

TOBRAMYCIN MYLAN



1. Product Name

Tobramycin Mylan, 80 mg/ 2 mL, solution for injection.

2. Qualitative and Quantitative Composition

Each mL of solution for injection contains 40 mg of tobramycin.

Each 2 mL vial contains 80 mg of tobramycin.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Tobramycin Mylan is a clear colourless liquid

4. Clinical Particulars

4.1 Therapeutic indications

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

- Septicaemia in the neonate, child, and adult caused by *P aeruginosa*, *E coli*, and *Klebsiella sp*
- Lower respiratory tract infections caused by *P aeruginosa*, *Klebsiella sp*, *Enterobacter sp*, *Serratia sp*, *E coli*, and *S aureus* (penicillinase and non-penicillinase-producing strains)
- Serious central-nervous-system infections (meningitis) caused by susceptible organisms
- Intra-abdominal infections, including peritonitis, caused by *E coli*, *Klebsiella sp*, and *Enterobacter sp*
- Skin, bone, and skin-structure infections (including burns) caused by *P aeruginosa*, *Proteus sp*, *E coli*, *Klebsiella sp*, *Enterobacter sp*, and *S aureus*
- Complicated and recurrent urinary tract infections caused by *P aeruginosa*, *Proteus sp* (indole-positive and indole-negative), *E coli*, *Klebsiella sp*, *Enterobacter sp*, *Serratia sp*, *S aureus*, *Providencia sp*, and *Citrobacter sp*.

Aminoglycosides, including tobramycin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity. Tobramycin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic medicines are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

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

The decision to continue therapy with tobramycin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in section 4.4.

4.2 Dose and method of administration

Tobramycin may be given intramuscularly or intravenously. Recommended dosages are the same for both routes. The patient's pretreatment body weight should be obtained for calculation of correct dosage. It is desirable to measure both peak and trough serum concentrations (see section 4.4). Prior to administration, parenteral medicines should be inspected visually for particulate matter and discoloration whenever solution and container permit.

Administration for patients with normal renal function

Adults with serious infections

Three mg/kg/day in three equal doses every eight hours (see Table 1).

In adults with normal renal function, mild to moderate urinary tract infections have responded to a dosage of 2 to 3 mg/kg/day, administered as a single daily intramuscular injection.

Adults with life-threatening Infections

Up to 5 mg/kg/day may be administered in three or four equal doses (see Table 1). The 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 (see section 4.4).

To achieve therapeutic serum levels in patients with cystic fibrosis, it may be necessary to administer up to 8 to 10 mg/kg/day in equally divided doses. Because serum concentrations of tobramycin vary from one patient to another, serum levels should be monitored.

Children

6 to 7.5 mg/kg/day in three or four equally divided doses (2 to 2.5 mg/kg every eight hours or 1.5 to 1.89 mg/kg every six hours).

Premature or full-term neonates one week of age or less

Up to 4 mg/kg/day may be administered in two equal doses every 12 hours. It is desirable to limit treatment to a short term. The usual duration of treatment is seven to 10 days. A longer course of therapy may be necessary in difficult and complicated infections. In such cases, monitoring of renal, auditory, and vestibular functions is advised, because neurotoxicity is more likely to occur when treatment is extended longer than 10 days.

TABLE 1
DOSAGE SCHEDULE GUIDE FOR ADULTS WITH NORMAL RENAL FUNCTION
(Dosage at 8-hour intervals)

Patient body weight (kg)	Usual dose for serious infections 1 mg/kg every 8 hours (total, 3 mg/kg/day)		Maximum dose for life-threatening infections (<u>reduce as soon as possible</u>) 1.66 mg/kg every 8 hours (Total, 5 mg/kg/day)	
	mg/dose	mL/dose	mg/dose	mL/dose
120	120mg	3 mL	200mg	5 mL
115	115mg	2.9 mL	191mg	4.75 mL
110	110mg	2.75 mL	183mg	4.5 mL
105	105mg	2.6 mL	175mg	4.4 mL
100	100mg	2.5 mL	166mg	4.2 mL
95	95mg	2.4 mL	158mg	4 mL
90	90mg	2.25 mL	150mg	3.75 mL
85	85mg	2.1 mL	141mg	3.5 mL

