PRODUCT MONOGRAPH

PrTobramycin for Injection U.S.P.

1.2 g Tobramycin (as tobramycin sulphate)/Vial

Antibiotic

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

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PrTOBRAMYCIN FOR INJECTION U.S.P.

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	1.2 g tobramycin (as tobramycin sulphate) powder per single unit vial	Nil

INDICATIONS AND CLINICAL USE

Tobramycin for Injection USP may be indicated for the treatment of the following infections when caused by susceptible organisms: septicemia, complicated and recurrent urinary tract infections, lower respiratory infections, serious skin and soft tissue infections including burns and peritonitis and central nervous system infections caused by organisms resistant to antibiotics usually considered efficacious in these infections.

Tobramycin for Injection U.S.P. is usually active against most strains of the following organisms in vitro and in clinical infections:

Pseudomonas aeruginosa
Proteus sp. (Indole-positive and indole-negative),
including Proteus mirabilis, Morganella morganii
Providencia rettgeri, and Proteus vulgaris
Escherichia coli
Klebsiella-Enterobacter-Serratia group
Citrobacter sp.
Providencia sp.
Staphylococci, including Staphylococcus aureus
(coagulase-positive and coagulase-negative)

Tobramycin for Injection U.S.P. may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Appropriate sensitivity studies should be performed to determine the susceptibility of the

causative organism to Tobramycin for Injection U.S.P. Clinical judgment and anticipated bacteriological findings may permit the start of therapy before results of susceptibility studies are obtained.

Note: If susceptibility tests show that the causative organism is resistant to Tobramycin for Injection U.S.P., other appropriate therapy should be instituted.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Tobramycin for Injection U.S.P. and other antibacterial drugs, Tobramycin for Injection U.S.P. should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Tobramycin for Injection U.S.P. is contraindicated in patients with known hyper-sensitivity to tobramycin or any other aminoglycoside. Cross-allergenicity to other aminoglycosides has been established.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Patients treated with Tobramycin for Injection U.S.P. or other aminoglycosides should be under close clinical observation because these drugs have an inherent potential for causing ototoxicity and nephrotoxicity.

General:
Peak and trough serum concentrations of aminoglycosides should be monitored periodically during therapy to assure adequate levels and to avoid potentially toxic levels. Prolonged serum concentrations above 12 mg/L should be avoided. Rising trough levels (above 2 mg/L) may indicate tissue accumulation. Such accumulation, excessive peak concentrations, advanced age, and cumulative dose may contribute to ototoxicity and nephrotoxicity.

Concurrent and/or sequential use of other potentially neurotoxic and/or nephrotoxic drugs, particularly other aminoglycosides (e.g. amikacin, streptomycin, neomycin, kanamycin, gentamicin, and paromomycin), amphotericin B, cephaloridine, viomycin, polymyxin B, colistin, cisplatin, and vancomycin, requires careful monitoring. Other factors that may increase patient risk are advanced age and dehydration.

Tobramycin for Injection U.S.P. should not be used concurrently with potent diuretics because some diuretics themselves cause ototoxicity.

Neuromuscular block and respiratory paralysis have been reported in cats receiving very high doses of tobramycin (40 mg/kg). The possibility that these phenomena may occur in man should be considered if Tobramycin for Injection U.S.P. is administered to patients who are also receiving general anesthesia and/or neuromuscular blocking agents such as succinylcholine and tubocurarine, or in patients with myasthenia gravis or Parkinson's disease.

Tobramycin for Injection U.S.P. should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug. If overgrowth of non-susceptible organisms occurs, appropriate therapy should be initiated, and if necessary, the drug withdrawn.

Although not indicated for intraocular and/or subconjunctival use, there have been reports of macular necrosis following this type of injection of aminoglycosides, including tobramycin.

Renal:
Both vestibular and auditory toxicity can occur. Impairment of eighth-nerve function is most likely in patients with pre-existing renal damage, especially if the drug is administered for longer periods or in higher doses than those recommended.

Patients with known or suspected impairment of renal function should be under close clinical observation, and renal and eighth-nerve function should be monitored during therapy.
Such monitoring is also recommended during the treatment of patients in whom renal function is initially normal, but in whom oliguria or evidence of nitrogen retention (increasing BUN, NPN, or creatinine) develops during therapy. Evidence of developing impairment in renal, vestibular, and/or auditory function requires careful observance of dosage adjustments. (See Table 1) Discontinuation of the drug may be indicated.

Pregnant Women:
Safety for use in pregnancy has not been established. Animal and human studies have demonstrated that there is a maternal-fetal transfer of tobramycin. No reports to date have revealed teratogenic effects in humans. However, one study in guinea pigs using high doses (50 to 100 mg/kg) in the last four weeks of pregnancy revealed a low incidence of ototoxicity in the newborn.

