Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tobramycin 40 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 40 mg tobramycin.

Excipient with known effect
Each vial contains 2.4mg sodium metabisulphite (E223) per ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

Tobramycin Solution for injection (single dose regimen) is indicated in the treatment of the following serious infections caused by susceptible micro-organisms:

- The treatment of lower respiratory tract infections, including pneumonia, bronchopneumonia and acute bronchitis in adults with normal renal function. (see section 4.4).

4.2 Posology and method of administration

Posology

Tobramycin Solution for Injection may be given intramuscularly or intravenously and the dosage is the same for either route of administration. To calculate the correct dosage, the patient's pre-treatment bodyweight should be obtained.

To ensure the correct dosage is given, it is recommended that both peak and trough levels should be determined whenever possible. 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.

The usual length of treatment is seven to ten days. However, in difficult and complicated infections, a longer course of therapy may be necessary. In such cases monitoring of renal, auditory and vestibular functions is advised because neurotoxicity is more likely to occur when treatment is extended longer than ten days.

Patients with Normal Renal Function

Adults

For adults with serious infections the usual recommended dosage is 3 mg/kg/day, administered in three equal doses every eight hours (see Table 1).

Patients with life-threatening infections, dosages up to 5 mg/kg/day may be administered in three or four equal dosages. The dosage should be reduced to 3 mg/kg/day as soon as clinically indicated. Dosage should not exceed 5 mg/kg/day, unless serum levels are monitored in order to prevent increased toxicity due to excessive blood levels (see section 4.4).

Alternatively a dose of 3 - 5 mg/kg may be administered as a single daily dose (see section 4.4).

It may be necessary to administer up to 8 to 10 mg/kg/day in equally divided doses, or up to 15 mg/kg in a single daily dose to achieve therapeutic serum levels for patients with cystic fibrosis. Serum levels should be monitored because serum concentrations of tobramycin vary from patient to patient.

In adults with normal renal function, mild to moderate infections of the urinary tract have responded to a dosage of 2 - 3 mg/kg/day administered as a single intramuscular injection (see section 5.2) (see Table 1).

Table 1 Dosage schedule for adults with normal renal function

			(Dosage at 8-hour intervals)			
Patient Weight	Usual dose for Serious Infections 1 mg/kg q 8 h. (Total 3 mg/kg/day)		Maximum dose for Life-threatening Infections (Reduce as soon as possible) 1.66 mg/kg q 8 h. (Total 5 mg/kg/day - unless monitored)		Dose for single daily Administration 3 - 5 mg/kg q 24 h (Total 3 - 5 mg/kg/day)	
kg	mg/dose	ml/dose*	mg/dose	ml/dose*	mg/dose	ml/dose*
120	120	3.0	200	5.0	360-600	9.0-15.0
100	100	2.5	166	4.0	300-500	7.5-12.5
80	80	2.0	133	3.0	240-400	6.0-10.0
60	60	1.5	100	2.5	180-300	4.5-7.5
40	40	1.0	66	1.6	120-200	3.0-5.0

* Applicable to 40 mg/ml product forms.

Elderly

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

Paediatric population
The recommended dosage is 6 - 7.5 mg/kg/day, administered in 3 or 4 equally divided doses. It may be necessary to administer higher doses in some patients.

Premature or Full-term Neonates
Dosages of up to 4 mg/kg/day may be administered in two equal doses every 12 hours, for children between 1.5 and 2.5 kg body weight (see section 5.2).

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

Patients with Impaired Renal Function (see section 5.2)

Following a loading dose of 1 mg/kg, subsequent dosage must be adjusted, either with lower doses administered at 8 hr intervals or with normal doses at prolonged intervals, (see Table 2). Both 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.

REGIMEN I - Reduced dosage at 8-hour intervals

An appropriate reduced dosage range can be found in the accompanying table, (Table 2) for any patient for whom the creatinine clearance or serum creatinine values are known. The choice of dose within the indicated range should be based on the severity of the infection, the sensitivity of the pathogen, and individual patient considerations, especially renal function. Another rough guide for determining reduced dosage at 8-hour intervals, e.g. 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/100 ml).

