Tobromycin Injection USP 20mg/2ml, 80mg/2ml, USP 1.2g/30ml

1. Name of the medicinal product

Tobromycin Injection USP 20mg/2ml Taj Pharma

Tobromycin Injection USP 80mg/2ml Taj Pharma

Tobromycin Injection USP 1.2g/30ml Taj Pharma

2. Qualitative and quantitative composition

a) Tobromycin Injection USP 20mg/2ml
Each ml contains:

Tobramycin sulfate equivalent to Tobramycin	**10mg**
Phenol	**5mg**
Sodium metabisulfide	**3.2mg**
EDTA disodium	**0.1mg**
Water for injection	**q.s**
Sulfuric acid for pH adjustment	

b) Tobromycin Injection USP 80mg/2ml
Each ml contains:

Tobramycin sulfate equivalent to Tobramycin	40mg
Phenol	5mg
Sodium metabisulfide	3.2mg
EDTA disodium	0.1mg
Sulfuric acid for pH adjustment	
Water for injection	q.s

c) Tobromycin Injection USP 1.2g/30ml
Each ml contains:

Tobramycin sulfate equivalent to Tobramycin	40mg
Phenol	5mg
Sodium metabisulfide	3.2mg
EDTA disodium	0.1mg
Sulfuric acid for pH adjustment	
Water for injection	q.s

Excipient(s) with known effect
Sodium metabisulfite: 1.4 mg/ml

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

A sterile, clear, colourless, aqueous solution for injection filled into rubber-stoppered vials.

4. Clinical particulars

4.1 Therapeutic indications
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Tobramycin Injection is indicated for the treatment of the following infections caused by susceptible micro-organisms:

Central nervous system infections, including meningitis, septicaemia and neonatal sepsis

Gastro-intestinal infections, including peritonitis, and other significant infections such as complicated and recurrent urinary tract infections, including pyelonephritis and cystitis

Lower respiratory tract infections, including pneumonia, bronchopneumonia and acute bronchitis

Skin, bone and soft tissue infections, including burns

Tobramycin Injection may be considered in serious staphylococcal infections for which penicillin or other less potentially toxic drugs are contra-indicated and when bacterial susceptibility testing and clinical judgement indicate its use.

See section 5.1 for species clinical breakpoints and prevalence of resistance of commonly susceptible bacterial species.

4.2 Posology and method of administration

Posology

The intramuscular dose is the same as the intravenous dose.

It is recommended that both peak and trough serum levels should be determined whenever possible to ensure the correct dosage is given. 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.

Patients with normal renal function

Adults: The usual recommended dosage for adults with serious infections is 3mg/kg/day, administered in three equal doses every eight hours (Table 1). For life-threatening infections, dosages up to 5mg/kg/day may be administered in three or four equal doses. The dosage should be reduced to 3mg/kg/day as soon as clinically indicated. To prevent increased toxicity due to excessive blood levels, dosage should not exceed 5mg/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 10mg/kg/day in equally divided doses. Because serum concentrations of tobramycin vary from one patient to another, serum levels should be monitored.

Table 1: DOSAGE SCHEDULE GUIDE FOR ADULTS WITH NORMAL RENAL FUNCTION (Dosage at 8-Hour Intervals)

Patient Weight kg	**Usual dose for serious infections 1mg/kg q 8 h (total 3mg/kg/day)**		**Maximum dose for life-threatening infections (reduce as soon as possible) 1.66mg/kg q 8 h (total 5mg/kg/day unless monitored)**	
	mg/dose	**ml/dose***	**mg/dose**	**ml/dose***
120	120	3.0	200	5.0
100	100	2.5	166	4.0
80	80	2.0	133	3.0
60	60	1.5	100	2.5
40	40	1.0	66	1.6

*Applicable to 40mg/ml product forms.

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

The elderly: As for adults, but see recommendations for patients with impaired renal function.

Obese patients: The appropriate dose may be calculated using the patient's estimated lean body weight, plus 40% of the excess, as the weight on which to determine mg/kg.

Paediatric population

Children: The recommended dosage is 6-7.5mg/kg/day, administered in three or four equally divided doses. In some patients it may be necessary to administer higher doses.