Susceptibility/Resistance:

Development of Drug Resistant Bacteria

Prescribing Tobramycin for Injection U.S.P. in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

ADVERSE REACTIONS

Adverse Drug Reaction Overview:

Nephrotoxicity:

Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, have been reported, especially in patients with a history of renal impairment who were treated for longer periods or with doses higher than those recommended.

Neurotoxicity:

Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported, especially in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and high frequency hearing loss.

Other adverse reactions that have been reported, and may be associated with tobramycin therapy, include increased serum transaminases (SGOT, SGPT), increased alkaline phosphatase and increased serum bilirubin; anemia, granulocytopenia, and thrombocytopenia; fever, rash, exfoliative dermatitis, itching, urticaria, nausea, vomiting, diarrhea, headache and lethargy. Local reaction at the site of injection has been reported.

DRUG INTERACTIONS

Drug-Drug Interactions:

Tobramycin for Injection U.S.P. should not be used concurrently with potent diuretics because some diuretics themselves cause ototoxicity.

Concomitant and/or sequential use of neurotoxic or nephrotoxic drugs requires careful monitoring (see WARNINGS AND PRECAUTIONS)

DOSAGE AND ROUTE OF ADMINISTRATION

Tobramycin for Injection USP is intended for intravenous infusion.

Recommended Dose and Dosage Adjustment:

Adults: The recommended dosage for patients with normal renal function is 1 mg/kg every eight hours, for a total of 3 mg/kg/day. Mild to moderate infections of the lower urinary tract have responded to doses of 2 to 3 mg/kg/day administered once daily. When renal tissue is involved or in serious infections, especially when there are signs of systemic involvement, two or three equally divided doses are recommended.

The usual dosage for patients weighing more than 60 kg is 80 mg (2 mL) every eight hours. For patients weighing 60 kg or less, the usual dosage is 60 mg (1.5 mL) every eight hours.
In patients with life-threatening infections, dosages up to 5 mg/kg/day may be administered in three or four equal doses. This dosage should be reduced to 3 mg/kg/day as soon as clinically indicated. To prevent increased toxicity due to excessive blood levels, dosage should not exceed 5 mg/kg/day unless serum levels are monitored.

Children: 6 to 7.5 mg/kg/day in 3 or 4 equally divided doses.

Neonates (one week of age or less): Dosage up to 4 mg/kg/day may be administered in two equal doses every twelve hours (See WARNINGS AND PRECAUTIONS).

The usual duration of treatment is seven to ten days. A longer course of therapy may be necessary in difficult and complicated infections. Monitoring of renal, auditory, and vestibular functions is advisable in these cases because neurotoxicity is more likely to occur when treatment is extended for longer than ten days.

Patients with Impaired Renal Function: Serum tobramycin concentrations should be monitored during therapy.

Following a loading dose of 1 mg/kg, subsequent dosage in these patients must be adjusted, either with lower doses administered at eight-hour intervals or with normal doses at prolonged intervals (See Table 1). Both regimens should be based on the BUN, the serum creatinine or the creatinine clearance of the patient, because these values correlate with the half-life of tobramycin.

Adjusted Dose at Eight-Hour Intervals (Regimen I): An appropriately reduced dosage range can be found in Table 1 for any patient for whom the BUN, creatinine clearance or serum creatinine values are known. The choice of dose within the indicated range should be based on the severity of the infection, the sensitivity of the pathogen, and individual patient considerations, especially renal function.

Adjusted Intervals Between Fixed Doses (Regimen II): Recommended intervals between doses are given in Table 1. As a general rule, the interval in hours can be determined by multiplying the patient's serum creatinine level by six.

Table 1: Two Maintenance Regimens Based on Renal Function and Body Weight following a Loading Dose of 1 mg/kg*

		REGIMEN I	OR	REGIMEN II
RENAL FUNCTION+		ADJUSTED DOSES OF 8-HOUR INTERVALS		ADJUSTED INTERVALS BETWEEN FIXED DOSES
SERUM CREATININE µmol/L	CREATININE CLEARANCE mL/s	WEIGHT 50-60 kg	60-80kg	WEIGHT/DOSE 50-60 kg: 60 mg 60-80 kg: 80 mg
≤115	≥1.17	60 mg	80 mg	q.8 h
125-170	1.15-0.67	30-60 mg	50-80 mg	q.12 h
175-290	0.65-0.33	20-25 mg	30-45 mg	q.18 h
300-470	0.32-0.17	10-18 mg	15-24 mg	q.24 h
475-660	0.15-0.08	5-9 mg	7-12 mg	q.36 h
≥670	≤0.07	2.5-4.5 mg	3.5-6 mg	q.48 h++

* For life-threatening infections, dosages 50% above those recommended may be used. The dosage should be reduced as soon as possible after improvement is noted.

