

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-789

APPROVED LABELING



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

45932/Issued: October 2003

TOBRAMYCIN

FOR INJECTION, USP

Rx only

This vial is intended for use by the hospital pharmacist in the extemporaneous preparation of IV solutions.

**PHARMACY BULK PACKAGE—
NOT FOR DIRECT INFUSION**

WARNINGS

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

Neurotoxicity, manifested as both auditory and vestibular ototoxicity, can occur. The auditory changes are irreversible, are usually bilateral, and may be partial or total. Eighth-nerve impairment and nephrotoxicity may develop, primarily in patients having preexisting renal damage and in those with normal renal function to whom aminoglycosides are administered for longer periods or in higher doses than those recommended. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching, and convulsions. The risk of aminoglycoside-induced hearing loss increases with the degree of exposure to either high peak or high trough serum concentrations. Patients who develop cochlear damage may not have symptoms during therapy to warn them of eighth-nerve toxicity, and partial or total irreversible bilateral deafness may continue to develop after the drug has been discontinued.

Rarely, nephrotoxicity may not become apparent until the first few days after cessation of therapy. Aminoglycoside-induced nephrotoxicity usually is reversible.

1 Renal and eighth-nerve function should be closely monitored in patients with known or
2 suspected renal impairment and also in those whose renal function is initially normal but who
3 develop signs of renal dysfunction during therapy. Peak and trough serum concentrations of
4 aminoglycosides should be monitored periodically during therapy to assure adequate levels and
5 to avoid potentially toxic levels. Prolonged serum concentrations above 12 mcg/mL should be
6 avoided. Rising trough levels (above 2 mcg/mL) may indicate tissue accumulation. Such
7 accumulation, excessive peak concentrations, advanced age, and cumulative dose may
8 contribute to ototoxicity and nephrotoxicity (see **PRECAUTIONS**). Urine should be examined for
9 decreased specific gravity and increased excretion of protein, cells, and casts. Blood urea
10 nitrogen, serum creatinine, and creatinine clearance should be measured periodically. When
11 feasible, it is recommended that serial audiograms be obtained in patients old enough to be
12 tested, particularly high-risk patients. Evidence of impairment of renal, vestibular, or auditory
13 function requires discontinuation of the drug or dosage adjustment.

14 Tobramycin should be used with caution in premature and neonatal infants because of
15 their renal immaturity and the resulting prolongation of serum half-life of the drug.

16 Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics,
17 particularly other aminoglycosides (eg, amikacin, streptomycin, neomycin, kanamycin,
18 gentamicin, and paromomycin), cephaloridine, viomycin, polymyxin B, colistin, cisplatin, and
19 vancomycin, should be avoided. Other factors that may increase patient risk are advanced age
20 and dehydration.

21 Aminoglycosides should not be given concurrently with potent diuretics, such as
22 ethacrynic acid and furosemide. Some diuretics themselves cause ototoxicity, and intravenously
23 administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in
24 serum and tissue.

25 Aminoglycosides can cause fetal harm when administered to a pregnant woman (see
26 **PRECAUTIONS**).

27
28
29
30 **DESCRIPTION:**

31 Tobramycin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from the
32 actinomycete *Streptomyces tenebrarius*. Tobramycin for Injection, USP is supplied as a sterile

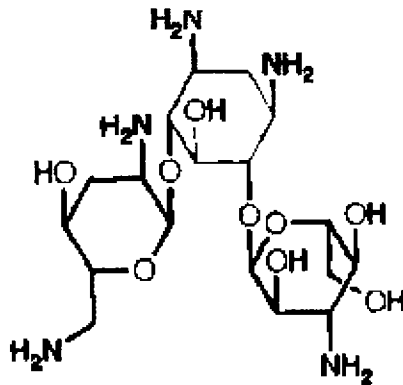
1 dry powder and is intended for reconstitution with 30 mL of Sterile Water for Injection, USP. Each
2 vial contains 1,200 mg of tobramycin activity. After dilution, the solution will contain 40 mg of
3 tobramycin per mL. The product contains no preservative or sodium bisulfite.