Premature or full-term neonates: Dosages of up to 4mg/kg/day may be administered in two equal doses every 12 hours, for those between 1.5 and 2.5kg body weight.

The usual duration of treatment is 7 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 for longer than 10 days.

Patients with impaired renal function

Following a loading dose of 1mg/kg, subsequent dosage in these patients must be adjusted, either with lower doses administered at eight-hour intervals or with normal doses at prolonged intervals (Table 2). Both of these regimens 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. Neither regimen should be used when dialysis is being performed.

Reduced dosage at eight-hour intervals (Regimen I): An appropriately reduced dosage range can be found in the accompanying table (Table 2) for any patient for whom the blood urea, creatinine clearance or serum creatinine values are known. The choice of dose within the indicated range should be based on the severity of the infection, the sensitivity of the pathogen, and individual patient considerations, especially renal function. An alternative 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 value (mg/100ml).

Normal dosage at prolonged intervals (Regimen II): Recommended intervals between doses are given in the accompanying table (Table 2). As a general rule, the dosage frequency in hours can be determined by multiplying the patient's serum creatinine level (mg/100ml) by six.

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 (see section 4.4).

Table 2: TWO MAINTENANCE REGIMENS BASED ON RENAL FUNCTION AND BODY WEIGHT FOLLOWING AN INITIAL DOSE OF 1MG/KG*

Renal function†					**Regimen I or**		**Regimen II**
					Adjusted doses at 8-hour intervals		**Normal dosage at prolonged intervals**
Blood urea		**Serum creatinine**		**Creatinine clearance**	**Weight**		**Weight/Dose**
mg/100ml	mmol/l	mg/100ml	mcmol/l	ml/min	50-60 kg	60-80 kg	50-60kg: 60mg 60-80kg: 80mg
Nor							

mal:							
<42	<7.0	<1.3	<114.9	>70	60 mg	80 mg	q 8 h
42-74	7.0-12.3	1.4-1.9	123.8-168	69-40	30-60 mg	50-80 mg	q 12 h
75-105	12.5-17.5	2.0-3.3	176.8-291.7	39-20	20-25 mg	30-45 mg	q 18 h
106-14	17.7-23.3	3.4-5.3	300.6-468.5	19-10	10-18 mg	15-24 mg	q 24 h
141-160	23.5-26.7	5.4-7.5	477.4-663	9-5	5-9mg	7-12 mg	q 36 h
>160	>26.7	>7.6	>671.8	<4	2.5-4.5 mg	3.5-6 mg	q 48 h§

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

†If used to estimate degree of renal impairment, blood urea and serum creatinine concentrations should reflect a steady state of renal uraemia.

§When dialysis is not being performed.

Following IM administration of a single dose of tobramycin of l mg/kg in adults with normal renal function, peak plasma tobramycin concentrations averaging 4-6 micrograms/ml are attained within 30-90 minutes; plasma concentrations of the drug are 1 microgram/ml or less at 8 hours. Following intravenous infusion of the same dose over 30-60 minutes, similar plasma concentrations of the drug are obtained.

In neonates, average peak plasma tobramycin concentrations of about 5 micrograms/ml are attained 30-60 minutes after a single IM dose of 2 mg/kg; plasma concentrations average 1-2 micrograms/ml at 12 hours.

Method of administration

Tobramycin Injection may be given intramuscularly or intravenously. The patient's pre-treatment body weight should be obtained for calculation of correct dosage.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Intrathecal administration.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to any aminoglycoside is a contra-indication to the use of tobramycin because of the known cross-allergenicity of drugs in this class.

4.4 Special warnings and precautions for use

Warnings

Tobramycin Injection contains sodium metabisulfite which 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, but it occurs more frequently in asthmatic patients.

Patients treated with tobramycin should be under close observation because tobramycin and other aminoglycoside antibiotics have an inherent potential for causing nephrotoxicity and ototoxicity.

Both vestibular and auditory ototoxicity can occur. The auditory changes are irreversible, are usually bilateral, and may be partial or total. 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. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching and convulsions. The risk of aminoglycoside-induced hearing loss increases with the degree of exposure to either high peak or high trough serum concentrations. Patients who develop cochlear damage may not have symptoms during therapy to warn them of eighth-nerve toxicity, and partial or total irreversible bilateral deafness may continue to develop after the drug has been discontinued. Rarely, nephrotoxicity may not become manifest until the first few days after cessation of therapy. Aminoglycoside-induced nephrotoxicity is usually reversible.

