AUSTRALIAN PRODUCT INFORMATION – DBL™ Tobramycin Injection (Tobramycin)

1. NAME OF THE MEDICINE

Tobramycin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The vials of DBL Tobramycin Injection BP contain 80 mg/2 mL tobramycin. The vials contain disodium edetate 0.2 mg, sodium metabisulfite 4.8 mg, sulfuric acid 34.6 mg and water for injections. In the manufacture of the vials, additional sulfuric acid and/or sodium hydroxide may have been added to adjust the pH.

Excipients with known effect

- Sodium metabisulfite

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

DBL Tobramycin Injection BP is a clear, colourless solution. The pH of the solution is approximately 5.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tobramycin is indicated in the treatment of the following serious infections caused by susceptible micro-organisms:

- central nervous system infections, including meningitis, septicaemia and neonatal sepsis;
- gastro-intestinal infections, including peritonitis;
- complicated and recurrent urinary tract infections such as pyelonephritis and cystitis;
- lower respiratory tract infections, including pneumonia, bronchopneumonia and acute bronchitis;
- bone, skin and skin structure infections, including burns.

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

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 organism is resistant to tobramycin, other appropriate therapy should be instituted. In patients in whom gram negative septicaemia, neonatal sepsis, or meningitis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, tobramycin therapy may be initiated before results of susceptibility studies are obtained. The decision to continue tobramycin therapy should be based upon the results of susceptibility studies, severity of the infection, and the important additional concepts discussed under section 4.4 Special warnings and precautions for use.

4.2 Dose and method of administration

Dosage

Adult

Tobramycin may be given intramuscularly or intravenously (see below) and the dosage is the same for either route of administration. It is recommended to measure both peak and trough serum concentrations whenever possible to ensure the correct dosage is given (see section 4.4 Special warnings and precautions for use). The patient's pretreatment body weight should be obtained for calculation of correct dosage. In obese patients, the appropriate dose may be calculated by using the patient's estimated lean body weight plus 40 percent of the excess as the basic weight on which to figure mg/kg. Blood levels should always be determined in patients with chronic infections such as cystic fibrosis, or where longer duration of treatment may be necessary, or in patients with decreased renal function.

In patients with extensive burns or cystic fibrosis, 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.

Intramuscular administration

Dosage for patients with normal renal function:

a. Serious infections: 3 mg/kg/day in three equal doses every eight hours.

b. Mild to moderate urinary tract infections: 2 to 3 mg/kg/day in two or three equally divided doses.

c. Life threatening infections: Dosages up to 5 mg/kg/day in 3 or 4 equal doses with reduction to 3 mg/kg/day as soon as clinically indicated. Dosage should not exceed 5 mg/kg/day unless serum levels are monitored.

The following table may be used as a guide:

DOSAGE SCHEDULE GUIDE FOR ADULTS WITH NORMAL RENAL FUNCTION

(Dosage at eight-hour intervals)

Patient bodyweight (kg)	Usual dose for serious infections 1 mg/kg every 8 hours (total 3 mg/kg/day)		Maximum dose for life-threatening infections 1.66 mg/kg every 8 hours (total 5 mg/kg/day with reduction to 3 mg/kg/day as soon as clinically indicated)	
	Dose every eight hours			
	mg/dose	mL/dose*	mg/dose	mL/dose*
120	120	3.0	200	5.0
110	110	2.75	183	4.5
100	100	2.5	166	4.2
90	90	2.25	150	3.75
80	80	2.0	133	3.3
70	70	1.75	116	2.9
60	60	1.5	100	2.5
50	50	1.25	83	2.1
40	40	1.0	66	1.6

*Applicable to all product forms except tobramycin paediatric injection (20 mg/2 mL)

The usual duration of treatment is seven to ten days. A longer course may be necessary in difficult 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 ten days.

Intravenous use

The intravenous dose is the same as the intramuscular dose. The usual volume of diluent for adult doses is 50 to 100 mL. For children, the volume of diluent should be proportionately less than for adults. The diluted solution should usually be infused over a period of 20 to 60minutes. Infusion periods of less than 20 minutes may cause peak serum levels to exceed 12 micrograms/mL (see section 4.4 Special warnings and precautions for use).

Paediatric

Tobramycin may be given intramuscularly or intravenously. For intravenous administration, the volume of diluent should be proportionately less than for adults.

1. Children and older infants: 6 to 7.5 mg/kg/day in 3 or 4 equally divided doses (2 to 2.5 mg/kg every eight hours, or 1.5 to 1.89 mg/kg every six hours).