4 Tobramycin sulfate is O-3-amino-3-deoxy-_-D-glucopyranosyl-(1_4)-O-[2,6-diamino-2,3,6-
5 trideoxy-_-D-ribo-hexopyranosyl-(1_6)]-2-deoxy-L-streptamine, sulfate (2:5)(salt) and has the
6 molecular formula $(C_{18}H_{37}N_5O_9)_2 \cdot 5H_2SO_4$. The molecular weight is 1425.45.

7 The structural formula for tobramycin is as follows:

8

9



10

11

12

13 The pharmacy bulk package of tobramycin is a sterile preparation for parenteral use that
14 contains multiple single doses. It is intended for use in a pharmacy admixture program. Package
15 use is restricted to the preparation of admixtures for intravenous infusion or to the filling of empty
16 sterile syringes for intravenous injections for patients with individualized dosing requirements.

17

18 **CLINICAL PHARMACOLOGY:**

19 Tobramycin is rapidly absorbed following intramuscular administration. Peak serum
20 concentrations of tobramycin occur between 30 and 90 minutes after intramuscular
21 administration. Following an intramuscular dose of 1 mg/kg of body weight, maximum serum
22 concentrations reach about 4 mcg/mL, and measurable levels persist for as long as 8 hours.
23 Therapeutic serum levels are generally considered to range from 4 to 6 mcg/mL. When
24 tobramycin is administered by intravenous infusion over a 1-hour period, the serum

1 concentrations are similar to those obtained by intramuscular administration. Tobramycin is
2 poorly absorbed from the gastrointestinal tract.

3 In patients with normal renal function, except neonates, tobramycin administered every 8
4 hours does not accumulate in the serum. However, in those patients with reduced renal function
5 and in neonates, the serum concentration of the antibiotic is usually higher and can be measured
6 for longer periods of time than in normal adults. Dosage for such patients must, therefore, be
7 adjusted accordingly (see **DOSAGE AND ADMINISTRATION**).

8 Following parenteral administration, little, if any, metabolic transformation occurs, and
9 tobramycin is eliminated almost exclusively by glomerular filtration. Renal clearance is similar to
10 that of endogenous creatinine. Ultrafiltration studies demonstrate that practically no serum
11 protein binding occurs. In patients with normal renal function, up to 84% of the dose is
12 recoverable from the urine in 8 hours and up to 93% in 24 hours.

13 Peak urine concentrations ranging from 75 to 100 mcg/mL have been observed following
14 the intramuscular injection of a single dose of 1 mg/kg. After several days of treatment, the
15 amount of tobramycin excreted in the urine approaches the daily dose administered. When renal
16 function is impaired, excretion of tobramycin is slowed, and accumulation of the drug may cause
17 toxic blood levels.

18 The serum half-life in normal individuals is 2 hours. An inverse relationship exists
19 between serum half-life and creatinine clearance, and the dosage schedule should be adjusted
20 according to the degree of renal impairment (see **DOSAGE AND ADMINISTRATION**). In
21 patients undergoing dialysis, 25% to 70% of the administered dose may be removed, depending
22 on the duration and type of dialysis.

23 Tobramycin can be detected in tissues and body fluids after parenteral administration.
24 Concentrations in bile and stools ordinarily have been low, which suggests minimum biliary
25 excretion. Tobramycin has appeared in low concentration in the cerebrospinal fluid following
26 parenteral administration, and concentrations are dependent on dose, rate of penetration, and
27 degree of meningeal inflammation. It has also been found in sputum, peritoneal fluid, synovial
28 fluid, and abscess fluids, and it crosses the placental membranes. Concentrations in the renal
29 cortex are several times higher than the usual serum levels.

30 Probenecid does not affect the renal tubular transport of tobramycin.

31

32 **Microbiology**

1 Tobramycin acts by inhibiting synthesis of protein in bacterial cells. *In vitro* tests demonstrate that
2 tobramycin is bactericidal.

3 Tobramycin has been shown to be active against most strains of the following organisms
4 both *in vitro* and in clinical infections as described in **INDICATIONS AND USAGE** section:

5 **Aerobic Gram-positive microorganisms**

6 *Staphylococcus aureus*

7 **Aerobic Gram-negative microorganisms**

8 *Citrobacter* species

9 *Enterobacter* species

10 *Escherichia coli*

11 *Klebsiella* species

12 *Morganella morganii*

13 *Pseudomonas aeruginosa*

14 *Proteus mirabilis*

15 *Proteus vulgaris*

16 *Providencia* species

17 *Serratia* species

18 Aminoglycosides have a low order of activity against most gram-positive organisms,
19 including *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and enterococci.

