Package leaflet: Information for the user

Tobramycin Injection 40 mg/ml

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1 What Tobramycin Injection is and what it is used for

Tobramycin Injection is a vial containing a solution for injection of the active ingredient tobramycin, which is an antibiotic.

Tobramycin Injection is used to treat the following infections caused by micro-organisms that can be killed by tobramycin:

- blood poisoning
- infection of the lining of the brain and other infections of the nervous system
- infection of the wall of the abdomen and other infections of the digestive system
- infection of the kidneys, bladder, and other infections of the urinary tract which have been difficult to treat with other antibiotics
- infection of lung tissue, the airways and other infections of the lower respiratory tract
- skin, bone and soft tissue infections, including burns.

2 What you need to know before you are given Tobramycin Injection

You should not be given Tobramycin Injection if:

- you are allergic to tobramycin, any aminoglycoside (similar antibiotic) or any of the other ingredients of this medicine (listed in section 6). An allergic reaction may include rash, itching, difficulty breathing or swelling of the face, lips, throat or tongue.

Tobramycin Injection must only be injected into a muscle or vein.

Warnings and precautions

Tell your doctor if you:

- have ever had an allergic reaction to a sulfate or bisulfite (preservatives)
- have a kidney disorder or need dialysis (you may need a reduced dose, especially if you are elderly)
- have a muscle disorder, such as myasthenia gravis, or Parkinson's disease
- are elderly or dehydrated (needing fluids).
- or your family members have a mitochondrial mutation disease (condition caused by variants in the genome of mitochondria, the parts of your cells which help make energy) or loss of hearing due to antibiotic medicines; certain mitochondrial mutations may increase your risk of hearing loss with this product.

Tobramycin Injection should be used with caution in premature and neonatal infants, and also in patients with extensive burns.

Tell your doctor if any of the above applies to you before this medicine is given to you.

Other medicines and Tobramycin Injection

Tell your doctor if you are taking, have recently taken or might take any other medicines. In particular, the following medicines may interact with this medicine:

- other aminoglycosides (similar antibiotics such as amikacin, streptomycin, neomycin, kanamycin, gentamicin or paromomycin)
- other antibiotics such as amphotericin B, cephaloridine, viomycin, polymyxin B, colistin, vancomycin, and cephalosporin antibiotics (such as cephalothin)
- cisplatin (a drug used for chemotherapy)
- diuretics (water tablets)
- medicines used as muscle relaxants during general anaesthesia.
- ciclosporin (used to reduce the activity of the immune system)
- neostigmine and pyridostigmine (for the treatment of muscle weakness)
- warfarin and phenindione (used to thin the blood).

It may still be alright for you to be given Tobramycin Injection and your doctor will be able to decide what is suitable for you.

Pregnancy, breast-feeding and fertility

You should not have Tobramycin Injection if you are pregnant unless your doctor tells you to. Tobramycin may harm the unborn baby.

You should not have Tobramycin Injection if you are breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Following rapid injection, Tobramycin Injection may cause muscle weakness or certain muscles not to work, and so may affect your ability to drive or use machines. If you are affected, you should not drive or operate heavy machinery until you feel it is safe to do so.

Tobramycin Injection contains Sodium metabisulfite (E223)

May rarely cause severe hypersensitivity reactions and bronchospasm (difficulty in breathing).

Information about Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium free'.

3 How you are given Tobramycin Injection

Dosage

A doctor or nurse will give you Tobramycin Injection.

INFORMATION FOR THE HEALTH CARE PROFESSIONAL

1. NAME OF THE MEDICINAL PRODUCT

Tobramycin Injection 40mg/1ml

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 intravenous and intramuscular 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. 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 recommended 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: TOBRAMYCIN MAINTENANCE REGIMENS BASED ON RENAL FUNCTION AND BODY WEIGHT FOLLOWING AN INITIAL DOSE OF 1mg/kg*

Renal function†			Regimen I Adjusted doses at 8 hour intervals		Regimen II Normal dosage at prolonged intervals	
Blood urea	Serum creatinine	Creatinine clearance	Weight		Weight/Dose	
mg/100ml mmol/l	mg/100ml mcmol/l	ml/min	50-60kg	60-80kg	50-60kg: 60mg 60-80kg: 80mg	
Normal:						
<42	<7.0	<1.3	<114.9	>70	60mg	80mg q 8 h
42-74	7.0-12.3	1.4-1.9	123.8-168	69-40	30-60mg	50-80mg q 12 h
75-105	12.5-17.5	2.0-3.3	176.8-291.7	39-20	20-25mg	30-45mg q 18 h
106-140	17.7-23.3	3.4-5.3	300.6-468.5	19-10	10-18mg	15-24mg q 24 h
141-160	23.5-26.7	5.4-7.5	477.4-663	9-5	5-9mg	7-12mg q 36 h
>160	>26.7	>7.6	>671.8	<4	3.5-4.5mg	3.5-6mg 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 I 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 2mg/kg; plasma concentrations average 1-2 micrograms/ml at 12 hours.

