PRESCRIBING INFORMATION

[Pr]Streptomycin for Injection, U.S.P.

Powder for Solution

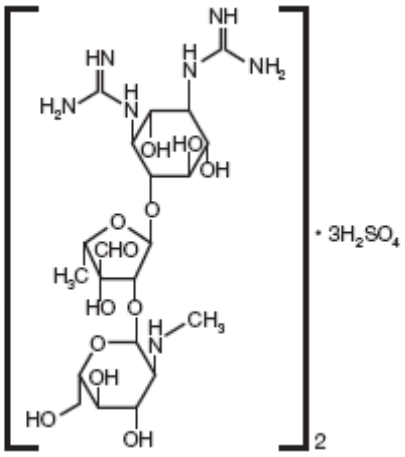
Aminoglycoside Antibiotic

SteriMax Inc.
2770 Portland Drive,
Oakville, ON
L6H 6R4

Date of Revision:
February 8, 2016

ACTIONS AND CLINICAL PHARMACOLOGY

Streptomycin is a water soluble aminoglycoside derived from *Streptomyces griseus.* It is marketed as the sulphate salt of streptomycin. The chemical name of streptomycin sulphate is D-Streptamine,*0*-2-deoxy-2-(methylamino)-α-L-glucopyranosyl-(1→2)-*0*-5-deoxy-3-*C*-formyl-α-L-lyxofuranosyl-(1→4)-*N,N*^{1}-bis(aminoiminomethyl)-,sulphate (2:3) (salt). The molecular formula for streptomycin sulphate is $(C_{21}H_{39}N_7O_{12})_2 \cdot 3H_2SO_4$ and the molecular weight is 1457.41. It has the following structural formula:



Streptomycin sulphate, equivalent to 1 g streptomycin/vial is supplied as a sterile nonpyrogenic lyophilized powder for intramuscular use after reconstitution.

After reconstitution the pH range for Sterile Streptomycin for Injection USP should be between 4.5 and 7.0 in a solution containing 200 mg of streptomycin activity per mL.

Each vial contains Streptomycin Sulphate USP equivalent to 1 g of streptomycin.

Pharmacology:

In recommended doses, Streptomycin is active against susceptible strains of many gram-negative and gram-positive organisms, and *M. tuberculosis.* When used alone, bacterial resistance has been shown to develop rapidly. Therefore, in the treatment of tuberculosis, it should be used in combination with other antitubercular drugs.

Pharmacokinetics:

Streptomycin is not absorbed from the gastro-intestinal tract when given orally and therefore should be administered parenterally for systemic action. Following intramuscular injection of 1 g of the drug, a peak serum level of 25 to 50 µg/mL is reached within 1 hour, diminishing slowly to about 50% after 5 to 6 hours. Appreciable concentrations are found in all organ tissues except the brain. Significant amounts have been found in pleural fluid and tuberculous cavities. Streptomycin passes through the placenta with serum levels in the cord blood similar to maternal levels. Small amounts are excreted in milk, saliva and sweat. Streptomycin is excreted rapidly in the urine by glomerular filtration. In patients with normal kidney function, between 29 and 89% of a single 600 mg dose is excreted within 24 hours. Any reduction of glomerular activity results in decreased excretion of the drug and concurrent rise in serum and tissue levels.

Sensitivity plate testing:

If the Kirby-Bauer method of disc sensitivity is used, a 10 µg Streptomycin disc should give a zone of over 15 mm when tested against a Streptomycin-sensitive bacterial strain.

INDICATIONS

Streptomycin is indicated for the treatment of individuals with moderate to severe infections caused by susceptible strains of microorganism in the specific conditions listed below:

1. *Mycobacterium tuberculosis:* Streptomycin may be indicated for all forms of this infection when the infecting organisms are susceptible. It should be used only in combination with other antituberculosis drugs. The common combined drug therapy is Streptomycin, PAS and isoniazid; this combination is effective only where the organisms are susceptible to the drugs being used in combination.

2. *Nontuberculosis infections:* Streptomycin should be used only in those serious nontuberculosis infections caused by organisms shown by in vitro sensitivity studies to be susceptible to it and when less potentially hazardous therapeutic agents are ineffective or contraindicated.
   a. *Pasteurella pestis* (plague).

b. *Pasteurella tularensis* (tularemia).

c. *Brucella.*

d. *Donovanosis* (granuloma inguinale).

e. *H. ducreyi* (chancroid).

f. *H. influenzae* (in respiratory, endocardial and meningeal infections – concomitantly with another antibacterial agent).

g. *K. pneumoniae pneumonia* (concomitantly with another antibacterial agent).

h. *E. coli, Proteus, A. aerogenes, K. pneumoniae,* and *Streptococcus faecalis* in urinary tract infections.

i. *Strep. viridans,* and *Strep. faecalis* (in endocardial infections – concomitantly with penicillin).

j. Gram-negative bacillary bacteremia (concomitantly with another antibacterial agent).