REGIMEN II - Normal dosage at prolonged intervals

Table 2 illustrates the recommended intervals between doses. As a general rule, the dosage frequency in hours can be determined by multiplying the patient's serum creatinine level (expressed as mg/100 ml) 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 a loading dose of 1 mg/kg*

Renal Function °			Regimen I Adjusted doses at 8-hour intervals		or Regimen II Normal dosage at prolonged intervals
Serum Creatinine		Creatinine Clearance	Weight		Weight/Dose 50 – 60 kg: 60 mg 60 – 80 kg: 80 mg
mg/100 ml	mmol/litres	ml/min	50-60 kg	60 – 80 kg	
<1.3	<114.9	>70	60 mg	80 mg	q. 8h
1.4 – 1.9	123.8 – 168	69 – 40	30 – 60 mg	50 – 80 mg	q. 12h
2.0 – 3.3	176.8 – 291.7	39 – 20	20 – 25 mg	30 – 45 mg	q. 18h
3.4 – 5.3	300.6 – 468.5	19 – 10	10 – 18 mg	15 – 24 mg	q. 24h
5.3 – 7.5	477.4 – 663	9 – 5	5 – 9 mg	7 – 12 mg	q. 36h
> 7.6	> 671.8	< 4	2.5 – 4.5 mg	3.5 – 6 mg	q. 48h†

* 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.
o If used to estimate degree of renal impairment, serum creatinine concentrations should reflect a steady state of renal azotaemia
† When dialysis is not being performed.

Method of administration
Precautions to be taken before handling or administering the medicinal product.

Intramuscular administration

Tobramycin Solution for injection may be administered by withdrawing the appropriate dose directly from the vial.

Intravenous administration

Tobramycin Solution for Injection may be given by intravenous infusion or by direct intravenous injection. When given by infusion,Tobramycin injection may be diluted (with 0.9% Sodium Chloride Intravenous Infusion or 5% Dextrose Intravenous

Infusion) to volumes of 50 – 100 ml for adult doses. 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 solution for injection may be administered by direct intravenous injection or into the tubing of a drip set. When given in this way, serum levels may exceed 12 mg/L for a short time (see section 4.4).

4.3 Contraindications

Intrathecal administration/

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

Because of the known cross-allergenicity of drugs in this class, hypersensitivity to any aminoglycoside is a contraindication to the use of tobramycin.

Administration to patients receiving potent diuretics such as frusemide or ethacrynic acid which have proved to be ototoxic.

4.4 Special warnings and precautions for use

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

Ototoxicity
Both vestibular and auditory ototoxicity can occur. Eighth 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 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.

Patients who develop cochlear damage may not have symptoms during therapy to warn of eighth-nerve toxicity, and partial or total irreversible bilateral deafness may continue to develop after the drug has been discontinued.

Nephrotoxicity
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.

Renal impairment
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.

Elderly
In elderly patients, it is particularly important to monitor renal function, when reduced renal function 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 possible, and prolonged concentrations above 12 mg/L should be avoided. A useful guideline would be to perform serum level assays after 2 or 3 doses and also at 3 or 4 day intervals during therapy, so that the dosage could be adjusted if necessary. Rising trough levels (above 2 mg/L) may indicate tissue accumulation. Such accumulation and cumulative dose may contribute to ototoxicity and nephrotoxicity. 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 section 4.2. 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 8 hours or just prior to the next dose of tobramycin.

Paediatric use
Tobramycin should be used with caution and in reduced dosage in premature and full term neonates infants younger than 6 weeks of age because of their renal immaturity and the resulting prolongation of serum half-life of drug.

There is insufficient information concerning the use of Tobramycin as a single daily dose in neonates and children (other than those with cystic fibrosis) to support the use of this dosage regimen in these patients. If Tobramycin Solution for Injection is to be administered to these patients as a single dose, carefully monitoring of renal and auditory function is recommended.