2. Neonates (one week of age or less): Up to 4 mg/kg per day may be administered in two equal doses every 12 hours.

Method of administration

Tobramycin may be given intramuscularly or intravenously.

Intravenous use

Tobramycin may be further diluted for infusion in Sodium Chloride Intravenous Infusion 0.9% or Glucose Intravenous Infusion 5%. To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2 to 8°C for not more than 24 hours.

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

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

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

Dosage adjustment

Renal impairment

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

Following a loading dose of 1 mg/kg, subsequent dosage must be adjusted either with lower doses at 8 hour intervals or with normal doses at prolonged intervals. Both methods are only guides to be used when serum levels of drug cannot be monitored. They are based on creatinine clearance or serum creatinine levels, because these values correlate with the half-life of tobramycin. Neither regimen should be used when dialysis is being performed.

<u>Reduced dosage at eight hour intervals (Regimen I):</u>

An appropriate reduced dosage range can be found in the accompanying table for any patient for whom the 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 susceptibility of the pathogen, and individual patient considerations, especially renal function. 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 expressed as mg percent.

<u>Prolonged intervals between fixed doses (Regimen II):</u>

Recommended intervals between doses are given in the accompanying table. As a general rule, the dosage frequency in hours can be determined by multiplying the patient's serum creatinine level expressed as mg percent by six.

The dosage schedule derived from either method should be used in conjunction with careful clinical and laboratory observations of the patient and should be modified as necessary (see section 4.4 Special warnings and precautions for use).

TWO MAINTENANCE REGIMENS BASED ON RENAL FUNCTION AND BODY WEIGHT FOLLOWING A LOADING DOSE OF 1 mg/kg*

Renal Function†			**REGIMEN I** Adjusted doses at 8 hour intervals		**REGIMEN II** Adjusted intervals between fixed dose	
Serum Creatinine		Creatinine Clearance	50 – 60 kg	60 – 80 kg	Fixed dose for	Fixed dose for
mg %	mmol/L	mL/min			50 – 60 kg = 60 mg	60 – 80 kg = 80 mg
< 1.4	< 0.12	> 69	60 mg	80 mg	8 h	
1.4 – 1.9	0.12 – 0.17	69 – 40	30 – 60 mg	50 – 80 mg	12 h	
2.0 – 3.3	0.18 – 0.29	39 – 20	20 – 25 mg	30 – 45 mg	18 h	
3.4 – 5.3	0.30 – 0.46	19 – 10	10 – 18 mg	15 – 24 mg	24 h	
5.4 – 7.5	0.47 – 0.66	9 – 5	5 – 9 mg	7 – 12 mg		
> 7.5	> 0.66	< 5	2.5 – 4.5 mg	3.5 – 6 mg		

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

†If used to estimate degree of renal impairment, serum creatinine concentrations should reflect a steady state of renal azotaemia.

4.3 Contraindications

Patients with a history of previous hypersensitivity to tobramycin or to any of the components of DBL Tobramycin Injection BP.

A history of hypersensitivity or serious toxic reactions (ototoxicity, nephrotoxicity) to aminoglycosides may also contraindicate the use of any other aminoglycoside because of the known cross-sensitivity of patients to drugs in this class.

Intrathecal administration.

4.4 Special warnings and precautions for use

Bacterial cultures should be obtained before and during treatment to isolate and identify aetiologic organisms and to test their susceptibility to tobramycin. If the organisms are resistant other appropriate therapy should be instituted. In patients in whom gram negative septicaemia, neonatal sepsis or meningitis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, tobramycin therapy may be initiated before results of susceptibility studies are obtained.

Clostridioides difficile-associated disease

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including tobramycin. A toxin produced with *Clostridioides difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridioides difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Nephrotoxicity and ototoxicity

As with other aminoglycosides, patients treated with aminoglycoside antibiotics should be under close clinical observation because these drugs have the inherent potential for causing ototoxicity and nephrotoxicity. Tobramycin has an inherent potential for causing ototoxicity and nephrotoxicity, particularly if patients have pre-existing renal damage or if the drug is administered for longer periods or at higher doses than those recommended.

