The potency is not less than 720 units/mg, calculated with reference to the dried substance. Very soluble in water; practically insoluble in dehydrated alcohol. A 25% solution in water has a pH of 4.5 to 7.0. Store in airtight containers.

USP 31 (Streptomycin Sulfate). A white or practically white, hygroscopic powder; odourless or with not more than a faint odour. It has a potency equivalent to not less than 650 micrograms and not more than 850 micrograms of streptomycin per mg. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform. A solution in water containing the equivalent of streptomycin 20% has a pH of 4.5 to 7.0. Store in airtight containers.

Incompatibility. Streptomycin sulfate is incompatible with acids and alkalis.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p.282. Like gentamicin the ototoxic effects of streptomycin are mainly vestibular rather than auditory. Ototoxicity has been seen in

infants whose mothers had been given streptomycin during pregnancy. However, streptomycin is reported to be somewhat less nephrotoxic than the other aminoglycosides.

Paraesthesia in and around the mouth is not uncommon after intramuscular injection of streptomycin, and other neurological symptoms, including peripheral neuropathies, optic neuritis, and scotoma have occasionally occurred. Intrathecal use has resulted in symptoms of meningeal inflammation including radiculitis, arachnoiditis, nerve root pain, and paraplegia, and some recommend that it be avoided. The risk of neurotoxic reactions is greater in patients with renal impairment or pre-renal azotaemia.

Hypersensitivity skin reactions are reported in about 5% of patients, and eosinophilia may occur. There have been reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, severe exfoliative dermatitis, and anaphylaxis. Sensitisation is common among those who handle streptomycin occupationally. Topical and inhalational use of streptomycin should be avoided. If necessary, hypersensitivity can usually be overcome by desensitisation. Aplastic anaemia and agranulocytosis have been reported rarely.

Although sources differ, it is usually suggested that peak plasma concentrations should be between 15 and 40 micrograms/mL, and trough concentrations below 3 to 5 micrograms/mL; in the UK the *BNF* recommends that trough concentrations in excess of 1 microgram/mL should be avoided in those over 50 years of age or those with renal impairment. A total cumulative dose in excess of 100 g may be associated with a higher incidence of adverse effects and should only be exceeded in exceptional circumstances.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving streptomycin, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

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)

Handling. Streptomycin may cause severe dermatitis in sensitised persons, and pharmacists, nurses, and others who handle the drug frequently should wear masks and rubber gloves.

Interactions

As for Gentamicin Sulfate, p.283.

Antimicrobial Action

Streptomycin has a mode of action and antimicrobial spectrum similar to that of gentamicin (p.283), although most strains of *Pseudomonas aeruginosa* are resistant. It is effective against *Yersinia pestis, Francisella tularensis*, and *Brucella* spp. Streptomycin has particular activity against *Mycobacterium tuberculosis*.

Resistance to streptomycin has often been reported and may develop in strains which are initially sensitive within a few days or weeks of beginning therapy. The widespread emergence of resistance has largely halted its use in infections due to the common Gram-negative aerobes. Primary resistance in *M. tuberculosis* is relatively uncommon in the UK and USA but may be seen in a third or more of cases in the Far East.

Both low-level and high-level resistance have been reported; the latter is thought to be due to mutation of the ribosomal binding site of the antibiotic and cannot be overcome by the synergistic use of another drug such as a beta lactam, whereas strains with moderate resistance due to decreased uptake or permeability of streptomycin may respond to combined use.

Organisms resistant to framycetin, kanamycin, neomycin, and paromomycin usually show cross-resistance to streptomycin, although streptomycin-resistant strains sometimes respond to one of these drugs.

◊ References.

1. Cooksey RC, *et al.* Characterization of streptomycin resistance mechanisms among Mycobacterium tuberculosis isolates from patients in New York City. *Antimicrob Agents Chemother* 1996; **40:** 1186–8.
2. Ho YII, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; **40:** 27–32.

Pharmacokinetics

As for Gentamicin Sulfate, p.284. After intramuscular injection of streptomycin, maximum concentration in the blood is reached in 0.5 to 2 hours but the time taken and the concentration attained, which may be as high as about 50 micrograms/mL after a dose of 1 g, vary considerably. The half-life of streptomycin is about 2.5 hours. About one-third of streptomycin in the circulation is bound to plasma proteins. It is rapidly excreted by glomerular filtration and the concentration of streptomycin in the urine is often very high, with about 30 to 90% of a dose usually being excreted within 24 hours. It is distributed into breast milk.

Uses and Administration

Streptomycin is an aminoglycoside antibacterial mainly used as a first-line drug, with other antimycobacterials, in the treatment of tuberculosis. It is given during the initial phase of treatment unless the risk of drug resistance is small. Streptomycin has been used, with a penicillin, as an alternative to gentamicin in the treatment of bacterial endocarditis. Streptomycin is effective in the treatment of plague, tularaemia, and, with a tetracycline, in brucellosis. It has also been used, with other drugs, in various other infections including mycetoma and Whipple's disease. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Streptomycin is mostly used as the sulfate but doses are expressed in terms of the base; 1.25 g of streptomycin sulfate is equivalent to about 1 g of streptomycin. It is given by intramuscular injection.

In the treatment of tuberculosis, streptomycin is given during the initial phase of short-course regimens in usual adult doses of 15 mg/kg daily, up to a maximum of 1 g daily. The maximum daily dose should be reduced to 500 to 750 mg in adults aged over 40 years, and in those weighing less than 50 kg. Dosage should also be reduced in those with renal impairment, in whom plasma-drug concentration should be monitored. Streptomycin may also be given as part of an intermittent regimen 2 or 3 times weekly. It has been given by the intrathecal route, together with intramuscular dosage, for tuberculous meningitis, but this is no longer recommended.