\+ If used to estimate degree of impairment, serum creatinine concentrations should reflect a steady state of renal azotemia.

++ When dialysis is not being performed.

Both of these regimens are suggested as guides to be used when serum levels of tobramycin cannot be measured directly. The appropriate dosage schedules derived from either regimen should be used in conjunction with careful clinical and laboratory observations of the patient and should be modified as necessary.

Dosage in Moderate to Marked Obesity: The appropriate dose may be calculated by using the patient's estimated lean body weight plus 40% of the excess as the basic weight on which to figure mg/kg.

Administration

Intravenous Administration:

Note: Tobramycin for Injection U.S.P. should not be physically premixed with other drugs but should be administered separately according to the recommended dose and route.

The concentration of Tobramycin for Injection U.S.P. in solution should not normally exceed 1 mg/mL for either adults or children. The solution should be infused over a period of 20 to 60 minutes. When it is necessary to restrict the volume of solution infused, a more concentrated solution may be used; however, it is important that the infusion time exceed five minutes to prevent excessively high serum concentrations. A volume control set is recommended for this administration.

Reconstitution:

Solution for reconstitution.
Sterile Water for Injection is used for reconstitution.

Table 2: Reconstitution Table for Pharmacy Bulk Vial

Vial Size (Pharmacy Bulk Vial)	Volume to be added to vial	Approximate Available Volume	Approximate Average Concentration of Tobramycin
1.2g Powder (as tobramycin sulfate)	30 mL	31.0 mL	38.70 mg/mL

Shake well until dissolved.

The Pharmacy Bulk Vial is intended only for intravenous infusion using diluent listed below upon dilution to 0.2mg - 1.0mg/mL tobramycin (by single puncture for multiple dispensing).

Solutions for I.V. Infusion:

0.9% Sodium Chloride Injection
Ringer's Solution
Lactated Ringer's Solution

OVERDOSAGE

Signs and Symptoms:

The severity of the signs and symptoms following a tobramycin overdose are dependent on the dose administered, the patient's renal function, state of hydration, and age and whether or not other medications with similar toxicities are being administered concurrently. Toxicity may occur in patients treated more than 10 days, given more than 5 mg/kg/day, children given more than 7.5 mg/kg/day, or patients with reduced renal function whose dose has not been appropriately adjusted.

Nephrotoxicity following the parenteral administration of an aminoglycoside is most closely related to the area under the curve of the serum concentration versus time graph. Nephrotoxicity is more likely if trough blood concentrations fail to fall below 2 mg/L and is also proportional to the average blood concentration. Patients who are elderly, have abnormal renal function, are receiving other nephrotoxic drugs, or are volume depleted are at greater risk for developing acute tubular necrosis. Auditory and vestibular toxicities have been associated with aminoglycoside overdose. These toxicities occur in patients treated longer than 10 days, in patients with abnormal renal function, in dehydrated patients, or in patients receiving medications with additive auditory toxicities. These patients may not have signs or symptoms or may experience dizziness, tinnitus, vertigo, and a loss of high tone acuity as ototoxicity progresses. Ototoxicity signs and symptoms may not begin to occur until long after the drug has been discontinued.

Neuromuscular blockade or respiratory paralysis may occur following administration of aminoglycosides. Neuromuscular blockade, prolonged respiratory paralysis, and respiratory failure may occur more commonly in patients with myasthenia gravis or Parkinson's disease. Prolonged respiratory paralysis may also occur in patients receiving decamethonium, tubocurarine, or succinylcholine. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but mechanical assistance may be necessary.

If tobramycin were ingested, toxicity would be less likely because aminoglycosides are poorly absorbed from an intact gastrointestinal tract.

Treatment:

The initial management in a tobramycin overdose is to assess respiration and if necessary, to establish an airway and ensure oxygenation and ventilation. Resuscitative measures should be initiated promptly if respiratory paralysis occurs.

Patients who have received an overdose of tobramycin and have normal renal function should be carefully hydrated to maintain a urine output of 3 to 5 mL/kg/hr. Fluid balance, creatinine clearance, and tobramycin plasma levels should be carefully monitored until the serum tobramycin level falls below 2 mg/L.

Patients in whom the elimination half-life is greater than 2 hours or whose renal function is abnormal may require more aggressive therapy. In such patients, hemodialysis may be beneficial.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action:

Like other aminoglycosides, the bactericidal activity of tobramycin is accomplished by specific inhibition of normal protein synthesis in susceptible bacteria, but at the present time, very little is known about the specific site(s) of this action. It is thought that inhibition of synthesis is due to an action on ribosomes that, in turn, causes bacterial misreading of messenger RNA.