Ototoxicity

Eighth cranial nerve impairment may develop in patients with pre-existing renal damage and if tobramycin is administered for longer periods or in higher doses than those recommended. Both vestibular and auditory ototoxicity can occur. The auditory changes are irreversible, usually bilateral, and may be partial or total. 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 of eighth cranial nerve toxicity, and partial or total irreversible bilateral deafness may continue to develop after the drug has been discontinued. Tobramycin is potentially nephrotoxic; therefore, renal and eighth cranial nerve function should be closely monitored. 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. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching, and convulsions.

Patients with mitochondrial DNA mutations, particularly the nucleotide 1555 A to G substitution in the 12S rRNA gene may be at higher risk for ototoxicity, even if the patient's aminoglycoside serum levels were within the recommended range. In case of family history of aminoglycoside induced deafness or known mitochondrial DNA mutations in the 12S rRNA gene, alternative treatments other than aminoglycosides should be considered.

Nephrotoxicity

Renal function should be closely monitored, particularly 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.

Tobramycin is selectively concentrated in renal cortical cells and it produces changes in proximal tubules. The drug causes renal impairment characterised by excretion of casts, oliguria, proteinuria and a progressive rise in blood urea and serum creatinine values.

Serum and urine should be monitored during therapy, including peak and trough drug levels; serum creatinine and creatinine clearance; serum calcium, magnesium, potassium, sodium levels and blood urea nitrogen; urinary specific gravity and excretion of protein, cells and casts.

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

Topical and other routes of administration

Although not indicated for local irrigation or application, aminoglycosides administered in this fashion may be absorbed in significant quantities from body surfaces and may cause neurotoxicity and nephrotoxicity. In addition, there have been reports of macular necrosis following intraocular and/or subconjunctival injection of aminoglycosides including tobramycin.

Use in patients with muscular disorders

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

Use during anaesthesia

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 the drug is administered to anaesthetised patients who are also receiving neuromuscular blocking agents such as suxamethonium (succinylcholine), tubocurarine or decamethonium or in patients receiving massive transfusions of citrated blood. If neuromuscular blockade occurs it may be reversed by the administration of calcium salts.

Use in patients with burns or cystic fibrosis

In patients with extensive burns or cystic fibrosis, altered pharmacokinetics may result in reduced serum drug levels. Dosage must be based on measured serum levels in these patients.

Superinfection

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

Allergic reactions

Administration of tobramycin may result in allergic reaction. Cross-allergenicity among aminoglycosides has been known to occur.

Other

DBL Tobramycin Injection BP contains sodium metabisulfite which may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.

Use in impaired renal, vestibular and/or auditory function

Evidence of impairment in renal, vestibular and/or auditory function requires discontinuation of the drug or at least reduction in dose if continuation of therapy is considered essential.

Patients with reduced renal function are particularly prone to the potential ototoxic and nephrotoxic effects of this drug, so dosage should be adjusted carefully on the basis of regular monitoring of serum drug concentrations and of renal function. Renal and eighth cranial nerve function should be closely monitored in patients in whom renal impairment is known or who develop signs of dysfunction during therapy.

In high risk patients, peak and trough serum levels of tobramycin should be measured periodically during therapy, and prolonged 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, dehydration, and cumulative dose may contribute to ototoxicity and nephrotoxicity. Urine should be examined for decreased specific gravity and increased excretion of protein, cells, and casts. Experience with gentamicin suggests that ototoxicity may develop at peak levels below 12 micrograms/mL. Care should be taken to avoid trough levels in excess of approximately 3 micrograms/mL in conjunction with a degree of renal failure and a treatment period beyond 10 to 14 days. It is particularly important to monitor serum levels closely in patients with known renal impairment.

A useful guideline would be to perform tobramycin serum level assays after 2 or 3 doses, so that the dosage could be adjusted if necessary, and also at 3 to 4 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 (see section 4.2 Dose and method of administration).

In order to measure the peak level, a serum sample should be drawn about 30 minutes after completion of the intravenous infusion or 1 hour after an intramuscular injection. Trough levels are measured by obtaining serum samples 8 hours after the dose 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.

Use in the elderly

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

Paediatric use

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. In neonates, infants and children, dosage reductions may also be necessary to avoid toxicity. Eighth cranial nerve toxicity should also be monitored.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Potent diuretics

If possible, do not give tobramycin in conjunction with etacrynic acid, furosemide (frusemide) or other potent diuretics which may themselves cause ototoxicity or enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Other neurotoxic and/or nephrotoxic agents

Concurrent and sequential use of other nephrotic, neurotoxic or ototoxic drugs, should be avoided.