Children and infants aged 1 month to 18 years with tuberculosis may be given streptomycin 20 to 40 mg/kg daily (to a maximum of 1 g daily).

In the treatment of non-tuberculous infections, streptomycin has been given in usual adult doses of 1 to 2 g daily in divided doses, depending on the susceptibility and severity of infection; children may be given 20 to 40 mg/kg daily (maximum 1 g daily), usually in 2 to 4 divided doses.

In all patients dosage should preferably be adjusted according to plasma-streptomycin concentrations, and particularly where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity. The course of treatment (other than in tuberculosis) should usually be limited to 7 to 14 days, and peak plasma concentrations should be between 15 and 40 micrograms/mL and trough concentrations below 3 to 5 micrograms/mL or below 1 microgram/mL in renal impairment or in those over 50 years of age. For discussion of the methods used to calculate aminoglycoside dosage requirements, see under Gentamicin Sulfate, p.284.

Streptomycin has also been used as the hydrochloride, the pantothenate, and as a complex with calcium chloride.

Administration and dosage. A report of the successful use of streptomycin 7 to 15 mg/kg as an intravenous infusion over 30 to 60 minutes in 4 patients with tuberculosis. Despite the view that streptomycin should be given intramuscularly because of the greater risk of toxicity with the intravenous route, this study was considered to indicate that intravenous use was feasible in selected patients unable to tolerate the intramuscular route.[1]

1. Driver AG, Worden JP. Intravenous streptomycin. *DICP Ann Pharmacother* 1990; **24:** 826–8.

Ménière's disease. Streptomycin and gentamicin have been used for medical ablation in advanced Ménière's disease (p.564). Systemic treatment has generally been limited by the development of chronic ataxia and oscillopsia (oscillating vision). However, streptomycin sulfate 1 g twice daily by intramuscular injection on 5 days each week for 2 weeks, repeated as necessary to a total dose of up to 60 g,[1,2] or 1 g twice daily for 5 days, followed if necessary by a further 3 days of treatment in the second week,[3] has produced improvements in vestibular symptoms without hearing loss in patients with Ménière's disease. Local (intratympanic) injections have also been tried,[4] but gentamicin is considered to be less toxic and is now generally preferred.

1. Shea JJ, *et al.* Long-term results of low dose intramuscular streptomycin for Ménière's disease. *Am J Otol* 1994; **15:** 540–4.
2. Balyan FR, *et al.* Titration streptomycin therapy in Meniere's disease: long-term results. *Otolaryngol Head Neck Surg* 1998; **118:** 261–6.
3. Graham MD. Bilateral Meniere's disease: treatment with intramuscular titration streptomycin sulfate. *Otolaryngol Clin North Am* 1997; **30:** 1097–1100.
4. Beck C, Schmidt CL. 10 Years of experience with intratympanally applied streptomycin (gentamycin) in the therapy of Morbus Menière. *Arch Otorhinolaryngol* 1978; **221:** 149–52.

Preparations

BP 2008: Streptomycin Injection;
USP 31: Streptomycin for Injection; Streptomycin Injection.

Proprietary Preparations (details are given in Part 3)

Cz.: Strepto-Fatol; ***Ger.:*** Strepto-Fatol; Strepto-Hefa; ***Gr.:*** Pan-Streptomycin†; ***India:*** Ambistryn-S; Cipstryn; ***Mex.:*** Bucomicina; Sulfestrep; ***S.Afr.:*** Bio-Strep; Novostrep†; Solustrep; ***Thai.:*** Strepto.

Multi-ingredient: ***Arg.:*** Estreptocarbocaftiazol; ***Braz.:*** Ortocilin†; ***India:*** Strepto-Erbazide†; ***Mex.:*** Aguipental; ***Port.:*** Bienterico.

Succinylsulfathiazole *(BAN, rINN)*

Succinilsolfatiazolo; Succinilsulfatiazol; Succinylsulfathiazol; Succinylsulfathiazolum; Succinylsulfathiazolum Monohydricum; Succinylsulfatiazol; Succinylsulphathiazole; Sukcinilsulfatiazolas; Sukcinylsulfathiazol monohydrát; Suksinyylisulfatiatsoli; Szukcinilszulfatiazol. 4′-(1,3-Thiazol-2-ylsulphamoyl)succinanilic acid monohydrate.

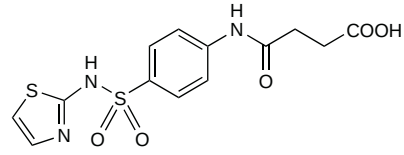
Сукцинилсульфатиазол

$C_{13}H_{13}N_3O_5S_2,H_2O$ = 373.4.

CAS — 116-43-8 (anhydrous succinylsulfathiazole).

ATC — A07AB04.

ATC Vet — QA07AB04.



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

Ph. Eur. 6.2 (Succinylsulfathiazole). A white or yellowish-white crystalline powder. Very slightly soluble in water; slightly soluble in acetone and in alcohol; dissolves in solutions of alkali hydroxides and carbonates. Protect from light.

Profile

Succinylsulfathiazole is a sulfonamide with properties similar to those of sulfamethoxazole (p.340). It is poorly absorbed and has been given for its antibacterial activity in the gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Venez.:*** Guanicar.