Human Pharmacology:

Peak serum concentrations of tobramycin occur between thirty and 130 minutes after intramuscular administration.

Table 4: Serum Concentrations After Single Intramuscular Doses

SERUM CONCENTRATION (mg/L)					
DOSE	½ hr.	1 hr.	2 hr.	4 hr.	8 hr.
25 mg	1.14	0.8	0.56	0.26	0.01
50 mg	2.09	1.95	1.26	0.56	0.1
75 mg	2.71	2.68	1.86	0.9	0.2
100 mg	2.95	3.25	2.61	1.36	0.41
200 mg	9.63	8.99	7.70	4.33	0.94

In patients with normal renal function, tobramycin administered every eight hours does not accumulate in the serum. A serum half-life of about 2 hours was reported for patients with normal renal function while in patients with impaired renal function serum half-life of the drug ranged from 5 to 47 hours. Dosage for such patients must, therefore, be adjusted accordingly (See DOSAGE AND ADMINISTRATION).

After intravenous administration, serum concentrations are similar to those following intramuscular injection, and are dose related.

Table 5: Intravenous Dose Infused Over 30-45 Minutes

SERUM CONCENTRATION (mg/L)						
DOSE	1/4 hr.	½ hr.	1 hr.	2 hr.	4 hr.	6 hr.
1 mg/kg	3.8	5.5	3.85	2.38	1.04	0.52
1.5 mg/kg	4.85	6.02	5.28	2.96	1.72	0.9

Pediatric studies indicate that although the serum half-life in neonates was found to be 2 or 3 times longer than in adults, no accumulation of tobramycin occurred even after multiple doses of 4 mg/kg/day.

Tobramycin is eliminated almost exclusively by glomerular filtration; renal clearance is similar to that of endogenous creatinine. Ultrafiltration studies demonstrate that practically no serum protein binding occurs. In patients with normal renal function, up to 84 percent of the dose is recoverable from the urine in eight hours and up to 93 percent in twenty-four hours.

Peak urine concentrations up to 100 mg/L have been observed after the intramuscular injection of a single dose of 1 mg/kg. After several days of treatment, the amount of tobramycin excreted in the urine approaches the daily dose administered.

An inverse relationship exists between half-life and creatinine clearance, and the dosage schedule should be adjusted according to the degree of renal impairment. In patients undergoing hemodialysis, 25 to 70 percent of the administered dose may be removed, depending upon the duration of hemodialysis. Peritoneal dialysis was considered to be less efficient.

Tobramycin can be detected in tissue and body fluids after parenteral administration. Concentrations in bile ordinarily have been low, which suggests minimum biliary excretion. Tobramycin has been found in low and unpredictable concentrations in the cerebrospinal fluid following parenteral administration and would be inadequate against many gram-negative organisms causing meningitis. It has also been found in sputum and in abscess fluids, though possibly in non-therapeutic concentrations. Tobramycin crosses the placental membranes producing, in one study, a fetal serum half-life of 3.2 hours and a peak serum concentration of 1.2 mg/L.

STORAGE AND STABILITY

The product, in its non-reconstituted form, should be stored at controlled room temperatures 15°C- 30°C. Tobramycin for Injection U.S.P. requires no refrigeration. Protect from light.

The Pharmacy Bulk Vial is intended for multiple dispensing for intravenous use employing a single puncture. Following reconstitution, the solution should be dispensed and diluted for use within 8 hours. Any unused reconstituted solution should be discarded after 8 hours. Tobramycin for Injection U.S.P. diluted with any of the solutions for I.V. infusion listed under the Reconstitution section in a concentration range of 1 mg/mL to 0.2 mg/mL should be used within 24 hours if kept at room temperature and 36 hours if stored under refrigeration.

Special Instructions:

- Pharmacy Bulk Vials contain no preservatives. Care must be taken to minimize the potential for inadvertent introduction of microorganisms during manipulation in the hospital environment.

- As with all parenteral drug products, reconstituted solution and intravenous admixture should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solution showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

- The availability of the Pharmacy Bulk Vial is restricted to hospitals with a recognized intravenous admixture program.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form: 1.2 g Tobramycin (as sulphate) lyophilized powder

Composition: Tobramycin for Injection U.S.P. Bulk Pharmacy Vials contain tobramycin sulfate with no preservatives. Sulfuric Acid and/or Sodium Hydroxide may have been added during manufacturing to adjust pH.

Packaging: Tobramycin for Injection U.S.P. (Pharmacy Bulk Package) is packaged in 50 ml glass vials containing 1.2 gm of Tobramycin (as sulphate) dry powder.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

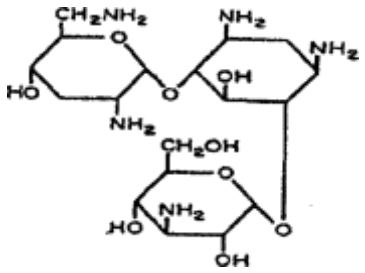
Drug Substance

Proper name: Tobramycin U.S.P.