NOTE: The use of Streptomycin should be limited to the treatment of infections caused by bacteria which have been shown to be susceptible to the antibacterial effects of streptomycin and which are not amenable to therapy with less potentially toxic agents.

CONTRAINDICATIONS

Streptomycin is contraindicated in those patients who have shown previous toxic or hypersensitivity reactions to it.

WARNINGS

For Intramuscular Use

EXTREME CAUTION IS ADVISED IN PEOPLE WITH VIII CRANIAL NERVE IMPAIRMENT. THE RISK OF SEVERE NEUROTOXIC REACTIONS IS SHARPLY INCREASED IN PATIENTS WITH IMPAIRED KIDNEY FUNCTION OR PRERENAL AZOTEMIA. THESE INCLUDE DISTURBANCES OF THE AUDITORY NERVE, OPTIC NERVE, PERIPHERAL NEURITIS, ARACHNOIDITIS, AND ENCEPHALOPATHY. RENAL FUNCTION SHOULD BE CAREFULLY DETERMINED AND PATIENTS WITH RENAL DAMAGE AND NITROGEN RETENTION SHOULD HAVE REDUCED DOSAGE. THE PEAK SERUM CONCENTRATION IN INDIVIDUALS WITH KIDNEY DAMAGE SHOULD NOT EXCEED 20 TO 25 µg/mL.

THE CONCURRENT OR SEQUENTIAL USE OF OTHER NEUROTOXIC AND/OR NEPHROTOXIC DRUGS WITH STREPTOMYCIN SULPHATE, PARTICULARLY NEOMYCIN, KANAMYCIN, GENTAMICIN, CEPHALORIDINE,

PAROMOMYCIN, VIOMYCIN, POLYMYXIN B, COLISTIN, AND TOBRAMYCIN SHOULD BE AVOIDED.

THE NEUROTOXICITY OF STREPTOMYCIN CAN RESULT IN RESPIRATORY PARALYSIS FROM NEUROMUSCULAR BLOCKAGE, ESPECIALLY WHEN THE DRUG IS GIVEN SOON AFTER ANESTHESIA AND THE USE OF MUSCLE RELAXANTS.

THE ADMINISTRATION OF STREPTOMYCIN IN PARENTERAL FORM SHOULD BE RESERVED FOR PATIENTS WHERE ADEQUATE LABORATORY FACILITIES ARE AVAILABLE AND CONSTANT SUPERVISION OF PATIENT IS POSSIBLE.

Ototoxicity:

Streptomycin may frequently affect the vestibular branch of the auditory nerve causing severe nausea, vomiting, and vertigo. The incidence is directly proportional to the duration and amount of the drug administered. Advanced age and renal impairment predispose to ototoxicity. Symptoms subside and recovery is usually complete following discontinuance of the drug.

Loss of hearing has been reported following long term therapy; however, ototoxic effect on the auditory branch of the eighth nerve is infrequent and is usually preceded by vestibular symptoms. Hearing loss, when extensive, is usually permanent.

Usage in Pregnancy:

Streptomycin should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus. Since Streptomycin readily crosses the placental barrier, caution in use of the drug is important to prevent ototoxicity in the fetus.

PRECAUTIONS

Baseline and periodic caloric stimulation tests and audiometric tests are advisable with extended Streptomycin therapy. Tinnitus, roaring noises, or a sense of fullness in the ears indicates need for audiometric examination or termination of Streptomycin therapy or both. (See **Adverse Reactions**).

Care should be taken by individuals handling or preparing Streptomycin for injection to avoid skin sensitivity reactions.

As with all intramuscular preparations, Streptomycin for Injection should be injected well within the body of a relatively large muscle. ADULTS: The preferred site is the upper outer quadrant of the buttock, (i.e. gluteus maximus), or the mid-lateral thigh. CHILDREN: It is recommended that intramuscular injections be given preferably in the mid-lateral muscles of the thigh. In infants and small children, the periphery of the upper outer quadrant of the gluteal region should be used only when necessary, such as in burn patients, in order to minimize the possibility of damage to the sciatic nerve.

The deltoid area should be used only if well developed such as in certain adults and older children, and then only with caution to avoid radial nerve injury, intramuscular injections should not be made into the lower and mid-third of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Injection sites should be alternated, and solutions of concentration greater than 500 mg/mL are not recommended.

As higher doses or more prolonged therapy with Streptomycin may be indicated for more severe or fulminating infections (endocarditis, meningitis, etc.) the physician should always take adequate measure to be immediately aware of any toxic signs or symptoms occurring in the patient as a result of Streptomycin therapy.

While disturbances in renal function due to Streptomycin have been reported in the past, purification of the drug has minimized this side effect. In the presence of pre-existing renal insufficiency, however, extreme caution must be exercised in the administration of Streptomycin. Since in severely uremic patients a single dose may produce reasonable high blood levels for several days, the cumulative effect may produce ototoxic sequelae. When Streptomycin must be given for prolonged periods of time, alkalinization of the urine may minimize or prevent renal irritation.