Method of administration

Tobramycin 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 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. 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 may need to be considered.

Both vestibular and auditory ototoxicity can occur. The auditory changes are irreversible and 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.

May rarely cause severe hypersensitivity reactions and bronchospasm. This medicinal product contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

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 pheninidone.

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. It allows continues monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard.

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, ATC code: J01GB01

Mode 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	S< 4mg/L and R > 4mg/L
For Acinetobacter	S< 4mg/L and R > 4mg/L
For Staphylococcus	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	Gram-negative aerobes
Staphylococcus aureus	*Citrobacter freundii*
Staphylococcus coagulase negative.	*Citrobacter koseri*
	Enterobacter aerogenes
Staphylococcus saprophyticus	*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	Gram-negative aerobes
Staphylococcus capitis	*Citrobacter spp - other*
Staphylococcus epidermidis	*Klebsiella ozaenae*
Staphylococcus haemolyticus	*Serratia liquefaciens*
Staphylococcus hominis	*Serratia marcescens*
Staphylococcus lugdunensis	*Serratia spp*
Staphylococcus warneri	

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 succinylcholine. Distribution 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

6.6 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

10. DATE OF REVISION OF THE TEXT

July 2021

FLYNN PHARMA LTD

The recommended dose is:

Adults: 3mg per kg of body weight every 24 hours, given as 3 doses of 1mg per kg of body weight every 8 hours. If you have a serious bacterial infection, your doctor may use larger doses.

Use in children and adolescents

Children: 6 to 7.5mg per kg of body weight every 24 hours, given as 3 or 4 equal doses.

Premature or new-born babies: Up to 4mg per kg of body weight every 24 hours, given as 2 equal doses every 12 hours.

Kidney disorder: If you have a kidney disorder, your doctor will reduce your dose. This may happen during your treatment.

The usual length of treatment is 7 to 10 days. If you are treated for longer than this, your doctor will need to test your kidneys and ears because they may be damaged by the treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very serious side effects

All medicines can cause allergic reactions, although serious allergic reactions are very rare. Tell your doctor straight away if you get any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body), or any of the following:

- severe peeling skin (exfoliative dermatitis)
- ringing or roaring in one or both ears (tinnitus)
- hearing loss in one or both ears
- dizziness
- sensation of spinning (vertigo)
- muscle twitching
- numbness or pins and needles
- fits
- changes in the number of different types of blood cells. You may notice unexplained bleeding or bruising (caused by low platelets) or are unable to fight off infections (reduced levels of white blood cells), feel tired all the time (reduced blood cells, anaemia) or have sudden fever or sore throat.*

These are serious side effects, and you may only notice them after you stop treatment. You should see your doctor immediately.

The following side effects have also been reported:

- effects on the kidneys causing an increase in waste products in the blood which are normally eliminated by them or the kidneys not to work properly
- reduced or no urine production
- cloudy urine (caused by protein or granules).

If you notice changes in your urine or the number of times you need to urinate, tell your doctor straight away.

Other side effects reported are:

- headache
- tiredness
- confusion and disorientation
- fever
- rash (with no other symptoms)
- itching
- feeling sick
- being sick
- diarrhoea
- pain at the injection site
- raised liver enzymes*
- the amount of calcium, magnesium, sodium and potassium in your blood may decrease (symptoms are muscle weakness, muscle cramps, feeling thirsty all the time, drinking all the time, urinating frequently, vomiting and, possibly, having a fit)*

*(these conditions would be detected in a blood test carried out by a doctor).

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store Tobramycin Injection

Your doctor or pharmacist knows how to store Tobramycin Injection.

Keep this medicine out of the sight and reach of children.

Store below 25°C.

Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use.These measures will help protect the environment.

6 Contents of the pack and other information

What Tobramycin Injection contains

Each 1ml solution contains 40mg of the active substance tobramycin.

The other ingredients are: phenol, sodium metabisulfite, disodium edetate, water for injection, sulfuric acid.

What Tobramycin Injection looks like and contents of the pack

Tobramycin Injection is a clear, colourless solution provided in rubber stoppered glass vials in individual cartons.

Marketing Authorisation Holder

Flynn Pharma Ltd
5th Floor, 40 Mespil Road
Dublin 4, IRELAND, D04 C2N4

Manufacturer

Vianex SA
12th km National Road
Athens-Lamia, 14451
Metamorphossis Attiki
Athens, Greece.

This leaflet was last revised in May 2022.

FLYNN PHARMA LTD

Artwork for:	**Flynn Pharma Limited**
Product name:	Tobramycin Injection
PL/PA no:	PL 13621/0059
Type:	Leaflet
Artwork dimensions:	115mm x 530mm
Profile supplied:	No. Estimated
Date of first artwork:	11 March 2019
Reason for request:	MAH address change
Version no:	11FP
Date of revision:	6 May 2022
Colours:	As swatch(es)
Font(s):	8pt FF Zwo equivalent to 9pt Times New Roman
Artwork software:	InDesign CS6
Proof software:	PDF
BAC ref:	Z459 (formerly Y431)

Black