Chemical name: 0-3-Amino-3-deoxy-%-D glucopyranosyl-(1→4)-0-[2,6-diamino-2,3,6-trideoxy-%-D-Ribo-hexopyranosyl-(1→6)]-2-deoxy-L-streptamine

Molecular formula and molecular mass:
$C_{18}H_{37}N_5O_9$
467.54

Structural formula:



Physicochemical properties:

Description: Tobramycin is a white to off-white hygroscopic powder. It is a basic aminocyclitol aminoglycoside, freely soluble in water.

pH: The pH of a 1:10 solution of tobramycin in water is between 9-11.

Melting Point: 174 - 185°C

MICROBIOLOGY

In vitro tests demonstrate that tobramycin is bactericidal and that it acts by inhibiting the synthesis of protein in bacterial cells.

Tobramycin is active against most strains of the following organisms:

- *Pseudomonas aeurginosa*
- *Proteus sp.* (indole-positive and indole-negative), including *Proteus mirabilis, Morganella morganii, Providencia rettgeri,* and *Proteus vulgaris*
- *Escherichia coli*
- *Klebsiella-Enterobacter-Serratia sp.*
- *Citrobacter sp.*
- *Providencia sp.*
- *Staphylococci,* including *Staphylococcus aureus* (coagulase-positive and coagulase-negative)

Although most strains of enterococci demonstrate *in vitro* resistance, some strains in this group are susceptible. *In vitro* studies have shown that an aminoglycoside combined with an antibiotic which interferes with cell-wall synthesis affects some enterococcal strains synergistically. The combination of penicillin G and tobramycin results in a synergistic bactericidal effect *in vitro* against certain strains of *Enterococcus faecalis* (formerly *Streptococus faecalis*). However, this combination is not synergistic against other closely related organisms, e.g. *Enterococcus faecium* (formerly *Streptococcus faecium*). Speciation of enterococci alone cannot be used to predict susceptibility. Susceptibility testing and tests for antibiotic synergism are, therefore, required.

Table 3: In-Vitro Susceptibility of Microorganisms to Tobramycin (Cumulative Percent of Strains Inhibited in Broth or Agar-Dilution Studies*)

Microorganism	No. of Strains	MIC mg/L									
		0.06	0.06-0.12	0.13-0.25	0.26-0.5	0.51-0.78	0.79-1.56	1.6-3.12	3.2-6.25	6.3-12.5	12.6-25
Ps. Aeruginosa	2888	6	18	40	63	70	91	96	97	98	99
Ps. Aeruginosa (gentamicin-resistant)	153		12	18	27	30	35	46	59	71	80
E. coli	2117		1	4	18	21	58	78	92	97	98
Proteus mirabilis (indole-negative)	1675			1	5	8	37	60	81	96	99
Proteus sp. (Indole-positive)	1213		2	4	16	20	51	71	83	92	96
Proteus sp. (Not specified)	76			1	12	12	42	97	100	100	100
Klebsiella sp.	1244	3	5	20	47	50	86	94	97	99	99
Klebsiella-Enterobacter sp.	721		3	22	48	54	83	94	97	98	99
Enterobacter sp.	1126	1	4	15	36	39	81	91	97	99	99
Serratia sp.	546				3	5	28	53	73	88	94
Providencia sp.	113			2	4	4	12	28	51	68	81
Citrobacter sp.	167		1	5	19	19	73	93	98	98	99
Staph. Aureus	2013	11	28	42	70	73	87	93	96	99	99
Streptococcus faecalis (group D)	448			1	2	2	3	4	14	38	61

*Inoculum did not exceed 10^5 organisms per mL in broth.

Susceptibility Plate Tests:

If the Bauer-Kirby-Sherris-Turck method of disk susceptibility testing is used (Am. J. Clin. Pathol., 45:493,1966), a disk containing a 10 µg tobramcyin should give a zone of inhibition of at least 15 mm when tested against a tobramycin susceptible bacterial strain and a zone of inhibition of 13 to 14 mm against strains of intermediate susceptibility, and a zone of inhibition of 12 mm or less against resistant organisms. The minimum inhibitory concentration correlates are ≤4 mg/L for susceptibility and ≥8 mg/L for resistance.

TOXICOLOGY

Acute Toxicity:

The acute toxicity of parenterally administered tobramycin was related to immediate CNS effects. Death often occurred within a few minutes after an intravenous dose and 20 minutes to 2 hours after subcutaneous administration. In a few rats and one guinea pig, delayed deaths were

attributed to renal injury.