80	80mg	2 mL	133mg	3.3 mL
75	75mg	1.9 mL	125mg	3.1 mL
70	70mg	1.75 mL	116mg	2.9 mL
65	65mg	1.6 mL	108mg	2.7 mL
60	60mg	1.5 mL	100mg	2.5 mL
55	55mg	1.4 mL	91mg	2.25 mL
50	50mg	1.25 mL	83mg	2.1 mL
45	45mg	1.1 mL	75mg	1.9 mL
40	40mg	1 mL	66mg	1.6 mL

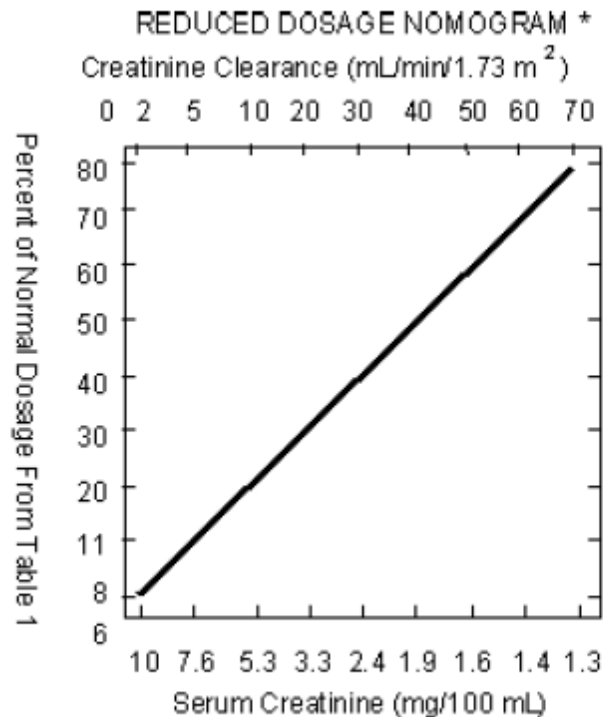
Administration for patients with impaired renal function

Whenever possible, 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 reduced doses administered at eight hour intervals or with normal doses given at prolonged intervals. Both of these methods are suggested as guides to be used when serum levels of tobramycin cannot be measured directly. They are based on either the creatinine clearance or the serum creatinine of the patient, because these values correlate with the half-life of tobramycin. The dosage schedules derived from either method should be used in conjunction with careful clinical and laboratory observations of the patient and should be modified as necessary. Neither method should be used when dialysis is being performed.

Reduced dosage at eight hour intervals

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

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



* Scales have been adjusted to facilitate dosage calculations

Normal dosage at prolonged intervals

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

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.

Method of administration

Intramuscular administration

Tobramycin may be administered by withdrawing the appropriate dose directly from a vial.

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 children, the volume of diluent should be proportionately less than 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 micrograms/mL (see section 4.4).

Tobramycin may be administered slowly by direct intravenous injection or into the tubing of a drip set. When tobramycin is given in this manner, serum levels may exceed 12 micrograms/mL for a short period of time.

4.3 Contraindications

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

Hypersensitivity to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Warnings

Patients treated with tobramycin and other aminoglycosides should be under close clinical observation, because these medicines 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 pre-existing renal damage and in those with normal renal function to whom aminoglycosides are administered for longer periods or in higher doses than 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 medicine has been discontinued. Rarely, nephrotoxicity may not become manifest until the first few days after cessation of therapy. Aminoglycoside-induced nephrotoxicity usually is reversible.

Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. 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 micrograms/mL should be avoided. Rising trough

levels (above 2 micrograms/mL) may indicate tissue accumulation. Such accumulation, excessive peak concentrations, advanced age, and cumulative dose may contribute to ototoxicity and nephrotoxicity (see section 4.4). Urine should be examined for decreased specific gravity and increased excretion of protein, cells, and casts. Blood urea nitrogen, serum creatinine, and creatinine clearance should be measured periodically. When feasible, it is recommended that serial audiograms be obtained in patients old enough to be tested, particularly high-risk patients. Evidence of impairment of renal, vestibular, or auditory function requires discontinuation of the medicine or dosage adjustment.

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.

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

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

Aminoglycosides can cause foetal harm when administered to a pregnant woman (see section 4.6).

Tobramycin Injection 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. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Precautions

Serum and urine specimens for examination should be collected during therapy, as recommended in the Warnings. Serum calcium, magnesium, and sodium should be monitored.