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

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 possible, it is recommended that serial audiograms be obtained in patients old enough to be tested, particularly high-risk patients.

In patients with extensive burns or cystic fibrosis, altered pharmacokinetics may result in reduced serum drug levels. In such patients treated with tobramycin, measurement of serum concentration is especially recommended as a basis for determination of appropriate dosage.

Cross-allergenicity with other aminoglycosides may occur.

Administration
Aminoglycosides may be absorbed in significant quantities from body surfaces for 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.

Effect on neuromuscular function
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.

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

Neurotoxic and / or nephrotoxic drugs
Concurrent and sequential use of other nephrotoxic, neurotoxic or ototoxic drugs, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, cisplatin, vancomycin and amikacin, should be avoided. Advanced age and dehydration may also increase patient risk. The concurrent and sequential use of other nephrotoxic drugs increases the risk of acute renal failure.

Other special populations
There is insufficient information about the pharmacokinetics and/or pharmacodynamics of Tobramycin as a single daily dose in patients with endocarditis, neutropenia, severe burns and impaired renal function. If Tobramycin Solution for Injection is to be administered to these patients, it should be given in divided doses, 8 hourly to patients with normal renal function and according to the schedule in Table 2 in patients with impaired renal function.

Excipient information
Tobramycin Solution for injection contains sodium metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm. The overall prevalence of sulphite sensitivity in the general population is unknown and probably low, but it occurs more frequently in asthmatic patients.

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

4.5 Interaction with other medicinal products and other forms of interaction

Neurotoxic and/or nephrotoxic drugs
Concurrent and/or sequential use of other potentially neurotoxic and/or nephrotoxic drugs, particularly other aminoglycosides (e.g. amikacin, streptomycin, neomycin, kanamycin, gentamicin and paro-momycin), amphotericin B, cephaloridine, viomycin, polymixin B, colistin, cisplatin (increased risk of nephrotoxicity and ototoxicity) and vancomycin, requires careful monitoring. Other factors that may increase patient risk are advanced age and dehydration.

Cephalosporins
Tobramycin used in conjunction with other antibacterials such as cephalosporins (notably cephalothin) and cyclosporins, there is an increased risk of nephrotoxicity.

Diuretics
Tobramycin should not be given concurrently with potent diuretics (see Contraindications). Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and in tissue.

General anaesthetics and neuromuscular blocking agents
Tobramycin may manifest its neuromuscular blocking action clinically with the appearance of respiratory paralysis particularly if given to patients receiving muscle relaxants and anaesthesia.

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 (40 mg/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.

Beta-lactam antibiotics
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.

Warfarin and phenindione
Tobramycin has been known to potentiate warfarin and phenindione.

Neostigmine and pyridostigmine
Tobramycin may antagonise the effect of neostigmine and pyridostigmine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Aminoglycoside antibiotics cross the placenta and can cause foetal harm when administered to a pregnant woman. Serious side effects to mother, foetus or new-born 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, kanamycin and gentamicin 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 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

The effect of tobramycin on the ability to drive or use machines has not been systematically evaluated.

4.8 Undesirable effects

Generally, the side-effects are dose-related. The most important side-effects are ototoxic reactions and events of nephrotoxicity. Due to the lack of clinical information available for this product, the frequency data has been compiled based upon the frequencies reported in the innovator product, [1] with additional events included following requests of health authorities within the European Union, [2] and data collected from spontaneous reporting. The frequencies listed are approximate as there is insufficient clinical documentation to calculate them accurately. In some circumstances, the events have been assigned to a category of "Not known (cannot be estimated from the available data)".

In some cases, toxic reactions may first appear after treatment has been discontinued. As a rule, the hearing impairment is irreversible and, initially, manifests itself as the loss of hearing of high frequencies. Cases of skin and mucosal reactions including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported, however, the relationship is unclear.