Therefore, renal and eighth cranial 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. Evidence of impairment in renal, vestibular and/or auditory function requires discontinuation of the drug or dosage adjustment.

Monitoring of renal function is particularly important in elderly patients who may have reduced renal function that may not be evident in the results of routine screening tests, such as blood urea or serum creatinine. A creatinine clearance determination may be more useful.

Serum concentrations should be monitored when feasible, and prolonged concentrations above 12mg/l should be avoided. Rising trough levels (above 2mg/l) may indicate tissue accumulation. 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 intervals adjusted according to the guidelines provided in the 'Posology and Method of Administration' section.

In order to measure the peak level, a serum sample should be drawn about 30 minutes following intravenous infusion or at one hour after intramuscular injection. Trough levels are measured by obtaining serum samples at eight hours or just prior to the next dose of tobramycin.

Urine should be examined for increased excretion of protein, cells and casts. Serum creatinine or creatinine clearance (preferred over blood urea) 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.

The risk of toxic reactions is low in patients with normal renal function who do not receive tobramycin in higher doses or for longer periods of time than those recommended.

Patients with reduced renal function, however, 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.

Precautions

General: Serum calcium, magnesium, and sodium should be monitored. It is particularly important to monitor serum levels closely in patients with known renal impairment.

In patients with extensive 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.

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.

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.

Neuromuscular blockade or respiratory paralysis may occur following rapid intravenous administration of many aminoglycosides and have been reported in cats receiving very high doses of tobramycin (40mg/kg). The possibility of prolonged secondary apnoea 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.

The inactivation of tobramycin by beta-lactam 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 if the drugs are administered by separate routes.

If overgrowth of non-susceptible organisms occurs, appropriate therapy should be initiated.

Paediatric population

Use in neonates: 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.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent and/or sequential use of other potentially neurotoxic and/or nephrotoxic drugs, particularly other aminoglycosides (eg, amikacin, streptomycin, neomycin, kanamycin, gentamicin and paromomycin), amphotericin B, cephaloridine, viomycin, polymyxin B, colistin, cisplatin and vancomycin, requires careful monitoring. Other factors that may increase patient risk are advanced age and dehydration.

Tobramycin should not be given concurrently with potent diuretics. Some

diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Antibacterials: Tobramycin used in conjunction with other antibacterials such as cephalosporins notably cephalothin, there is an increased risk of nephrotoxicity.

Muscle Relaxants: Enhanced blockade of respiratory paralysis can occur with skeletal muscle relaxants.

Cytotoxics and Cyclosporins: There is increased risk of nephrotoxicity and possibly ototoxicity with Cisplatin as well as increased risk of nephrotoxicity with cyclosporins.

Tobramycin has been known to potentiate warfarin and phenindione.

Cholinergics: Antagonism of effect of neostigmine and pyridostigmine.

4.6 Fertility, pregnancy and lactation

Pregnancy

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, but 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 whilst taking tobramycin, she should be informed of the potential hazard to the foetus.

Breast-feeding

Tobramycin is excreted in the breast milk and should be avoided in nursing women.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Renal function changes, as shown by rising blood urea 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. These changes can occur in patients with initially normal renal function.

Side-effects on both vestibular and auditory branches of the eighth cranial nerve have been reported, 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.

Other reported side-effects, possibly related to tobramycin, include increased AST, ALT and serum bilirubin; decreased serum calcium, magnesium, sodium and potassium; anaemia, granulocytopenia, thrombocytopenia, leucopenia, leucocytosis and eosinophilia; and fever, rash, exfoliative dermatitis, itching, urticaria, nausea, vomiting, diarrhoea, headache, lethargy, pain at the injection site, mental confusion and disorientation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

4.9 Overdose

Signs and Symptoms: Severity of the manifestations of a tobramycin overdose depend on the dose, the patient's renal function, state of hydration, age and whether concurrent medication with similar toxicities is being given. Toxicity may occur in patients treated for more than 10 days, given more than 5mg/kg/day, children given more than 7.5mg/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 AUC of serum concentration versus time. Nephrotoxicity is more likely if trough levels fail to fall below 2mg/l and is also proportional to the average blood concentration. Patients who are elderly, have renal impairment, 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 on other ototoxic drugs. These patients may not have signs or symptoms, or may experience dizziness, tinnitus, vertigo and a loss of high-tone acuity. Signs and symptoms may not occur until long after the drug has been discontinued.