The intravenous LD_{50} values ranged from 53 to 107 mg/kg for mice and 131 to 134 mg/kg for rats; while the subcutaneous LD_{50} values were 416 to 484 mg/kg for mice and 928 to 1028 mg/kg for rats.

Tobramycin was no more toxic in newborn rats than in rats of 5 to 6 weeks of age, but it was slightly more toxic in 3 month old animals.

Two dogs were treated with subcutaneous doses of 100 and 200 mg/kg. No effect was observed with the 100 mg dose. Retching and tremors occurred after the administration of the 200 mg dose. The animals appeared normal after 3 hours. Two dogs tolerated single intravenous doses of 100 mg/kg with emesis as the only observed sign of toxicity.

Two cats received subcutaneous doses of 200 mg/kg of tobramycin which produced marked CNS effects that persisted for more than 5 hours. Both animals appeared normal on the following day. An intravenous dose of 50 mg/kg in three cats produced a short-term ataxia. A dosage of 100 mg/kg caused convulsions and death.

Subacute Toxicity:

Rats:

In a study using 10 animals/sex/dose, rats given 30 daily subcutaneous doses of 30, 60, or 120 mg/kg of tobramycin survived, with the exception of 1 of 20 of the 120 mg/kg dosage group. There were no significant changes in appearance or behaviour. The 120 mg/kg regimen caused a slight retardation of growth in the females.

A slight renal toxicity was noted at all doses by virtue of an increase in SGOT, increased renal weights, and the histologic finding of a slight to moderate regeneration of renal cortical tubular epithelium. These effects were dose dependent.

In a similar study, rats tolerated 14 daily intravenous doses of 20-80mg/kg of tobramycin with no adverse effects other than those associated with CNS effects after rapid injection. Six of 10 of the animals of the 80 mg/kg group died shortly after tobramycin administration. The hematologic and blood chemistry data of the surviving animals were unaffected. The relative renal weights of the tobramycin-dosed animals were significantly greater than control. The effect was dose dependent.

No drug-related tissue changes were noted in rats of the 20 mg/kg group. A slight regeneration of renal cortical tubular epithelium was detected in 1 of 20 animals given 40 mg/kg and most of those given 80 mg/kg. It was concluded that the only hazard in administration of tobramycin by the intravenous route rather than by the subcutaneous route is that a too rapid intravenous injection can cause convulsions and death.

Dogs:

A study using 4 dogs for each daily intramuscular dose was carried out for 28 days. The appearance, behaviour, hematology and blood chemistry were unaffected by doses of 3.75 to 15 mg/kg. Histologic examination of the tissue revealed that a slight renal injury, as evidenced by the finding of a mild regeneration of the cortical tubular epithelium, had occurred at the upper dose.

In a further study with 4 dogs, a daily dose of 30 mg/kg was tolerated for 2 weeks with no apparent ill effects; but thereafter, anorexia, weight loss, hypoactivity, and a general CNS depression were noted. Two animals were killed during the fourth week because of morbidity. Renal tubular necrosis accompanied by regeneration of the tubular epithelium was noted in all animals of the 30 mg/kg group.

Dogs had a reduced tolerance for tobramycin dosage regimens of longer duration. In a study using 2 dogs/sex/dose for 90 days, a daily intramuscular dose of 3.75 or 7.5 mg/kg of tobramycin caused no changes in appearance, behaviour, or body weight, but 2 of 4 dogs on the 7.5 mg/kg dose had a mild degree of renal cortical tubular epithelial regeneration or a mild reparative nephrosis.

A daily dose of 15 mg/kg of tobramycin was well tolerated by 2 of 4 dogs. The other 2 dogs of this group had marked appetite suppression, weight loss and marked elevations in BUN and SGOT. One of these dogs became deaf on day 49. This dog also showed evidence of tobramycin accumulation. A mild to moderate reparative nephrosis and inflammatory reactions at the injection sites represented the only histologic evidence of tobramycin injury.

The daily intravenous administration of 7.5, 15 or 30 mg/kg of tobramycin for 2 dogs/sex/dose over 14 days caused no changes in appearance or behaviour except for a single emetic episode in one dog of the 30 mg/kg group. Blood serum concentrations of tobramycin one hour after intravenous injection were similar to those found one hour after intramuscular administration. The hematologic and blood chemistry parameters were not altered significantly. A slight to moderate proteinuria was detected in one or two dogs of each dosage regimen, and a slight glucosuria occurred in one animal of the 15 mg/kg group. There was no histologic evidence of tissue injury. It seems probable, however, on the basis of the results of intramuscular administration of similar doses, that renal injury would occur with more prolonged intravenous dosage.