The concurrent or sequential use of other neurotoxic and/or nephrotoxic drugs may enhance neurotoxicity or nephrotoxicity of tobramycin. This includes antibiotics, particularly other aminoglycosides and cephalosporins, particularly neomycin, streptomycin, kanamycin, gentamicin, paromomycin, viomycin, vancomycin, amikacin and cefaloridine, as well as polymyxin B, colistin and cisplatin. Other factors that may increase patient risk are advanced age and dehydration.

Beta-lactam antibiotics

Since aminoglycosides have been shown to be incompatible with some beta-lactams (penicillins and cephalosporins) *in vitro,* these antibiotics should be administered separately if both are required. Antagonism *in vivo* has been reported only in a few patients with severe renal impairment, in whom aminoglycoside activity was diminished. This inactivation has not been found in patients with normal renal function who have been given the drugs by separate routes of administration.

Neuromuscular blocking agents or other medications with neuromuscular blocking activity

Care is required if other drugs with a neuromuscular blocking action are given concomitantly with aminoglycosides (see section 4.4 Special warnings and precautions for use, Use during anaesthesia). The neuromuscular blocking properties of aminoglycosides may be sufficient to provoke severe respiratory depression in patients receiving general anaesthetics or opioids.

Cephalosporins

There is an increased risk of nephrotoxicity when tobramycin is used in conjunction with cephalosporins, particularly cefalotin.

Cisplatin/Ciclosporin

There is an increased risk of nephrotoxicity and possibly ototoxicity with cisplatin, and an increased risk of nephrotoxicity with ciclosporins.

Skeletal muscle relaxants

Enhanced neuromuscular blockade and respiratory paralysis may occur if tobramycin is given in conjunction with skeletal muscle relaxants such as suxamethonium, tubocurarine or decamethonium. This should be treated with calcium infusions.

Warfarin and phenindione

Tobramycin has been known to potentiate the effects of warfarin and phenindione.

Neostigmine and pyridostigmine

Antagonism of the effects of neostigmine and pyridostigmine.

Other

Amphotericin B

May produce renal toxicity by synergism.

Methoxyflurane

May produce additive or synergistic nephrotoxicity. Renal impairment may appear at lower than usual dosage levels of the drug.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy – Category D

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

Tobramycin and other aminoglycoside antibiotics cross the placenta membrane producing fetal serum levels 25 to 50% of those found in maternal serum and can cause fetal harm when administered to a pregnant woman. There is evidence of selective uptake of aminoglycosides by the fetal kidney resulting in cellular damage (probably reversible) to immature nephrons. Eighth cranial nerve damage has also been reported following in utero exposure to some of the aminoglycosides. Because of their chemical similarity, aminoglycosides must be considered potentially nephrotoxic and ototoxic to the fetus. It should also be noted that therapeutic blood levels in the mother do not equate with safety for the fetus.

The daily subcutaneous administration of tobramycin doses as great as 100 mg/kg to rats had no adverse effect on fertility or reproduction, nor did it affect fetal development. Daily subcutaneous doses of 20 - 40 mg/kg to pregnant rabbits caused anorexia, weight loss, and renal injury. Fifteen percent of the animals of the 20 mg/kg group and 85 percent of those of the 40 mg/kg group died or aborted. Fetal development appeared normal in these animals at the time of death or abortion. No drug-related abnormalities were noted in any of the progeny, despite the maternal toxicity.

Serious side effects to mother, fetus or newborn have been reported in the treatment of pregnant women with aminoglycosides (e.g. several reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy). Tobramycin

should not be administered to the pregnant patient unless the potential benefits clearly outweigh any potential risk. If tobramycin is used during pregnancy or if the patient becomes pregnant while taking tobramycin, she should be informed of the potential hazard to the fetus.

Use in lactation

Tobramycin is excreted in the breast milk with concentrations of 0.60 and 0.85 micrograms/mL at one and eight hours after an intramuscular dose of 80 mg. Because of the potential risk to the newborn it is recommended that breastfeeding be discontinued during therapy.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. Patients should refrain from driving or using machines until they know that the medicinal product does not negatively affect these abilities.

4.8 Adverse effects (undesirable effects)

As with other aminoglycosides, ototoxicity and nephrotoxicity can occur. The risk of adverse effects is increased in patients with poor renal function, the elderly, patients on prolonged treatment or with serious underlying pathology.

Tobramycin ototoxicity presents as vestibular dysfunction with or without high frequency hearing loss, similar to that of other aminoglycosides. In addition it may produce transient cochlear toxicity, perhaps due to a metabolic block.