Neuromuscular blockade or respiratory failure may occur following rapid intravenous administration of many aminoglycosides. These reactions and prolonged respiratory paralysis may occur more commonly in patients with myasthenia gravis or Parkinson's disease, or those receiving decamethonium, tubocurarine or succinylcholine. Neuromuscular blockade may be reversed by the administration of calcium salts, but mechanical assistance may be necessary.

Toxicity from ingested tobramycin is unlikely because aminoglycosides are poorly absorbed from an intact gastro-intestinal tract.

Treatment: Resuscitative measures should be initiated promptly if respiratory paralysis occurs. Neuromuscular blockade may be reversed by giving calcium salts. Fluid balance, creatinine clearance and tobramycin plasma levels should be carefully monitored until the tobramycin level falls below 2mg/l. Haemodialysis or peritoneal dialysis will help remove tobramycin from the blood. Between 25% and 70% of the administered dose may be removed, depending on the duration and type of dialysis employed; haemodialysis is the more effective method.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aminoglycoside antibacterials.

Mechanism of action

in vitro tests demonstrate that tobramycin is bactericidal and that it acts by inhibiting the synthesis of protein in bacterial cells.

EUCAST Clinical MIC Breakpoints

The non-species related breakpoints for susceptible (S) and resistant (R) species are: S≤ 2mg/L and R > 4mg/L

For Enterobacteriacaea	S< 2mg/L and R > 4mg/L
For Pseudomonas For Acinetobacter	S< 4mg/L and R > 4mg/L
For Staphylococcus	S< 4mg/L and R > 4mg/L
	S< 1mg/L and R > 1mg/L

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly Susceptible Species
Gram-positive aerobes
Staphylococcus aureus
Staphylococcus coagulase negative
Staphylococcus saprophyticus
Gram-negative aerobes
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Enterobacter sakazakii
Enterobacter spp
Escherihia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Klebsiella spp
Morganella morganii
Proteus mirabilis
Proteus spp
Proteus vulgaris
Pseudomonas aeruginosa
Species for which acquired resistance may be a problem
Gram-positive aerobes
Staphylococcus capitis
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
Staphylococcus lugdunensis
Staphylococcus warnerii
Gram-negative aerobes
Citrobacter spp – other
Klebsiella ozaenae
Serratia liquefaciens
Serratia marcescens
Serratia spp

Inherently resistant organisms

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 emphasised.

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

The combination of tobramycin and carbenicillin is synergistic in vitro against most strains of Ps. aeruginosa. Other Gram-negative organisms may be affected synergistically by the combination of tobramycin and a cephalosporin.

5.2 Pharmacokinetic properties
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 'Posology and Method of Administration'). 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 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.

5.3 Preclinical safety data
There are no preclinical data of relevance to the prescriber.

6. Pharmaceutical particulars

6.1 List of excipients
Phenol, Sodium metabisulfite, Disodium edetate

Water for injection, Sulfuric acid

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
Two years

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Rubber stoppered glass vials in individual cartons.

6.6 Special precautions for disposal and other handling
Prior to administration, parenteral drug products should be inspected visually for particulate matter and discolouration whenever solution and container permit.

Intramuscular administration: Tobramycin Injection may be administered by withdrawing the appropriate dose directly from the vial.

Intravenous administration: For intravenous administration, the usual volume of diluent (0.9% Sodium Chloride Intravenous

Infusion BP or 5% Dextrose Intravenous Infusion BP) for adult doses is 50-100ml. For children, the volume of diluent should be proportionately less than for adults. The diluted solution should be infused over a period of 20-60 minutes avoiding admixture with any other drug. Tobramycin Injection may be administered slowly by direct intravenous injection or into the tubing of a drip set. When given in this way, serum levels may exceed 12mg/l for a short time (see 'Contra-indications, Warnings, etc.').

No special requirements for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7.Manufactured in India by:

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