A syndrome of apparent central nervous system depression, characterized by stupor and flaccidity, at times to the extent of coma and deep respiratory depression, has been reported in very young infants in whom Streptomycin

dosage had materially exceeded the recommended limits. Thus, infants should not receive Streptomycin in excess of the recommended dosage.

In the treatment of venereal infections such as granuloma inguinale, and chancroid, if concomitant syphilis is suspected, suitable laboratory procedures such as dark field examination should be performed before the start of treatment, and monthly serologic tests should be done for at least four months.

As with other antibiotics, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be instituted.

ADVERSE REACTIONS

The following reactions are common: ototoxicity-nausea, vomiting and vertigo, paresthesia of face, rash, fever, urticaria, angioneurotic edema, and eosinophilia.

The following reactions are less frequent: deafness, exfoliative dermatitis, anaphylaxis, azotemia, leucopenia, thrombocytopenia, pancytopenia, hemolytic anemia, muscular weakness, and amblyopia.

Vestibular dysfunction resulting from the parenteral administration of Streptomycin is cumulatively related to the total daily dose. When 1.8 to 2.0 g/day are given, symptoms are likely to develop in the large percentage of patients, especially in the elderly or patients with impaired renal function, within 4 weeks. Therefore, it is recommended that caloric and audiometric tests be done prior to, during, and following intensive therapy with Streptomycin in order to

facilitate detection of any vestibular dysfunction and/or impairment of hearing which may occur.

Vestibular symptoms generally appear early and usually are reversible with early detection and cessation of administration of the drug. After 2 to 3 months, gross vestibular symptoms usually disappear except for the relative inability to walk in total darkness or on very rough terrain.

Clinical judgement as to termination of therapy must be exercised when side effects occur.

DOSAGE AND ADMINISTRATION

INTRAMUSCULAR ROUTE ONLY

1. Tuberculosis: All forms when organisms are known or believed to be drug susceptible.

   Adult, combined therapy: Streptomycin – 1 g daily with PAS 5 g t.i.d. and isoniazid 200 to 300 mg daily. Elderly patients should have a smaller daily dose of Streptomycin, based on age, renal function, and eighth nerve function. Ultimately Streptomycin should be discontinued or reduced in dosage to 1 g, 2 to 3 times weekly. Therapy with Streptomycin may be terminated when toxic symptoms have appeared, when impeding toxicity is feared, when organisms become resistant, or when full treatment effect has been obtained. The total period of drug treatment of tuberculosis is a

minimum of 1 year; however, indications of terminating therapy with Streptomycin may occur at any time as noted above.

2. Tularemia: 1 to 2 g daily in divided doses for 7 to 10 days until the patient is afebrile for 5 to 7 days.
3. Plague: 2 to 4 g daily in divided doses until the patient is afebrile for at least 3 days.
4. a. Bacterial endocarditis: In penicillin-sensitive alpha and nonhemolytic streptococcal endocarditis (penicillin sensitive to 0.1 µg/mL or less), streptomycin may be used for 2 week treatment concomitantly with penicillin. Streptomycin dosage is 1 g b.i.d. for 1 week, and 0.5 g b.i.d. for the 2nd week. If the patient is over 60 years of age, the dosage should be 0.5 g b.i.d. for the entire 2-week period.

   b. Enterococcal endocarditis: Streptomycin in doses of 1 g b.i.d. for 2 weeks and 0.5 g b.i.d. for 4 weeks is given in combination with penicillin. Ototoxicity may require termination of Streptomycin prior to completion of the 6 week course of treatment.
5. For use concomitantly with other agents to which the infecting organism is also sensitive: Streptomycin in these conditions is considered as a drug of secondary choice: gram-negative bacillary bacteremia, meningitis, and pneumonia; brucellosis, granuloma inguinale, chancroid, and urinary tract infection.

For adults:

a. With severe fulminating infection: 2 to 4 g daily, administered intramuscularly in divided doses every 6 to 12 hours.

b. With less severe infections and with highly susceptible organisms: 1 to 2 g daily.

For children:

20 to 40 mg per kg of body weight daily (8 to 20 mg per pound) in divided doses every 6 to 12 hours. (Particular care should be taken to avoid excessive dosage in children).

The dry lyophilized powder is dissolved by adding Water for Injection USP in an amount to yield the desired concentration as indicated in the following table:

Approx. Conc. mg/mL	**Volume (mL) of Diluent**
200	4.2
250	3.2
400	1.8

Sterile reconstituted solutions should be protected from light. Reconstituted solution should be used within 24 hours and any remainder discarded.

HOW SUPPLIED

Streptomycin for Injection U.S.P. is supplied in vials containing streptomycin sulphate equivalent to 1 g streptomycin base activity per vial.

Store dry powder at controlled room temperature 15°C - 30°C.

SteriMax Inc.

2770 Portland Drive,

Oakville, ON

L6H 6R4

www.sterimaxinc.com – 1-800-881-3500