More common adverse reactions

Ear and labyrinth disorders

Ototoxicity occurs as the drug penetrates into the inner ear during periods of high serum concentration. Both auditory and vestibular branches of the eighth cranial nerve may be adversely affected. Ototoxicity initially manifests as vestibular dysfunction with or without loss of high-tone activity, similar to that of other aminoglycosides. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss. Hearing loss is usually irreversible. Ototoxic damage may progress in some patients even after the drug is discontinued. Factors associated with increased incidence of ototoxicity include advanced age, underlying renal disease, previous auditory damage, duration of treatment, elevated body temperature, low haematocrit, severity of illness and total dose of drug.

Renal and urinary disorders

Patients with pre-existing renal impairment who are treated for longer periods or with higher doses than those recommended are at greater risk. Nephrotoxicity and acute kidney injury manifests as changes in renal function: rising serum urea, blood urea nitrogen (BUN), nonprotein nitrogen (NPN) and serum creatinine and by oliguria, cylindruria, and increased proteinuria. This has been reported especially in patients with a history of renal impairment who are treated for longer periods or with higher doses than those recommended. Nephrotoxicity may be increased by the concurrent administration of other drugs (see section 4.5 Interactions with other medicines and other forms of interactions). Patients with pre-

existing renal impairment are at greatest risk. Adverse renal effects can occur in patients with initially normal renal function.

Gastrointestinal disorders

Nausea, vomiting and diarrhoea.

Less common reactions

Musculoskeletal

The aminoglycosides are known to possess neuromuscular blocking effects and to be capable of exacerbating impairment of neuromuscular transmission in clinical conditions such as myasthenia gravis or severe hypocalcaemia, or when used in conjunction with nondepolarising neuromuscular relaxants such as d-tubocurarine.

Neuromuscular blockade may result in weakness of skeletal muscles and respiratory depression especially in patients with myasthenia gravis, severe hypocalcaemia or who have recently received other neuromuscular blocking agents. Peritoneal lavage with tobramycin could precipitate apnoea because high concentrations of drug come in contact with the diaphragm. Rarely blockade has been observed following intramuscular or intravenous injection. Tobramycin is usually safely used prior to surgery if given in recommended single doses.

Skin and subcutaneous tissue disorders

Maculopapular rash, urticaria, itching.

Rare reactions

Investigations

Some patients with malignant diseases have developed a complex metabolic syndrome of 2 to 8 weeks duration after administration of tobramycin, including hypocalcaemia, hypomagnesaemia, hypokalaemia, hypo-albuminaemia, hypophosphataemia and hypouricaemia.

Other reported abnormalities include increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum bilirubin and alkaline phosphatase.

Blood and lymphatic system disorders

Anaemia, granulocytopenia and thrombocytopenia; eosinophilia and leukopenia.

Immune system disorders

Fever, rash, itching, urticaria. Adverse effects on the immune response via inhibition of chemotaxis and microbicidal activity of phagocytes have been reported. Angioedema, exfoliative dermatitis, stomatitis and anaphylaxis are hypersensitivity reactions reported with aminoglycosides in general.

Nervous system and psychiatric disorders

Lethargy, mental confusion and disorientation. Acute brain syndrome has been reported in an elderly patient after four days of therapy with tobramycin. The delirium was reversed after drug discontinuance.

Neurotoxicity is rare with tobramycin. Peripheral neuropathy, paraesthesia and muscle weakness have been reported.

General disorders and administration site conditions

Pain after intramuscular administration and thrombophlebitis after intravenous administration.

Frequency not known (cannot be estimated from available data)

Blood and lymphatic system disorders

Leukocytosis.

Nervous system disorders

Dizziness, headache.

Investigations

Blood sodium decrease.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

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, age and whether or not other medications with similar toxicities are being administered concurrently. Toxicity may occur in patients treated for 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 to 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 or ototoxic 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 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 suxamethonium.

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

Treatment

In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in the patient. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but controlled or assisted ventilation may be necessary.

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 2 hours or whose renal function is abnormal may require more aggressive therapy. In such patients, haemodialysis may be beneficial.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Tobramycin is an aminoglycoside antibiotic obtained from cultures of *Streptomyces tenebrarius*.

Tobramycin is bactericidal in activity. It enters the cells via a complex active transport mechanism and exerts its activity primarily on the 30S ribosomal subunit, interfering with initial and subsequent steps in protein synthesis. It also acts to induce misreading of the genetic code of the mRNA template, resulting in incorporation of incorrect amino acids.

