

## Tobramycin for injection, USP

1.2 g tobramycin/vial

### Antibiotic

### ACTION

Like other aminoglycosides, tobramycin binds to proteins on the 30S ribosome of bacteria thereby inhibiting protein synthesis, particularly the initiation step. Inhibition of protein synthesis is not a lethal event in bacteria as is destruction of the cell envelope. Nevertheless, the aminoglycosides bind so strongly to their receptors that the binding is essentially irreversible and the end result is death of the bacterial cell.

Aminoglycosides also cause misreading of the genetic code, so that incorrect amino acids are incorporated into the proteins of the bacterial cell. This mechanism is probably less important than inhibition of protein synthesis in killing cells.

After intravenous administration, serum concentrations of tobramycin are similar to those following intramuscular injection, and are dose related. The serum half-life is about 2 hours for patients with normal renal function and ranges from 5 to 47 hours for patients with impaired renal function. Tobramycin is eliminated exclusively by glomerular filtration. Tobramycin is not protein bound to any degree.

### INDICATIONS

Tobramycin 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 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.; and Staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative).

Tobramycin 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. 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, other appropriate therapy should be instituted.

### CONTRAINDICATIONS

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

### WARNINGS

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

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.

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 should not be used concurrently with potent diuretics because some diuretics themselves cause ototoxicity.

Tobramycin sulfate contains sodium bisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people.

### Pregnancy

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.

### PRECAUTIONS

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 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 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.

### ADVERSE REACTIONS

#### 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.

### SYMPTOMS AND TREATMENT OF 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 in 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.

### DOSAGE AND ADMINISTRATION

Tobramycin may be given intramuscularly or intravenously. The intravenous dose is the same as the intramuscular dose.

#### Dosage

##### 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 **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\***

Renal Function*		REGIMEN I		OR	REGIMEN II
		Adjusted Doses of 8-Hour Intervals		Adjusted Intervals Between Fixed Doses	
Serum Creatinine μmol/L	Creatinine Clearance mL/s	Weight		Weight/Dose 50 - 60 kg: 60 mg 60 - 80 kg: 80 mg	
		50 - 60 kg	60 - 80 kg		
≤ 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

Tobramycin Injection may be administered by the intramuscular or intravenous route.

##### Intravenous Administration:

This route is recommended when the intramuscular route is not feasible, e.g., in the presence of shock, hematologic disorders, severe burns, or reduced muscle mass.

The concentration of tobramycin 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 exceeds five minutes to prevent excessively high serum concentrations. A volume control set is recommended for this administration.

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

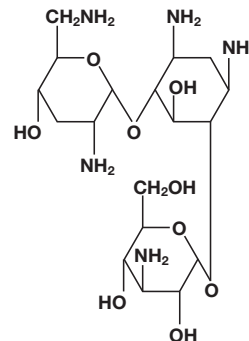
### PHARMACEUTICAL INFORMATION

#### Drug Substance

**Proper Name:** Tobramycin

**Chemical Name:** *O*-3-Amino-3-deoxy- $\alpha$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-*O*-[2,6-diamino-2,3,6-trideoxy- $\alpha$ -D-ribo-hexopyranosyl-(1 $\rightarrow$ 6)]-2-deoxystreptamine

#### Structural Formula:



**Molecular Formula:** C<sub>18</sub>H<sub>37</sub>N<sub>5</sub>O<sub>9</sub>

**Molecular Weight:** 467.54

**Description:** Tobramycin is a white to off-white hygroscopic powder. It is a basic aminocyclitol aminoglycoside, freely soluble in water. A 10% solution in water has a pH of 9 to 11. Melting range = 172 - 178°C.

## DOSAGE FORM

### Composition

#### Tobramycin for Injection, 1.2 g/vial:

Tobramycin for Injection, USP Pharmacy Bulk Vials contain lyophilized tobramycin sulfate equivalent to 1.2 g tobramycin with no preservatives.

## RECONSTITUTION

### Solutions for Reconstitution

Sterile Water for Injection

Vial Size	Volume to be added to vial	Approximate Available Volume	Approximate Average Concentration
1.2 g Powder (Bulk Pharmacy Vial)	30 mL	31.0 mL	40 mg/mL

Shake well until dissolved.

The Pharmacy Bulk Vial is intended only for intravenous infusion (by single puncture for multiple dispensing).

### Solutions for IV Infusion

5% Dextrose in Water

0.9% Sodium Chloride Injection

## STABILITY OF SOLUTION

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.

Reconstituted solution of Tobramycin for Injection, USP diluted with any of the solutions for i.v. infusion listed above in 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.

As with all parenteral drug products, intravenous admixture should be inspected visually for clarity, particulate matter, precipitation, discoloration and leakage prior to administration whenever solution and container permit. Discard unused portion.

## STORAGE

Tobramycin for Injection, USP should be stored at controlled room temperatures below 30°C. Tobramycin for Injection requires no 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.

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

## AVAILABILITY OF DOSAGE FORMS

Tobramycin is available in the following forms and package sizes:

#### C300351 Tobramycin for Injection, 1.2 g/vial:

Each vial contains lyophilized tobramycin sulfate equivalent to 1.2 g of tobramycin, in 50 mL Pharmacy Bulk Vial, packaged in cartons of 6 vials.

TOBRAMYCIN FOR INJECTION, USP BULK PHARMACY VIAL DOES NOT CONTAIN ANY PRESERVATIVES.

Vial stoppers do not contain natural rubber latex.