NEW ZEALAND DATA SHEET

TOBRAMYCIN VIATRIS

1. Product Name

Tobramycin Viatris, 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 Viatris 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 discolouration 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 (reduce as soon as possible) 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

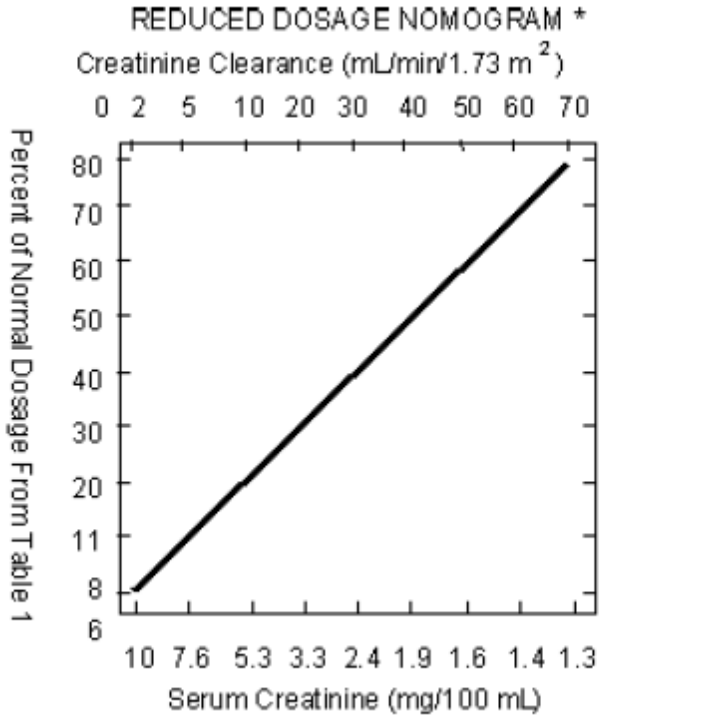
Administration for patients with impaired renal function

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.

Intrathecal administration.

4.4 Special warnings and precautions for use

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 pseudomembranous colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Therefore, patients with diarrhoea must be monitored carefully. Mild cases usually respond to medication 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 aminologlycoside antibiotics should be under close clinical observation because these medicines have an 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 medicine 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 recommended. Neurotoxicity in the form of 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 auditory 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. 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 spasms/twitching, and convulsions.

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 selective concentrated in renal cortical cells and it produces changes in proximal tubules. The medicine 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 of medication levels; serum creatinine and creatinine clearance; serum calcium, magnesium, potassium, sodium levels and blood urea nitrogen. The serum concentration of aminoglycosides must be monitored during treatment with a view to avoid potentially toxic concentrations. This is particularly important in patients with renal impairment. Urine must be analysed with regard to reduced density and increased sediment of protein, red and white blood cells, epithelial cells and cylinders.

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

Use in impaired renal, vestibular and/or auditory function

Evidence of impairment in renal, vestibular, and/or auditory function requires discontinuation of the medicine 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 medication, so dosage should be adjusted carefully on the basis of regular monitoring of serum medication 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 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 (see 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.

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 medicines 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 medication 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 excessive burns or cystic fibrosis, altered pharmacokinetics may result in reduced serum concentrations of aminoglycosides. 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 non-susceptible 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

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.

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

4.5 Interaction with other medicines and other forms of interaction

Other neurotoxic and/or nephrotoxic agents

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

The concurrent or sequential use of other neurotoxic and/or nephrotoxic medicines may enhance neurotoxicity or nephrotoxicity of tobramycin. This includes antibiotics, particularly other aminoglycosides and cefalosporins, 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 as advanced age and dehydration.

Potent diuretics

Tobramycin must not be given in conjunction with etacrynic acid, furosemide or other potent diuretics which may themselves cause ototoxicity or enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Beta-lactam antibiotics

Since aminoglycosides have been shown to be incompatible with some ß-lactam (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 medicines by separate routes of administration.

Neuromuscular blocking agents or other medications with neuromuscular blocking activity

Care is required if other medicines with a neuromuscular blocking action are given concomitantly with aminoglycosides (see section 4.4). The neuromuscular blocking properties of aminoglycosides may be sufficient to provoke neuromuscular blockade, severe respiratory paralysis and/or depression in patients receiving general anaesthetics, opioids or skeletal muscle relaxants.

Cefalosporins

There is an increased risk of nephrotoxicity when tobramycin is used in conjunction with cefalosporins, 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 medication.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category D

Category D: Medications 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 medications may also have adverse pharmacological effects. Accompanying text above 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 update 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 medication-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.

Breastfeeding

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 if the potential risk (e.g. ototoxicity and/or nephrotoxicity) 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 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 medicine 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, cochlear involvement with tinnitus, distorted auditory perception, roaring in the ears and hearing loss. Hearing loss is usually irreversible. Ototoxic damage may progress in some patients even after the medicine 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 medicine.

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 medicines (see section 4.5). 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, diarrhoea, oral fungal infection.

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 medication 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 medication 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 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://pophealth.my.site.com/carmreportnz/s/.

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 or ototoxic 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 overdosage, consider the possibility of multiple medicine overdoses, interaction among medicines, and unusual medication kinetics in your 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 tobramcyin 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 morganii, 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

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 medication 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 medication 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 medication 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 average 8.7 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. In patients undergoing dialysis, 25% to 70% of the administered dose may be removed, depending on the duration and type of dialysis.

6. Pharmaceutical Particulars

6.1 List of excipients

Tobramycin Viatris 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.

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.

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

Viatris Ltd
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9. Date of First Approval

18 February 2016

10. Date of Revision of the Text

17 September 2024

Summary table of changes

Section	Summary of new information
All	Replacement of the word “drug” to “medication Minor editorial changes Minor formatting changes
4.4	Addition of warning regarding diarrhoea Additional information regarding nephrotoxicity
4.5	Updated information regarding conjunction use with diuretics and/or neuromuscular blocking agents
4.6	Example of risks if Tobramycin is used during breastfeeding
4.8	Updated symptoms of ototoxicity Addition of oral fungal infection as an ADR Updated ADR reporting website