Cats:

In a study using 2 animals/sex/dose, cats were given daily subcutaneous doses of 25 or 50 mg/kg. The 25 mg/kg dose was tolerated by 4 cats for 65 doses with no apparent vestibular injury. Hemorrhagic cystitis and urinary tract blockage due to urolithiasis in one male cat were considered unrelated to the drug, but coexistent renal cortical tubular necrosis with epithelial regeneration in the same cat were probably drug-related. One other cat had slight regeneration of renal cortical tubular epithelium. The 50 mg/kg/day dosage was poorly tolerated by all 4 cats.

One cat was sacrificed after 25 doses, and another after 40 doses, because of poor physical condition. Tobramycin administration was terminated for the other 2 cats of this group on day 40. All 4 animals had severe vestibular injury. The 2 cats sacrificed during treatment had moderate renal tubular necrosis. A lack of histological evidence of renal injury in the 2 cats that were sacrificed 34 days after a 40 dose treatment, plus the finding of regenerative cortical tubular epithelium in animals killed during treatment suggested that moderate renal injury, occurring as the result of tobramycin administration, may be reversible.

In a second study, 6 cats received tobramycin in a dosage of 35 mg/kg/day causing a marked reduction in PRN times in all six cats within 20 to 47 days.

Guinea Pigs:

In a study using guinea pigs, a daily 50 mg/kg dose of tobramycin had no effect on growth or on auditory function in a 4-week period. A 100 mg/kg dose caused a 25% retardation of growth, as compared with controls. No hearing impairment was noted at 2 weeks, but some loss was detected at 4 weeks.

In a further study, daily doses of 150 to 200 mg/kg markedly depressed growth and was lethal to 40% of the animals within 6 weeks. Cochlear injury that occurred in 40% of the surviving animals was verified by electrophysiologic and histopathologic methods.

Teratology and Reproduction:

Daily subcutaneous administration of tobramycin given in 50 and 100 mg/kg doses to rats (30 animals/sex/dose) during all phases of the reproductive cycle, had no adverse effect on fertility or reproductive performance, nor did it affect the progeny.

In a further study, pregnant rats were given subcutaneous doses of 50 and 100 mg/kg of tobramycin from gestation days 14 through 20. Reparative nephrosis was detected in 6 of 25 of the 50 mg/kg group and 22 of 25 of the 100 mg/kg group at necropsy. There was no adverse effect on reproduction indices, nor on the growth of the progeny.

Daily subcutaneous doses of 20 or 40 mg/kg of tobramycin were given to pregnant rabbits (15 animals/dose) during organogenesis and early fetal development (gestation days 6-18).

A marked anorexia and weight loss occurred in several animals; 3 of the 20 mg/kg group and 13 of the 40 mg/kg group died or aborted prior to gestation day 28. Drug-induced renal injury was evident in most of the animals that received the antibiotic. Fetal development appeared normal in all of the dams, including those that died or aborted. No drug-related abnormalities were detected in any of the progeny. It was concluded that daily subcutaneous doses as great as 40 mg/kg were not teratogenic in the rabbit, despite marked maternal toxicity.

A 25 to 200 mg/kg daily dose of tobramycin to mice during the period of organogenesis produced no embryocidal or teratogenic effect.

Daily doses of tobramycin 100 mg/kg/day administered to pregnant guinea pigs in early gestation, from the beginning of the second week to the end of the fifth week, resulted in hearing loss and histological damage to the six mothers. The litters born to these females, however, showed no hearing loss or damage to the inner ear. In contrast, when tobramycin was administered at 50 or 100 mg/kg daily to females in the terminal four weeks of gestation, one of eighteen newborn animals had pinna reflex loss at 20,000 Hz and four of thirty-eight had unilateral, incomplete loss of outer hair cells at the basal end of the cochlea.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

[PR]Tobramycin for Injection U.S.P.

This leaflet is part III of a three-part "Product Monograph" published when Tobramycin for Injection U.S.P. was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Tobramycin for Injection U.S.P. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Tobramycin for Injection U.S.P. is an antibiotic for intravenous infusion used to treat resistant infections of the respiratory tract, blood, urinary tract and central nervous system, as well as serious skin and soft tissue infections.

Antibacterial drugs like Tobramycin for Injection U.S.P. treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, Tobramycin for Injection U.S.P. should be used exactly as directed. Misuse or overuse of Tobramycin for Injection U.S.P. could lead to the growth of bacteria that will not be killed by Tobramycin for Injection U.S.P. (resistance). This means that Tobramycin for Injection U.S.P. may not work for you in the future. Do not share your medicine.

What it does:

Tobramycin for Injection U.S.P. is believed to interfere with the bacteria's normal protein synthesis so that it cannot grow or function properly.