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

A useful guideline would be to perform serum level assays after two or three doses, so that the dosage could be adjusted if necessary, and also at three to four-day intervals during therapy. In the event of changing renal function, more frequent serum levels should be obtained and the dosage or dosage interval adjusted according to the guidelines provided in section 4.2. In order to measure the peak level, a serum sample should be drawn about 30 minutes following intravenous infusion or one hour after an intramuscular injection. Trough levels are measured by obtaining serum samples at eight hours or just prior to the next dose of tobramycin. These suggested time intervals are intended only as guidelines and may vary according to institutional practices. It is important, however, that there be consistency within the individual patient programme unless computerised pharmacokinetic dosing programmes are available in the institution. These serum-level assays may be especially useful for monitoring the treatment of severely ill patients with changing renal function or of those infected with less sensitive organisms or those receiving maximum dosage. Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of tobramycin (40 mg/kg). The possibility that prolonged or secondary apnoea may occur should be considered if tobramycin is administered to anaesthetised patients who are also receiving neuromuscular blocking agents, such as succinylcholine, tubocurarine, or decamethonium, or to patients receiving massive transfusions of citrated blood. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts.

Cross-allergenicity among aminoglycosides has been demonstrated.

In patients with excessive burns, altered pharmacokinetics may result in reduced serum concentrations of aminoglycosides. In such patients treated with tobramycin, measurement of serum concentration is especially recommended as a basis for determination of appropriate dosage.

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

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

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

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

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.

See section 4.5 regarding concurrent use of potent diuretics and concurrent and sequential use of other neurotoxic or nephrotoxic medicines.

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

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

Use in children

See section 4.2

4.5 Interaction with other medicines and other forms of interaction

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly other aminoglycosides (e.g., amikacin, streptomycin, neomycin, kanamycin, gentamicin, and paromomycin), cephaloridine, viomycin, polymyxin B, colistin, cisplatin, and vancomycin, should be avoided (see section 4.4).

Aminoglycosides should not be given concurrently with potent diuretics, such as ethacrynic acid and furosemide (see section 4.4).

The inactivation of tobramycin and other aminoglycosides by β -lactam-type antibiotics (penicillins or cephalosporins) has been demonstrated *in vitro* and in patients with severe renal impairment. Such inactivation has not been found in patients with normal renal function who have been given the medicines by separate routes of administration (see section 4.4).

4.6 Fertility, pregnancy and lactation

Use in pregnancy

Category D

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

Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying text above should be consulted for further details.

Use in lactation

Aminoglycosides are excreted in breast milk in small but variable amounts, but problems in nursing infants have not been documented because of their poor gastrointestinal absorption.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Neurotoxicity

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

Nephrotoxicity

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

Clinical studies and studies in experimental animals have been conducted to compare the nephrotoxic potential of tobramycin and gentamicin. In some of the clinical studies and in the animal studies, tobramycin caused nephrotoxicity significantly less frequently than gentamicin. In some other clinical studies, no significant difference in the incidence of nephrotoxicity between tobramycin and gentamicin was found.

Other reported adverse reactions possibly related to tobramycin include anaemia, granulocytopenia, and thrombocytopenia; and fever, rash, exfoliative dermatitis, itching, urticaria, nausea, vomiting, diarrhoea, headache, lethargy, pain at the injection site, mental confusion, and disorientation. Laboratory abnormalities possibly related to tobramycin sulfate include increased serum transaminases (SGOT, SGPT); increased serum LDH and bilirubin; decreased serum calcium, magnesium, sodium and potassium; and leukopenia, leukocytosis, and eosinophilia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

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 concentrations versus time graph. Nephrotoxicity is more likely if trough blood concentrations fail to fall below 2 micrograms/mL and is also proportional to the average blood concentration. Patients who are elderly, have abnormal renal function, are receiving other nephrotoxic medicines, 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 medicine 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.

Management

In managing overdose, consider the possibility of multiple medicine overdoses, interaction among medicines, and unusual drug kinetics in your patient.

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

Patients that have received an overdose of tobramycin and have normal renal function should be adequately 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 micrograms/mL. Patients in whom the elimination half-life is greater than two hours or whose renal function is abnormal may require more aggressive therapy. In such patients, haemodialysis may be beneficial.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: aminoglycoside antibacterial, ATC code: J01GB01

Mechanism of action

Tobramycin Injection is an aminoglycoside antibiotic for parenteral administration. Tobramycin is bactericidal and acts by inhibiting the synthesis of protein in bacterial cells. 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*, *Proteus morgani*, *P. rettgeri*, and *P. vulgaris*.