20 Although most strains of enterococci demonstrate *in vitro* resistance, some strains in this
21 group are susceptible. *In vitro* studies have shown that an aminoglycoside combined with an
22 antibiotic that interferes with cell-wall synthesis affects some enterococcal strains synergistically.
23 The combination of penicillin G and tobramycin results in a synergistic bactericidal effect *in vitro*
24 against certain strains of *Enterococcus faecalis*. However, this combination is not synergistic
25 against other closely related organisms, eg, *Enterococcus faecium*. Speciation of enterococci
26 alone cannot be used to predict susceptibility. Susceptibility testing and tests for antibiotic
27 synergism are emphasized.

28 Cross resistance between aminoglycosides may occur.

29

30 **Susceptibility Tests**

31 **Diffusion Techniques**

1 Quantitative methods that require measurement of zone diameters give the most precise
2 estimates of susceptibility of bacteria to antimicrobial agents. One such procedure is the National
3 Committee for Clinical Laboratory Standards (NCCLS)-approved procedure.¹ This method has
4 been recommended for use with disks to test susceptibility to tobramycin. Interpretation involves
5 correlation of the diameters obtained in the disk test with minimum inhibitory concentrations (MIC)
6 for tobramycin.

7 Reports from the laboratory giving results of the standard single-disk susceptibility test
8 with a 10-mcg tobramycin disk should be interpreted according to the following criteria:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥15	(S) Susceptible
13-14	(I) Intermediate
≤12	(R) Resistant

9

10 A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally
11 achievable blood levels. A report of "Intermediate" suggests that the organism would be
12 susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high
13 antimicrobial levels are obtained. A report of "Resistant" indicates that achievable concentrations
14 are unlikely to be inhibitory and other therapy should be selected.

15

16 Standardized procedures require the use of laboratory control organisms. The
17 10-mcg tobramycin disk should give the following zone diameters:

<u>Organism</u>	<u>Zone Diameter (mm)</u>
<i>E. coli</i> ATCC 25922	18-26
<i>P. aeruginosa</i> ATCC 27853	19-25
<i>S. aureus</i> ATCC 25923	19-29

18

19

20

21

22 **Dilution techniques**

23 Broth and agar dilution methods, such as those recommended by the NCCLS², may be used to
24 determine MICs of tobramycin. MIC test results should be interpreted according to the following
25 criteria:

<u>MIC (mcg/mL)</u>	<u>Interpretation</u>
≤4	(S) Susceptible
8	(I) Intermediate
≥16	(R) Resistant

26

1 As with standard diffusion methods, dilution procedures require the use of laboratory
2 control organisms. Tobramycin laboratory reagent should give the following MIC values:

<u>Organism</u>	<u>MIC Range (mcg/mL)</u>
<i>E. faecalis</i> ATCC 29212	8-32
<i>E. coli</i> ATCC 25922	0.25-1
<i>P. aeruginosa</i> ATCC 27853	0.25-1
<i>S. aureus</i> ATCC 29213	0.12-1

3

4 **INDICATIONS AND USAGE:**

5 Tobramycin for Injection, USP is indicated for the treatment of serious bacterial infections caused
6 by susceptible strains of the designated microorganisms in the diseases listed below:

7 Septicemia in the pediatric patient and adult caused by *P. aeruginosa*, *E. coli*, and
8 *Klebsiella* spp.

9 Lower respiratory tract infections caused by *P. aeruginosa*, *Klebsiella* spp, *Enterobacter*
10 spp, *Serratia* spp, *E.coli*, and *S. aureus* (penicillinase- and non-penicillinase-producing strains).

11 Serious central-nervous-system infections (meningitis) caused by susceptible organisms.

12 Intra-abdominal infections, including peritonitis, caused by *E. coli*, *Klebsiella* spp, and
13 *Enterobacter* spp.

14 Skin, bone, and skin structure infections caused by *P. aeruginosa*, *Proteus* spp,
15 *E. coli*, *Klebsiella* spp, *Enterobacter* spp, and *S. aureus*.