When it should be used:

Tobramycin for Injection USP may be indicated for the treatment of the following infections when caused by susceptible organisms: septicemia, complicated and recurrent urinary tract infections, lower respiratory infections, serious skin and soft tissue infections including burns and peritonitis and central nervous system infections caused by organisms resistant to antibiotics usually considered efficacious in these infections.

Tobramycin for Injection U.S.P. is usually active against most strains of the following organisms in vitro and in clinical infections:

Pseudomonas aeruginosa
Proteus sp. (Indole-positive and indole-negative),
including Proteus mirabilis, Morganella morganii
Providencia rettgeri, and Proteus vulgaris
Escherichia coli
Klebsiella-Enterobacter-Serratia group
Citrobacter sp.
Providencia sp.
Staphylococci, including Staphylococcus aureus
(coagulase-positive and coagulase-negative)

When it should not be used:

If you are allergic (hypersensitive) to tobramycin or other aminoglycosides.

What the medical ingredients are:

tobramycin sulphate

IMPORTANT: PLEASE READ

What the important non-medicinal ingredients are:

Sulfuric Acid and/or Sodium Hydroxide may have been added during manufacturing to adjust pH.

What dosage forms it comes in:

Each multi-dose vial contains tobramycin sulphate equivalent to 1.2 g tobramycin.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Patients treated with Tobramycin for Injection U.S.P. or other aminoglycosides should be under close clinical observation because these drugs have an inherent potential for causing ototoxicity and nephrotoxicity.

Tobramycin for Injection U.S.P. and other similar aminoglycosides have been known to cause hearing and balance problems (ototoxicity) and kidney problems (nephrotoxicity). Your doctor will observe you carefully for warning signs of these events after giving you Tobramycin for Injection U.S.P.

Before using Tobramycin for Injection U.S.P., tell your doctor if you (or your child) have or have had:

* Drug allergies
* Hearing or balance problem
* Kidney problems
* Myasthenia gravis (a muscle condition)
* Parkinson's Disease

Tell your doctor if you are pregnant, breastfeeding, are planning to become pregnant.

Your doctor may monitor the level of Tobramycin for Injection U.S.P. in your blood through blood tests, especially if you are taking medications.

INTERACTIONS WITH THIS MEDICATION

Tobramycin for Injection U.S.P. may interact with other medications. Tell your doctor if you (or your child) are taking any medications, especially the following:

* Aminoglycosides (e.g. amikacin, streptomycin, neomycin, kanamycin, gentamycin, paramomycin)
* Amphotericin B
* Anaesthetics
* Cephaloridin
* Cisplatin
* Diuretics (specifically potent diuretics)
* Polymyxin B
* Succinylcholine
* Tubocurarine
* Vancomycin
* Viomycin

PROPER USE OF THIS MEDICATION

Tobramycin for Injection U.S.P. is for intravenous infusion only.

Usual dose:

The amount of antibiotic you (or your child) will receive will be determined by your healthcare professional. It is dependant upon a number of factors, including your age, weight, type of infection, and any pre-existing medical conditions.

IMPORTANT: PLEASE READ

You may receive Tobramycin for Injection U.S.P. several times a day over a period of 7-10 days.

Overdose:

Your healthcare professional is trained to recognize the symptoms of an overdose, and deal with its symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You may experience side effects from using Tobramycin for Injection U.S.P. including:

* Diarrhea
* Fever
* Headache
* Hives
* Itching or skin irritation
* Nausea
* Rash
* Reaction at the injection site
* Tiredness
* Vomiting

Tell your doctor if you notice any of the above.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
Symptom / Effect		**Only if severe**	**In all cases**	
Uncommon	**-Kidney problems (decreased urination)**		✓	✓
	-Hearing and balance problems (loss of hearing, ringing in the ears, dizziness, loss of balance)		✓	✓
	-Anemia (symptoms include weakness, exhastion, pale skin)		✓	✓
	-Unusual respiratory difficulties (difficulty breathing)		✓	✓

There are also other effects which can occur while you are taking tobramycin. These more rarely include kidney and respiratory difficulties. Nerve problems such as hearing, balance, or dizziness, which you may not have experienced before, can occur when you are being administered the drug or may appear weeks after taking it. It is important that you immediately advise your doctor of such events.

This is not a complete list of side effects. For any unexpected effects while taking Tobramycin for Injection, U.S.P. contact your doctor or pharmacist.

HOW TO STORE IT

Tobramycin for Injection U.S.P. in powder form should be stored at room temperature (15 - 30 ° C).

IMPORTANT: PLEASE READ

Protect from light.

Do not use if the solution is hazy, discoloured, leaking, or contains particulate matter (precipitate).

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

Note: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.sterimaxinc.com or by contacting the sponsor, SteriMax Inc., at: 1-800-881-3550

This leaflet was prepared by SteriMax Inc.

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