	Common (≥1/100 to <1/10)	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very Rare (<1/10,000)**	**Not known**
Infections and infestations					Superinfection (with tobramycin-resistant bacteria), Oral fungal infection, Genital fungal infection (reported in females).
Blood and lymphatic system disorders	Eosinophilia	Leukocytosis	Anaemia, Granulocytopenia, Leukopenia, Thrombocytopenia		
Immune system disorders			Hypersensitivity[1], Anaphylactic reaction		
Nervous system disorders		Headache	Paraesthesia, Lethargy	Convulsion	Stupor
Psychiatric disorders			Confusional state, Disorientation		
Ear and labyrinth disorders	Cochlear function disorder, and Vestibular disorders (in patients with impaired renal function), Irreversible ototoxicity and/or vestibular toxicity (particularly during long-term treatment or at high doses).	Vestibular nerve damage, with effects including Dizziness, Vertigo, and cochlear effects with Tinnitus, Hypoacusis, and Hearing impaired (in patients with normal renal function).[2]			
Vascular disorders	Thrombo-phle bitis				
Respiratory, thoracic and mediastinal disorders		Dyspnoea, Rhonchi, Dysphonia, Cough, Pharyngitis	Sputum increased, Haemoptysis		
Gastrointestinal		Nausea,	Diarrhoea		

disorders		Vomiting			
Skin and subcurtaneous tissue disorders		Rash, Pruritus, Urticaria			
Musculoskeletal and connective tissue disorders				Muscular weakness or suppressed breathing through neuromuscular blockade. Muscle twitching	
Renal and urinary disorders	Effects on renal function in patients with impaired renal function. Oliguria	Effects on renal function in patients with normal renal function.[3]		Renal failure acute.	
General disorders and adminstration site conditions	Injection site reaction, Injection site pain.		Pyrexia		
Investigations	Transaminases increased, Blood urea increased, Blood creatinine increased	Blood alkaline phosphatase increased, Blood lactate dehydrogenase increased, Blood bilirubin increased	Blood calcium decreased, Blood magnesium decreased, Blood sodium decreased, and Blood potassium decreased		
Cardiac disorders			Palpitations		
Eye disorders			Blurred vision		

[1.] Hypersensitivity reactions of a varying degree of severity may occur, e.g, as Exanthema, Pruritus, Pyrexia, up to the point of Anaphylactic shock, or as Dermatitis exfoliative or Toxic epidermal necrolysis. Because of the sodium metabisulphite content, hypersensitivity reactions may also occur in rare cases, particularly in bronchial asthmatics. These may take the form of Bronchospasm, Vomiting, Diarrhoea, Wheezing, Asthma, Cognitive disorder, or Shock).

[2.] Undesirable effects affecting the vestibular and cochlear branches of the eighth cranial nerve were observed. These manifest themselves as rotary or staggering vertigo, roaring or ringing sounds in the ears and reduced hearing sensitivity. Hearing loss is normally irreversible and manifests itself first of all as reduced perception in the high-frequency range.

[3.] Impaired renal function manifests itself as a progressive elevation in serum levels of creatinine, urea nitrogen and residual nitrogen, as well as oliguria, cylindruria and progressive proteinuria. It is noted in particular in patients with a known history of renal disease, which has been treated over a long period or with unusually high doses. Even in patients with initial normal renal function, impaired renal function may occur

* No events were identified with a frequency of **Very common (≥ 1/10)**

[1] Nebcina, Meda AB, Summary of Product Characteristics dated 09 November 2007.

[2] Additional data was gathered from the information in the SmPCs used for Germany (dated 2004) and The Netherlands (dated 2008)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

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 concentrations versus time. Nephrotoxicity is more likely if trough levels fail to fall below 2 micrograms/ml 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 or auditory and vestibular toxicity. 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.

