SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Streptomycin (as sulfate) 1g powder for injection[1]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each glass vial contains streptomycin sulfate equivalent to 1 g streptomycin (base)

3. PHARMACEUTICAL FORM

Powder for injection.

Vials containing white or almost white powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Streptomycin (as sulfate) 1 g powder for injection is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by streptomycin -sensitive strains of *Mycobacterium tuberculosis*. Streptomycin injection is indicated as a second-line antimycobacterial drug when first-line drugs cannot be used because of resistance or intolerance. Streptomycin should only be used when other second-line injectable agents, aminoglycosides or capreomycin, cannot be used.

Consideration should be given to official treatment guidelines for tuberculosis e.g. WHO guidelines including:

- Companion handbook to the WHO guidelines for the programmatic management of drug resistant tuberculosis. WHO, 2014
- WHO treatment guidelines for drug-resistant tuberculosis. WHO, 2016 update

4.2 Posology and method of administration

Posology

Adults
The usual dose is 15 mg/kg once daily on 5–7 days each week up to a maximum daily dose of 1 g. Patients weighing less than 50 kg may not tolerate doses above 500–750 mg daily.

Obese individuals
Markedly obese individuals should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supra-therapeutic concentrations.

For dosing, use adjusted weight as follows: Ideal body weight +40% of excess weight.

- Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft
- Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft

One inch=2.5 cm, 5 ft=152 cm.

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

Adults aged over 59 years
Patients over 59 years may not be able to tolerate more than 500–750 mg daily, therefore the recommended dose for patients in this age group is 10 mg/kg/dose (max 750 mg) 5-7 times per week or 2-3 times per week after the initial period. Alternatively the dose can be 15 mg/kg/dose 3 times per week.

Patients with renal impairment
Dosage should also be reduced in those with renal impairment, in whom plasma-drug concentration should be monitored. The recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receiving haemodialysis is 12–15 mg/kg/dose two or three times per week (not daily).

Caution should be used in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity. If on dialysis, the dose should be administered after dialysis.

Plasma concentrations
Peak plasma concentrations should be between 15 and 40 micrograms/mL, and trough (pre-dose) concentrations below 3 to 5 micrograms/mL. Trough concentrations in excess of 1 microgram/mL should be avoided in those over 50 years of age or those with renal impairment.

Children
The recommended dose in children is 20–40 mg/kg/day, 5–7 days per week, up to a maximum daily dose of 1 g.

Method of administration

The product is reconstituted by adding 4.2 mL of water for injection into the vial, which results in a solution of 200 mg of streptomycin activity per mL.

Streptomycin is normally given by the intramuscular route, but can be given intravenously when intramuscular administration is not feasible. Streptomycin should be stopped if toxic symptoms appear, if impending toxicity is feared, if organisms become resistant, or when full treatment effect has been obtained.

Intramuscular injection
Adults: The preferred site is the upper outer quadrant of the buttock, (i.e., gluteus maximus), or the mid-lateral thigh. 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.

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, in order to minimize the possibility of damage to the sciatic nerve.

Intravenous injection or infusion
After reconstitution chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions of the reconstituted infusion fluid prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

4.3 Contraindications

- Hypersensitivity to streptomycin. Clinically significant hypersensitivity to other aminoglycosides may contraindicate the use of streptomycin because of the known cross-sensitivity of patients to drugs in this class.
- Pregnancy: congenital deafness was seen with streptomycin use during pregnancy.

4.4 Special warnings and special precautions for use

Warnings
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.

Ototoxicity: Both vestibular and auditory dysfunction can follow the administration of streptomycin The degree of impairment is directly proportional to the dose and duration of streptomycin administration, to the age of the patient, to the level of renal function and to the amount of underlying existing auditory dysfunction. The ototoxic effects of the aminoglycosides, including streptomycin, are potentiated by the co-administration of ethacrynic acid, mannitol, furosemide and possibly other diuretics.

The use of streptomycin in patients with auditory impairment must be undertaken with great caution, and the risk of additional eighth cranial nerve impairment should be weighed against the potential benefits of treatment. Appropriate monitoring and early discontinuation of the drug may permit recovery prior to irreversible damage to the sensorineural cells.

Nephrotoxicity: Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See section above for dosage under renal disease or dialysis. The drug is variably cleared by haemodialysis.

Neurotoxicity: The risk of severe neurotoxic reactions is sharply increased in patients with impaired renal function or pre-renal azotemia. These include disturbances of vestibular and cochlear function, optic nerve dysfunction, peripheral neuritis, arachnoiditis, and encephalopathy may also occur. 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. The incidence of clinically detectable, irreversible vestibular damage is particularly high in patients treated with streptomycin.

The concurrent or sequential use of other neurotoxic and/or nephrotoxic drugs with streptomycin sulfate should be avoided (see section 4.5).

The neurotoxicity of streptomycin can result in respiratory paralysis from neuromuscular blockage, especially when the drug is given soon after the use of anesthesia or muscle relaxants.

Use in hepatic disease: Drug concentrations are not affected by hepatic disease (a larger volume of distribution for alcoholic cirrhotic patients with ascites can be expected). Streptomycin is presumed to be safe in severe liver disease; however, it should be used with caution as patients with severe liver disease may progress rapidly to hepatorenal syndrome.

Resistance: Streptomycin must be used in conjunction with adequate doses of other antituberculous drugs. The use of streptomycin alone allows the rapid development of strains resistant to it.

Precautions
Hypersensitivity reactions are rare. If they do occur (usually during the first weeks of treatment), streptomycin should be withdrawn immediately. Once fever and skin rash have resolved, desensitization may be attempted (see section 4.8).