16 Complicated and recurrent urinary tract infections caused by *P. aeruginosa*, *Proteus* spp,
17 (indole-positive and indole-negative), *E. coli*, *Klebsiella* spp, *Enterobacter* spp, *Serratia* spp, *S.*
18 *aureus*, *Providencia* spp, and *Citrobacter* spp.

19 Aminoglycosides, including tobramycin sulfate injection, USP are not indicated in
20 uncomplicated initial episodes of urinary tract infections unless the causative organisms are not
21 susceptible to antibiotics having less potential toxicity. Tobramycin for Injection, USP may be
22 considered in serious staphylococcal infections when penicillin or other potentially less toxic
23 drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate
24 its use.

25 Bacterial cultures should be obtained prior to and during treatment to isolate and identify
26 etiologic organisms and to test their susceptibility to tobramycin. If susceptibility tests show that
27 the causative organisms are resistant to tobramycin, other appropriate therapy should be
28 instituted. In patients in whom a serious life-threatening gram-negative infection is suspected,
29 including those in whom concurrent therapy with a penicillin or cephalosporin and an
30 aminoglycoside may be indicated, treatment with tobramycin may be initiated before the results

1 of susceptibility studies are obtained. The decision to continue therapy with tobramycin should be
2 based on the results of susceptibility studies, the severity of the infection, and the important
3 additional concepts discussed in the **WARNINGS** box above.

4

5 **CONTRAINDICATIONS:**

6 A hypersensitivity to any aminoglycoside is a contraindication to the use of tobramycin. A history
7 of hypersensitivity or serious toxic reactions to aminoglycosides may also contraindicate the use
8 of any other aminoglycoside because of the known cross-sensitivity of patients to drugs in this
9 class.

10

11 **WARNINGS:**

12 See **WARNINGS** box above.

13 Serious allergic reactions including anaphylaxis and dermatologic reactions including
14 exfoliative dermatitis, toxic epidermal necrolysis, erythema multiforme, and Stevens-Johnson
15 Syndrome have been reported rarely in patients on tobramycin therapy. Although rare, fatalities
16 have been reported (see **CONTRAINDICATIONS**).

17 If an allergic reaction occurs, the drug should be discontinued and appropriate therapy
18 instituted.

19

20

21

22

23 **PRECAUTIONS:**

24 Serum and urine specimens for examination should be collected during therapy, as
25 recommended in the **WARNINGS** box. Serum calcium, magnesium, and sodium should be
26 monitored.

27 Peak and trough serum levels should be measured periodically during therapy. Prolonged
28 concentrations above 12 mcg/mL should be avoided. Rising trough levels (above 2 mcg/mL) may
29 indicate tissue accumulation. Such accumulation, advanced age, and cumulative dosage may
30 contribute to ototoxicity and nephrotoxicity. It is particularly important to monitor serum levels
31 closely in patients with known renal impairment.

1 A useful guideline would be to perform serum level assays after 2 or 3 doses, so that the
2 dosage could be adjusted if necessary, and at 3- to 4-day intervals during therapy. In the event
3 of changing renal function, more frequent serum levels should be obtained and the dosage or
4 dosage interval adjusted according to the guidelines provided in **DOSAGE AND**
5 **ADMINISTRATION.**

6 In order to measure the peak level, a serum sample should be drawn about 30 minutes
7 following intravenous infusion or 1 hour after an intramuscular injection. Trough levels are
8 measured by obtaining serum samples at 8 hours or just prior to the next dose of tobramycin.
9 These suggested time intervals are intended only as guidelines and may vary according to
10 institutional practices. It is important, however, that there be consistency within the individual
11 patient program unless computerized pharmacokinetic dosing programs are available in the
12 institution. These serum-level assays may be especially useful for monitoring the treatment of
13 severely ill patients with changing renal function or of those infected with less susceptible
14 organisms or those receiving maximum dosage.

15 Neuromuscular blockade and respiratory paralysis have been reported in cats receiving
16 very high doses of tobramycin (40 mg/kg). The possibility of prolonged or secondary apnea
17 should be considered if tobramycin is administered to anesthetized patients who are also
18 receiving neuromuscular blocking agents, such as succinylcholine, tubocurarine, or
19 decamethonium, or to patients receiving massive transfusions of citrated blood. If neuromuscular
20 blockade occurs, it may be reversed by the administration of calcium salts.