Tobramycin, in common with all other aminoglycosides, is primarily antibacterial against aerobic gram-negative bacilli. Tobramycin is considered more active than most other aminoglycosides against *Pseudomonas aeruginosa*.

Tobramycin is usually active against most strains of the following organisms:

- *Pseudomonas aeruginosa*
- Proteus species (indole-positive and indole-negative) including: *Pr. mirabilis*;
- *Pr. morganii; Pr. rettgeri* and *Pr. vulgaris*
- *Escherichia coli*
- Klebsiella, Enterobacter, Serratia species
- Citrobacter species
- Providencia species
- Staphylococci, including *Staph. aureus* (coagulase-positive and coagulase-negative).

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

Some strains of Group D *streptococci* are susceptible *in vitro* although most strains of *enterococci* show resistance. *In vitro* studies have shown that an aminoglycoside combined with an antibiotic which interferes with cell wall synthesis affects some group D streptococcal strains synergistically. The combination of benzylpenicillin and tobramycin results in a synergistic bactericidal effect *in vitro* against certain strains of *S. faecalis*. However, this combination is not synergistic against other closely related organisms, e.g. *S. faecium*. Specification of group D *streptococci* alone cannot, therefore, be used to predict susceptibility. Susceptibility testing and tests for antibiotic synergism are emphasised.

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

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Following intramuscular administration of a single dose of tobramycin 1 mg/kg in adults with normal renal function, peak plasma tobramycin concentrations averaging 4 to 6 micrograms per mL are obtained within 30 to 90 minutes; plasma concentrations of the drug are 1 microgram per mL or less at 8 hours. Following intravenous infusion of the same dose over 30 to 60 minutes, similar plasma concentrations of the drug are obtained. Tobramycin is poorly absorbed from the gastrointestinal tract. After injection tobramycin has been detected in body fluids but concentrations in the cerebrospinal fluid are low even when there is meningeal inflammation.

Distribution

Protein binding of tobramycin has been reported as zero.

Excretion

The major route of elimination is renal and the drug is eliminated almost entirely by glomerular filtration. The plasma elimination half-life of tobramycin is usually 2 to 3 hours in adults with normal renal function and is reported to range from 5 to 70 hours in adults with impaired renal function. In full-term infants the plasma elimination half-life is reported to average 4.6 hours and in low birth-weight infants it averages 8.7 hours.

Peak urine concentrations ranging from 75 to 100 micrograms per mL 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 amount administered. When renal function is impaired, excretion of tobramycin is slowed, and accumulation of the drug may cause toxic blood levels. In patients undergoing dialysis, 25 to 70% of the administered dose may be removed, depending on the duration and type of dialysis.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate

Sodium metabisulfite

Sulfuric acid

Water for injections

Sodium hydroxide

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

DBL Tobramycin Injection BP should be stored below 25°C. Protect from light.

6.5 Nature and contents of container

Strength	Pack Size
80 mg (80,000 IU) tobramycin/2 mL	5 vials

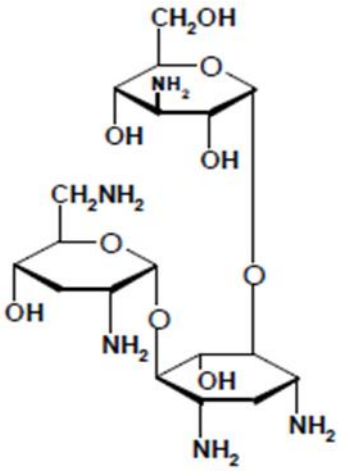
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Tobramycin is a white or almost white hygroscopic powder. It is freely soluble in water, very slightly soluble in alcohol and practically insoluble in chloroform and in ether.

Chemical structure



Chemical name: 6-*O*-(3-amino-3-deoxy-alpha-*D*-glucopyranosyl)-2-deoxy-4-*O*-(2,6-diamino-2,3,6-trideoxy-alpha-*D*-*ribo*-hexopyranosyl)-*D*-streptamine.

Molecular formula: $C_{18}H_{37}N_5O_9$

Molecular weight: 467.5

CAS number

32986-56-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

22 August 2000

10. DATE OF REVISION

16 December 2022

Summary Table of Changes

Section changed	Summary of new information
4.2	Addition of text for serum level determination in patients with extensive burns, longer treatment duration required, chronic infections e.g. cystic fibrosis, or decreased renal function. Extend time range for intravenous infusion.