As streptomycin is potentially ototoxic, hearing (e.g. by audiometry) and vestibular function should be assessed before starting treatment and at monthly intervals during treatment.

Both the elderly and patients with renal impairment are vulnerable to dose-related toxic effects resulting from accumulation. Streptomycin should be used with caution in patients with renal insufficiency, because of the increased risk of nephrotoxicity and ototoxicity (see section 4.2). Where possible, serum levels should be monitored periodically and dosage adjusted appropriately to ensure that plasma concentrations, as measured when the next dose is due, do not exceed 4 μg/ml.

Protective gloves should be worn when streptomycin injections are administered, to avoid sensitization dermatitis.

4.5 Interaction with other medicinal products and other forms of interaction

Simultaneous administration of other antituberculous drugs which also have ototoxic and nephrotoxic potential (e.g. capreomycin, viomycin) is not recommended. Also, other ototoxic or nephrotoxic drugs should not be administered to patients receiving streptomycin. These include other aminoglycoside antibiotics, amphotericin B, cefalosporins, ciclosporin, cisplatin, vancomycin and loop diuretics (e.g. furosemide and etacrynic acid).

Streptomycin may potentiate the effect of neuromuscular blocking agents administered during anaesthesia..

Renal excretion of zalcitabine may be reduced by aminoglycosides.

4.6 Fertility, pregnancy and lactation

Pregnancy
Studies in animals have shown reproductive toxicity (see section 5.3) and there are isolated case reports of deaf children born to women who received streptomycin in pregnancy. Therefore streptomycin should not be used during pregnancy.

Lactation
Streptomycin passes into milk, but at therapeutic doses no effects on the breastfed newborns/infants are anticipated. Streptomycin can be used while breast-feeding.

Fertility
There are no data on fertility.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for symptoms of vestibular toxicity (see sections 4.4 and 4.8) while taking streptomycin and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects

The following undesirable effects have been recorded but reliable information on frequency of occurrence is not available.

The following reactions are common: vestibular ototoxicity (nausea, vomiting, and vertigo), paraesthesia of face, rash, fever, urticarial, angioedema and eosinophilia.

The following reactions are less frequent: cochlear ototoxicity (deafness), exfoliative dermatitis, anaphylaxis, azotemia, leucopenia, thrombocytopenia, pancytopenia, haemolytic anaemia, aplastic anaemia, agranulocytosis, lupoid reactions, muscular weakness, and amblyopia.

Description of selected adverse reactions

Nephrotoxicity
Although streptomycin is the least nephrotoxic of the aminoglycosides, nephrotoxicity does occur rarely. If urinary output falls, albuminuria occurs or tubular casts are detected in the urine, streptomycin should be stopped and renal function should be evaluated.

Vestibular toxicity
Vestibular dysfunction resulting from the parenteral administration of streptomycin is cumulatively related to the total daily dose. 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.

Ototoxicity
Like other aminoglycosides, streptomycin can produce irreversible, cumulative ototoxicity. This affects both the cochlea (manifest as hearing loss, initially of higher tones, and which, because speech recognition relies greatly on lower frequencies, may not be at first apparent) and the vestibular system (manifest as dizziness or vertigo). Ototoxicity is increased with advanced age and prolonged use.

Paraesthesia
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. The risk of neurotoxic reactions is greater in patients with renal impairment or pre-renal azotaemia.

Skin reactions
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.

Electrolyte abnormalities
Electrolyte abnormalities including hypokalaemia, hypocalcaemia and hypomagnesaemia can occur.

Hypersensitivity
Cutaneous hypersensitivity reactions can occur (see section 4.4).

Injection-site reactions
Streptomycin injections are painful. Rash, induration, or sterile abscesses can form at injection sites.

4.9 Overdose

Signs and symptoms
Nephrotoxicity and ototoxicity can occur. Neuromuscular blockage or respiratory paralysis following rapid intravenous administration may also occur.

If streptomycin is ingested, toxicity is unlikely because there is no significant oral absorption

Treatment
Haemodialysis can be beneficial. There is no specific antidote and treatment is supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aminoglycoside antibacterials, ATC Code J01GA01

Streptomycin is an aminoglycoside antibiotic and is active against *Mycobacterium tuberculosis*.

Mechanism of action.: Aminoglycosides are taken up into sensitive bacterial cells by an active transport process. Within the cell they bind to the 30S, and to some extent to the 50S, subunits of the bacterial ribosome, inhibiting protein synthesis and generating errors in the transcription of the genetic code.

There are high rates of streptomycin resistance in strains of Multi Drug Resistant-Tuberculosis; therefore, streptomycin is not considered a second-line anti-tuberculosis injectable agent. 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.

5.2 Pharmacokinetic Properties

Streptomycin and other aminoglycosides are poorly absorbed from the gastrointestinal tract but are rapidly absorbed after intramuscular injection. After intramuscular injection of streptomycin, peak plasma concentrations occur 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.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber in addition to those summarised in other sections of the summary of product characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not applicable

6.2 Incompatibilities

Streptomycin sulfate is incompatible with acids and alkalis.

6.3 Shelf life

24 months

Reconstituted solutions of streptomycin may be stored at 2-8℃ for 24 hours.

Reconstituted product should be used within 24 hours.

6.4 Special precautions for storage

Store below 30℃ and protect from light and humidity.

6.5 Nature and contents of container

Type III glass vial closed with chlorobutyl rubber stopper and sealed with flip-off aluminium cap. 10 vials in a carton box.

6.6 Instructions for use and handling and disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

TB296

9. DATE OF FIRST PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

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References

General reference sources for this SmPC include:

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Section 5.1

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