21 Cross-allergenicity among aminoglycosides has been demonstrated.

22 In patients with extensive burns or cystic fibrosis, altered pharmacokinetics may result in
23 reduced serum concentrations of aminoglycosides. In such patients treated with tobramycin,
24 measurement of serum concentration is especially important as a basis for determination of
25 appropriate dosage.

26 Elderly patients may have reduced renal function that may not be evident in the results of
27 routine screening tests, such as BUN or serum creatinine. A creatinine clearance determination
28 may be more useful. Monitoring of renal function during treatment with aminoglycosides is
29 particularly important in such patients.

30 An increased incidence of nephrotoxicity has been reported following concomitant
31 administration of aminoglycoside antibiotics and cephalosporins.

1 Aminoglycosides should be used with caution in patients with muscular disorders, such as
2 myasthenia gravis or parkinsonism, since these drugs may aggravate muscle weakness because
3 of their potential curare-like effect on neuromuscular function.

4 Aminoglycosides may be absorbed in significant quantities from body surfaces after local
5 irrigation or application and may cause neurotoxicity and nephrotoxicity.

6 Aminoglycosides have not been approved for intraocular and/or subconjunctival use.
7 Physicians are advised that macular necrosis has been reported following administration of
8 aminoglycosides, including tobramycin, by these routes.

9 See **WARNINGS** box regarding concurrent use of potent diuretics and concurrent and
10 sequential use of other neurotoxic or nephrotoxic drugs.

11 The inactivation of tobramycin and other aminoglycosides by β -lactam-type antibiotics
12 (penicillins or cephalosporins) has been demonstrated *in vitro* and in patients with severe renal
13 impairment. Such inactivation has not been found in patients with normal renal function who
14 have been given the drugs by separate routes of administration.

15 Therapy with tobramycin may result in overgrowth of nonsusceptible organisms. If
16 overgrowth of nonsusceptible organisms occurs, appropriate therapy should be initiated.

17

18 ***Pregnancy Category D***

19 Aminoglycosides can cause fetal harm when administered to a pregnant woman.
20 Aminoglycoside antibiotics cross the placenta, and there have been several reports of total
21 irreversible bilateral congenital deafness in children whose mothers received streptomycin during
22 pregnancy. Serious side effects to mother, fetus, or newborn have not been reported in the
23 treatment of pregnant women with other aminoglycosides. If tobramycin is used during
24 pregnancy or if the patient becomes pregnant while taking tobramycin, she should be apprised of
25 the potential hazard to the fetus.

26

27 ***Pediatric Use***

28 See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION**.

29

30 ***Geriatric Use***

31 Elderly patients may be at a higher risk of developing nephrotoxicity and ototoxicity

1 while receiving tobramycin (see **WARNINGS, PRECAUTIONS, and OVERDOSAGE**). Other
2 factors that may contribute to nephrotoxicity and ototoxicity are rising trough levels, excessive
3 peak concentrations, dehydration, concomitant use of other neurotoxic or nephrotoxic drugs, and
4 cumulative dose. Peak and trough serum levels should be measured periodically during therapy
5 to assure adequate levels and to avoid potentially toxic levels (see **WARNINGS** and
6 **PRECAUTIONS**).

7 Tobramycin is known to be substantially excreted by the kidney, and the risk of toxic
8 reactions to this drug may be greater in patients with impaired renal function. Dose reduction is
9 required for patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**).
10 Elderly patients may have reduced renal function that may not be evident in the results of routine
11 screening tests, such as BUN or serum creatinine. A creatinine clearance determination may be
12 more useful. Monitoring of renal function during treatment with aminoglycosides is particularly
13 important in the elderly (see **PRECAUTIONS**).

14 This product does not contain sodium.

15

16 **ADVERSE REACTIONS:**

17 ***Neurotoxicity***

18 Adverse effects on both the vestibular and auditory branches of the eighth nerve have been
19 noted, especially in patients receiving high doses or prolonged therapy, in those given previous
20 courses of therapy with an ototoxin, and in cases of dehydration. Symptoms include dizziness,
21 vertigo, tinnitus, roaring in the ears, and hearing loss. Hearing loss is usually irreversible and is
22 manifested initially by diminution of high-tone acuity. Tobramycin and gentamicin sulfates closely
23 parallel each other in regard to ototoxic potential.