Escherichia coli

Klebsiella-Enterobacter-Serratia group

Citrobacter sp

Providencia sp

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

Aminoglycosides have a low order of activity against most gram-positive organisms, including *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and enterococci. Although most strains of enterococci demonstrate *in vitro* resistance, some strains are susceptible. *In vitro* studies have shown that an aminoglycoside combined with an antibiotic that 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, *Streptococcus 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 emphasized.

Cross-resistance between aminoglycosides occurs and depends largely on inactivation by bacterial enzymes.

Susceptibility tests

If the FDA Standardised Disc Test method (formerly the Bauer-Kirby-Sherris-Turck method) of disk susceptibility testing is used, a disk containing 10 micrograms tobramycin should give a zone of at least 15 mm when tested against a tobramycin-susceptible bacterial strain, a zone of 13 to 14 mm against strains of intermediate susceptibility, and a zone of 12 mm more or less against resistant organisms. The minimum inhibitory concentration correlates are 4 micrograms/mL for susceptibility and 8 micrograms/mL for resistance.

5.2 Pharmacokinetic properties

Tobramycin is rapidly absorbed following intramuscular administration. Peak serum concentrations of tobramycin occur between 30 and 90 minutes after intramuscular administration. Following an intramuscular dose of 1 mg/kg of body weight, maximum serum concentrations reach about 4 micrograms/mL, and measurable levels persist for as long as eight hours. Therapeutic serum levels are generally considered to range from 4 to 6 micrograms/mL. When tobramycin sulfate is administered by intravenous infusion over a one-hour period, the serum concentrations are similar to those obtained by intramuscular administration. Tobramycin is poorly absorbed from the gastrointestinal tract.

Following bolus intravenous injection of a single dose of 1.5 mg/kg, peak serum levels occurred rapidly and ranged from 9.2 to 29.8 micrograms/mL. These levels fell to less than 11 micrograms/mL within 15 minutes. In patients with normal renal function, except neonates, tobramycin administered every eight hours does not accumulate in the serum. However, in those patients with reduced renal function and in neonates, the serum concentration of the antibiotic is usually higher and can be measured for longer periods of time than in normal adults. Dosage for such patients must, therefore, be adjusted accordingly (see section 4.2). Following parenteral administration, little, if any, metabolic transformation occurs, and 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% of the dose is recoverable from the urine in eight hours and up to 93% in 24 hours.

Peak urine concentrations ranging from 75 to 100 micrograms/mL have been observed following 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. When renal function is

impaired, excretion of tobramycin is slowed, and accumulation of the medicine may cause toxic blood levels.

The serum half-life in normal individuals is two hours. An inverse relationship exists between serum half-life and creatinine clearance, and the dosage schedule should be adjusted according to the degree of renal impairment (see section 4.2). In patients undergoing dialysis, 25% to 70% of the administered dose may be removed, depending on the duration and type of dialysis.

Tobramycin can be detected in tissues and body fluids after parenteral administration. Concentrations in bile and stools ordinarily have been low, which suggests minimum biliary excretion. Tobramycin has appeared in low concentration in the cerebrospinal fluid following parenteral administration, and concentrations are dependent on dose, rate of penetration, and degree of meningeal inflammation. It has also been found in sputum, peritoneal fluid, synovial fluid, and abscess fluids, and it crosses the placental membranes. Concentrations in the renal cortex are several times higher than the usual serum levels. Tobramycin serum levels may be somewhat lower than expected in adults with a large volume of extracellular fluid. Also, it has been reported that the serum half-life of tobramycin in severely burned patients may be decreased and this may result in lower serum levels. Probenecid does not affect the renal tubular transport of tobramycin.

6. Pharmaceutical Particulars

6.1 *List of excipients*

Tobramycin Mylan 80 mg/2 mL vials also contain:

- water for injection,
- disodium edetate,
- sulfuric acid
- sodium bisulfite
- sodium hydroxide may have been added to adjust pH.

6.2 *Incompatibilities*

This medicine must not be mixed with other medicines except those mention in section 6.6.

6.3 *Shelf life*

2 years.

6.4 *Special precautions for storage*

Store at or below 25°C.

Protect from light.

6.5 *Nature and contents of container*

2 mL Type I glass vials with bromobutyl stopper in packs of five vials.

6.6 *Special precautions for disposal and other handling*

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 children, the volume of diluent should be proportionately less than for adults.

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

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

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
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Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

18 February 2016

10. Date of Revision of the Text

20 July 2018 Revised to SmPC format.