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

Treatment of Overdose:

Resuscitative measures should be initiated promptly if respiratory paralysis occurs. 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 in the event of overdosage or toxic reactions. Depending on the duration and type of dialysis employed, approximately 25-70% of the administered dose may be removed. Haemodialysis is the more effective method. Calcium salts given intravenously have been used to counter neuromuscular blockade, the effectiveness of neostigmine has been variable. Mechanical assistance may be necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tobramycin is bactericidal in activity. ATC code: J01GB01

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

Tobramycin, in common with all other aminoglycosides, is primarily antibacterial against aerobic Gram-negative bacilli.

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 4-6 micrograms/ml are obtained 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. Tobramycin is poorly absorbed from the gastrointestinal tract.

Distribution
After injection tobramycin has been detected in body fluids but concentrations in the cerebrospinal fluid are low even when there is meningeal inflammation. Most bodily compartments and tissues including the inner ear and kidneys become progressively saturated with aminoglycosides over the course of therapy, and the drug is slowly released from these areas. It has been postulated that this accumulation may account for the ototoxicity and nephrotoxicity associated with aminoglycosides. In general, aminoglycosides such as tobramycin readily cross the placenta. Small amounts of the drugs are also distributed into bile, saliva, sweat, tears, sputum, and milk. Protein binding of tobramycin has been reported as zero.

Elimination

The major route of elimination is renal and the drug is eliminated almost entirely by glomerular filtration.

The plasma elimination half-life of tobramycin is usually 2-3 hours in adults with normal renal function and is reported to range from 5 to 70 hours in adults with impaired renal function.

Peak urine concentrations ranging from 75 to 100 micrograms/ml have been observed after the intramuscular injection of a single dose of 1 mg/kg. After several days of treatment, the amount of tobramycin excreted in the urine approaches the daily amount administered.

Patients with Normal Renal Function
Following IM administration of a single dose of tobramycin of 1 mg/kg in adults with normal renal function, peak plasma tobramycin concentrations averaging 4-6 microgram/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.

Patients with Impaired Renal Function
When renal function is impaired, excretion of tobramycin is slowed, and accumulation of the drug may cause toxic blood levels. In patients undergoing dialysis, 25 to 70% of the administered dose may be removed, depending on the duration and type of dialysis.

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

In full-term infants the plasma elimination half-life is reported to average 4.6 hours and in low birth-weight infants it averages 8.7 hours.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to the information already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulphite (E223)
Disodium edetate
Sulphuric acid (E513)
Sodium hydroxide (for ph adjustment)
Water for injections

6.2 Incompatibilities

Incompatibility or loss of activity has been reported between tobramycin sulfate and some cephalosporins and penicillins and also heparin sodium. Solutions with clindamycin phosphate in glucose injection are reported to be unstable.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 3 years.

Once opened: Use immediately. Discard any unused portion.

Chemical and physical in-use stability has been demonstrated in dextrose 5% and sodium chloride 0.9 % infusion solutions for 24 hours at 24°C in the presence of light.

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the vial in the outer carton in order to protect from light.

Please refer to section 6.3 for storage precautions after dilution.

6.5 Nature and contents of container

Tobramycin injection is supplied in Type I clear glass vials with rubber elastomeric closures, containing 1 ml of sterile solution of tobramycin 40 mg/ml, 2 ml of sterile solution of tobramycin 80 mg/2 ml or 6 ml of sterile solution of tobramycin 240 mg/6 ml.

Pack sizes: 5 x 1ml, 5 x 2ml, 1 x 6ml, 5 x 6ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Single use only. Discard any unused contents.

When given by infusion, Tobramycin Injection may be diluted (with 0.9% Sodium Chloride Intravenous Infusion or 5% Dextrose Intravenous Infusion) to volumes of 50-100 ml for adult doses. For children, the volume of diluent should be proportionately less than for adults.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland Unlimited Company
The Watermarque Building
Ringsend Road
Dublin 4
D04 K7N3
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/207/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th July 1993

Date of last renewal: 14th July 2008

10 DATE OF REVISION OF THE TEXT

December 2024