24

25 ***Nephrotoxicity***

26 Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria,
27 cylindruria, and increased proteinuria, have been reported, especially in patients with a history of
28 renal impairment who are treated for longer periods or with higher doses than those
29 recommended. Adverse renal effects can occur in patients with initially normal renal function.

30 Clinical studies and studies in experimental animals have been conducted to compare the
31 nephrotoxic potential of tobramycin and gentamicin. In some of the clinical studies and in the
32 animal studies, tobramycin caused nephrotoxicity significantly less frequently than gentamicin. In

1 some other clinical studies, no significant difference in the incidence of nephrotoxicity between
2 tobramycin and gentamicin was found.

3 Other reported adverse reactions possibly related to tobramycin include anemia,
4 granulocytopenia, and thrombocytopenia; and fever, rash, exfoliative dermatitis, itching, urticaria,
5 nausea, vomiting, diarrhea, headache, lethargy, pain at the injection site, mental confusion, and
6 disorientation. Laboratory abnormalities possibly related to tobramycin include increased serum
7 transaminases (AST, ALT); increased serum LDH and bilirubin; decreased serum calcium,
8 magnesium, sodium, and potassium; and leukopenia, leukocytosis, and eosinophilia.

9

10 **OVERDOSAGE:**

11 ***Signs and Symptoms***

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

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

29 Neuromuscular blockade or respiratory paralysis may occur following administration of
30 aminoglycosides. Neuromuscular blockade, respiratory failure, and prolonged respiratory
31 paralysis may occur more commonly in patients with myasthenia gravis or Parkinson's disease.
32 Prolonged respiratory paralysis may also occur in patients receiving decamethonium,

1 tubocurarine, or succinylcholine. If neuromuscular blockade occurs, it may be reversed by the
2 administration of calcium salts but mechanical assistance may be necessary.

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

5

6 ***Treatment***

7 In all cases of suspected overdose, call your Regional Poison Control Center to obtain the
8 most up-to-date information about the treatment of overdose. This recommendation is made
9 because, in general, information regarding the treatment of overdose may change more rapidly
10 than the package insert. In managing overdose, consider the possibility of multiple drug
11 overdoses, interaction among drugs, and unusual drug kinetics in your patient.

12 The initial intervention in a tobramycin overdose is to establish an airway and ensure
13 oxygenation and ventilation. Resuscitative measures should be initiated promptly if respiratory
14 paralysis occurs.

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

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

22

23 **DOSAGE AND ADMINISTRATION:**

24 The patient's pretreatment body weight should be obtained for calculation of correct dosage. It is
25 desirable to measure both peak and trough serum concentrations (see **WARNINGS** box and
26 **PRECAUTIONS**).

27

28 ***Administration for Patients with Normal Renal Function***

29 **Adults with Serious Infections**

30 3 mg/kg/day in 3 equal doses every 8 hours (see Table 1).

31

32 **Adults with Life-Threatening Infections**

1 Up to 5 mg/kg/day may be administered in 3 or 4 equal doses (see Table 1). The dosage should
 2 be reduced to 3 mg/kg/day as soon as clinically indicated. To prevent increased toxicity due to
 3 excessive blood levels, dosage should not exceed 5 mg/kg/day unless serum levels are
 4 monitored (see **WARNINGS** box and **PRECAUTIONS**.)

