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 for injection contains 40 mg tobramycin.

Each 1 ml vial contains 40 mg of tobramycin.

Each 2 ml vial contains 80 mg of tobramycin.

Each 6 ml vial contains 240 mg of tobramycin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tobramycin 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.

4.2 Posology and method of administration

Posology

Tobramycin 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 body weight should be obtained.

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.

Duration of treatment

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).

It may be necessary to administer up to 8 to 10 mg/kg/day in equally divided doses, 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 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)	
Kg	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 40 mg/ml product forms.

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.

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.

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.

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.

Patients with impaired renal function

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, (see 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, 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		Regimen II Normal dosage at prolonged intervals
Serum Creatinine		Creatinine Clearance	Weight		Weight/Dose 50-60 kg : 60 mg
mg/100 ml	µmol/litre	ml/min	50-60 kg	60-80 kg	60-80 kg : 80 mg
< 1.3	<114.9	>70	60mg	80mg	q. 8h
1.4 - 1.9	123.8 - 168	69 – 40	30 - 60mg	50 - 80mg	q. 12h
2.0 - 3.3	176.8 - 291.7	39 – 20	20 - 25mg	30 - 45mg	q. 18h
3.4 - 5.3	300.6 - 468.5	19 – 10	10 - 18mg	15 - 24mg	q. 24h
5.4 - 7.5	477.4 - 663	9 – 5	5 - 9mg	7 - 12mg	q. 36h
> 7.6	> 671.8	<4	2.5 - 4.5mg	3.5 - 6mg	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.

° If used to estimate degree of renal impairment, serum creatinine concentrations should reflect a steady state of renal uraemia

† When dialysis is not being performed.

Method of administration

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

Intramuscular administration

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

Intravenous administration

Tobramycin 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 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 12 mg/litre for a short time. (see section 4.4).

4.3 Contraindications

Intrathecal administration.

Hypersensitivity to the active substance 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.

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.

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/litre 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 (see 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.

Renal impairment
In patients with normal renal function who do not receive tobramycin in higher doses or for longer periods of time than those recommended, the risk of toxic reactions is low. However, patients with reduced renal function are 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.

Neurotoxic and / or nephrotoxic drugs
Concurrent and sequential use of other nephrotic, 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.

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

General
It is desirable to measure both peak and trough serum concentrations as high doses of drug may be associated with a greater risk of toxicity.

Cross-allergenicity among aminoglycosides has been known to occur. Patients treated with aminoglycoside antibiotics such as tobramycin should be under close clinical observation because these drugs have an inherent potential for causing nephrotoxicity and ototoxicity.

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. Dosage must be based on measured serum levels in these patients.

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.

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.

Beta-lactam antibiotics
The inactivation of tobramycin by beta-lactam-type antibiotics (penicillins or cephalosporins) has been demonstrated in vitro and in patients with severe renal impairment. Such in activation has not been found in patients with normal renal function if the drugs are administered by separate routes.

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

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

Excipient information
Tobramycin 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

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

Antifungals: Amphotericin B may produce synergistic renal toxicity.

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

General anaesthetics and Neuromuscular Blocking Agents: Concurrent use of tobramycin with general anaesthetics (e.g. succinylcholine, tubocurarine) may potentiate neuromuscular blockade and cause respiratory paralysis.

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

Aminoglycoside antibiotics cross the placenta and can cause foetal harm when administered to a pregnant woman. Serious side effects to mother, foetus or newborn have been reported in the treatment of pregnant women with aminoglycosides (e.g., several reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy). Tobramycin should not be administered to the pregnant patient unless the potential benefits clearly outweigh any potential risk. If tobramycin is used during pregnancy or if the patient becomes pregnant 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

The frequency grouping is defined using the following convention: Very common (≥1/10); 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); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders	
Not known	Anaemia, granulocytopenia, thrombocytopenia, leucopenia, leucocytosis, eosinophilia
Immune system disorders	
Not known	Hypersensitivity
Psychiatric disorders:	
Not known	Mental confusion, disorientation
Nervous system disorders	
Not known	Dizziness, headache, lethargy
Ear and labyrinth disorders[1]	
Not known	Hearing loss, tinnitus, vertigo
Gastrointestinal disorders:	
Not known	Nausea, vomiting, diarrhea
Skin and subcutaneous tissue disorders:	
Not known	Dermatitis exfoliative, rash, itching, urticaria
Renal and urinary disorders[2]	
Not known	Acute kidney injury, blood creatinine increased, blood urea increased, proteinuria, oliguria, cylindruria
General disorders and administration site conditions	
Not known	Fever, pain at injection site
Investigations	
Not known	Blood bilirubin increased, aspartate aminotransferase increased, alanine aminotransferase increased, blood calcium decreased, blood magnesium decreased, blood sodium decreased, blood potassium decreased

[1] In patients receiving high doses or prolonged therapy, side effects on both vestibular and auditory branches of the eighth cranial nerve have been reported. Similar effects have been noted in those given previous courses of therapy with an ototoxin, and in cases of dehydration. Symptoms include vertigo, tinnitus, roaring in the ears and hearing loss. Hearing loss is usually irreversible and is manifested initially by

diminution of high tone acuity.

[2] Renal function changes have been reported, especially in patients with a history of renal impairment who are treated for longer periods or with higher doses than these recommended. These changes can occur in patients with initially normal renal function.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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. 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. Fluid balance, creatinine clearance and tobramycin plasma levels should be carefully monitored until the tobramycin level falls below 2mg/l. 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: Aminoglycoside Antibacterials, ATC Code: J01G B01

Mechanism of action

Tobramycin is bactericidal in activity. 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. Tobramycin is considered more active than most other aminoglycosides against Pseudomonas aeruginosa.

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

Proteus species (indole-positive and indole-negative) including:

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

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

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

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

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.

Elimination

The major route of elimination is renal and the drug is eliminated almost entirely by glomerular filtration. Protein binding of tobramycin has been reported as zero. 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. In full- term infants the plasma elimination half-life is reported to average 4.6 hours and in low birth-weight infants it averages 8.7 hours.

Peak urine concentrations ranging from 75 to 100 microgram/ml have been observed after the intramuscular injection of a single dose of 1 mg/kg. After several days of treatment, the amount of tobramycin excreted in the urine approaches the daily amount administered. When renal function is impaired, excretion of tobramycin is slowed, and accumulation of the drug may cause toxic blood levels. In patients undergoing dialysis, 25 to 70% of the administered dose may be removed, depending on the duration and type of dialysis.

5.3 Preclinical Safety Data

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
Disodium edetate
Sulphuric acid
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.

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

6.3 Shelf life

As packaged for sale –
40 mg/1 ml and 80 mg/2 ml presentations – 3years
240 mg/6 ml presentation – 2 years

After dilution –
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

As packaged for sale – Do not store above 25°C. Keep the vial in the outer carton in order to protect from light.

After dilution – see section 6.3.

6.5 Nature and Contents of Container

40 mg/1 ml and 80 mg/2 ml presentation – clear Type I glass vials with elastomeric stoppers in packs of 5 vials.
240 mg/6 ml presentation – clear Type I glass vials with elastomeric stoppers in packs of 1 or 5 vials.

Not all presentations above 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.

Use in the paediatric population
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

Hospira UK Limited
Walton Oaks
Walton-On-The-Hill
Dorking Road
Tadworth
Surrey
KT20 7NS
UK

8 MARKETING AUTHORISATION NUMBER(S)

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