5

		Table 1.			
		DOSAGE SCHEDULE GUIDE FOR ADULTS WITH NORMAL RENAL FUNCTION			
		(Dosage at 8-Hour Intervals)			
For Patient Weighing kg lb		Usual Dose for Serious Infections		Maximum Dose for Life-Threatening Infections (Reduce as soon as possible)	
		1 mg/kg q8h (Total, 3 mg/kg/day)		1.66 mg/kg q8h (Total, 5 mg/kg/day)	
		<u>mg/dose</u>	<u>mL/dose*</u>	<u>mg/dose</u>	<u>mL/dose*</u>
		q8h		q8h	
120	264	120 mg	3 mL	200 mg	5 mL
115	253	115 mg	2.9 mL	191 mg	4.75 mL
110	242	110 mg	2.75 mL	183 mg	4.5 mL
105	231	105 mg	2.6 mL	175 mg	4.4 mL
100	220	100 mg	2.5 mL	166 mg	4.2 mL
95	209	95 mg	2.4 mL	158 mg	4 mL
90	198	90 mg	2.25 mL	150 mg	3.75 mL
85	187	85 mg	2.1 mL	141 mg	3.5 mL
80	176	80 mg	2 mL	133 mg	3.3 mL
75	165	75 mg	1.9 mL	125 mg	3.1 mL
70	154	70 mg	1.75 mL	116 mg	2.9 mL
65	143	65 mg	1.6 mL	108 mg	2.7 mL
60	132	60 mg	1.5 mL	100 mg	2.5 mL
55	121	55 mg	1.4 mL	91 mg	2.25 mL
50	110	50 mg	1.25 mL	83 mg	2.1 mL
45	99	45 mg	1.1 mL	75 mg	1.9 mL
40	88	40 mg	1 mL	66 mg	1.6 mL

6 * Applicable to all product forms except tobramycin injection, USP, (Pediatric).

7

8 **Pediatric patients (greater than 1 week of age)**

9 6 to 7.5 mg/kg/day in 3 or 4 equally divided doses (2 to 2.5 mg/kg every 8 hours or 1.5 to 1.89
 10 mg/kg every 6 hours).

11

12 **Premature or full-term neonates 1 week of age or less**

13 Up to 4 mg/kg/day may be administered in 2 equal doses every 12 hours.

14 It is desirable to limit treatment to a short term. The usual duration of treatment is 7 to 10
 15 days. A longer course of therapy may be necessary in difficult and complicated infections. In
 16 such cases, monitoring of renal, auditory, and vestibular functions is advised, because
 17 neurotoxicity is more likely to occur when treatment is extended longer than 10 days.

1

2 ***Dosage in Patients with Cystic Fibrosis***

3 In patients with cystic fibrosis, altered pharmacokinetics may result in reduced serum
4 concentrations of aminoglycosides. Measurement of tobramycin serum concentration during
5 treatment is especially important as a basis for determining appropriate dose. In patients with
6 severe cystic fibrosis, an initial dosing regimen of 10 mg/kg/day in 4 equally divided doses is
7 recommended. This dosing regimen is suggested only as a guide. The serum levels of
8 tobramycin should be measured directly during treatment due to wide interpatient variability.

9

10 ***Administration for Patients with Impaired Renal Function***

11 Whenever possible, serum tobramycin concentrations should be monitored during therapy.

12 Following a loading dose of 1 mg/kg, subsequent dosage in these patients must be
13 adjusted, either with reduced doses administered at 8-hour intervals or with normal doses given
14 at prolonged intervals. Both of these methods are suggested as guides to be used when serum
15 levels of tobramycin cannot be measured directly. They are based on either the creatinine
16 clearance level or the serum creatinine level of the patient because these values correlate with
17 the half-life of tobramycin. The dosage schedule derived from either method should be used in
18 conjunction with careful clinical and laboratory observations of the patient and should be modified
19 as necessary. Neither method should be used when dialysis is being performed.

20

21 **Reduced dosage at 8-hour intervals**

22 When the creatinine clearance rate is 70 mL or less per minute or when the serum creatinine
23 value is known, the amount of the reduced dose can be determined by multiplying the normal
24 dose from Table 1 by the percent of normal dose from the accompanying nomogram.

25 An alternate rough guide for determining reduced dosage at 8-hour intervals (for patients
26 whose steady-state serum creatinine values are known) is to divide the normally recommended
27 dose by the patient's serum creatinine.

28

29 **Normal dosage at prolonged intervals**

30 If the creatinine clearance rate is not available and the patient's condition is stable, a dosage
31 frequency *in hours* for the dosage given in Table 1 can be determined by multiplying the patient's
32 serum creatinine by 6.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32

Dosage in Obese Patients

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.

Intravenous Administration

For intravenous administration, the usual volume of diluent (0.9% Sodium Chloride Injection or 5% Dextrose Injection) is 50 to 100 mL for adult doses. For pediatric patients, the volume of diluent should be proportionately less than that for adults. The diluted solution usually should be infused over a period of 20 to 60 minutes. Infusion periods of less than 20 minutes are not recommended because peak serum levels may exceed 12 mcg/mL (see **WARNINGS** box):

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

PREPARATION AND STORAGE:

Directions for Proper Use of Pharmacy Bulk Package—Not for direct infusion

The pharmacy bulk package is for use in the Hospital Pharmacy Admixture Service and only in a suitable work area, such as a laminar flow hood. Using aseptic technique, the closure may be penetrated only 1 time after reconstitution using a suitable sterile transfer device or dispensing set, which allows measured dispensing of the contents. Use of a syringe and needle is not recommended as it may cause leakage. After entry, entire contents of bulk vial should be dispensed within 24 hours.

Tobramycin for Injection, USP is supplied as a dry powder. The contents of the vial should be diluted with 30 mL of Sterile Water for Injection, USP, to provide a solution containing 40 mg of tobramycin per mL. Prior to reconstitution, the vial should be stored at controlled room temperature, 15° to 30°C (59° to 86°F). After reconstitution, the solution should be kept in a refrigerator and used within 96 hours. If kept at room temperature, the solution must be used within 24 hours.

Prior to administration, parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit.

1 **HOW SUPPLIED:**

2 **Product** **NDC**
3 **No.** **No.**
4 300351 63323-303-51

Tobramycin for Injection, USP equivalent to 1.2 g
tobramycin in a 50 mL *pharmacy bulk package vial*,
packaged in trays of 6.

5
6
7
8 Vial stoppers do not contain natural rubber latex.

9

10

11 **REFERENCES:**

- 12 1. National Committee for Clinical Laboratory Standards, Performance Standards for
13 Antimicrobial Disk Susceptibility Tests—Sixth Edition. Approved Standard NCCLS Document
14 M2-A6, Vol. 17, No.1, NCCLS, Wayne, PA, 1997.
- 15 2. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial
16 Susceptibility Tests for Bacteria that Grow Aerobically—Fourth Edition. Approved Standard
17 NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, 1997.

18

19

20

21



24

25 45932

26 Issued: October 2003

402063

APP Inc. Tobramycin 50mL Pharma-Sling Die # 16A

NDC 63323-303-51

NDC 63323-303-51 300351

TOBRAMYCIN
FOR INJECTION, USP

PHARMACY BILT FACILITY
NOT FOR DIRECT PATIENT USE

equivalent to

1.2g

Tobramycin

Rx only



Black 185 Red

READ INSERT FOR IMPORTANT SAFETY INFORMATION AND DOSING GUIDELINES
 Each vial contains 1200 mg of Tobramycin activity.
PREPARATION OF SOLUTION: Add 30 mL of Sterile Water for Injection, USP to provide a solution containing 40 mg of Tobramycin per mL. **SHAKE WELL.**
Prior to Reconstitution: Store at Controlled Room Temperature 15° to 30°C (59° to 86°F).
After Reconstitution: Store in a refrigerator and use within 96 hours. If kept at room temperature, use within 24 hours.
Preservative Free
 Vial stoppers do not contain natural rubber latex.

Tobramycin For Injection, USP

Schaumburg, IL 60173

VIAL ENTRY:

Date _____

Time _____

Pharma-Sling (Does Not Print)

402063

LEFT
HERE

NOC 63321-303-51 300351

TOBRAMYCIN

FOR INJECTION, USP

PHARMACY BULK PACKAGE
NOT FOR DIRECT INJECTION

equivalent to

120

Tobramycin

Rx only

READ INSERT FOR IMPORTANT SAFETY
INFORMATION AND DOSING GUIDELINES.
Each vial contains 1200 mg of Tobramycin
activity.

PREPARATION OF SOLUTION: Add 30 mL
of Sterile Water for Injection, USP to
provide a solution containing 40 mg of
Tobramycin per mL.

Prior to Reconstitution: Store at
Controlled Room Temperature 15° to 30°C
(59° to 86°F).

After Reconstitution: Store in a refrigerator
and use within 96 hours. If kept at room
temperature, use within 24 hours.

Preservative Free

Vial stoppers do not contain natural rubber
latex.



Schaumburg, IL 60173

42689

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Janice Soreth
7/13/04 06:10:41 PM