Approved Professional Information for TOBRAMYCIN 80 mg/2 ml FRESENIUS

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

TOBRAMYCIN 80 mg/2 ml FRESENIUS solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 40 mg tobramycin as the sulphate.

Excipients with known effect:

Preservative: Benzyl alcohol 0,9 % *v/v:* 0,018 ml/2 ml.

Antioxidant: Sodium metabisulphite 0,32 % *m/v:* 6,4 mg/2 ml.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.

A clear, colourless solution in clear 2 ml vials.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TOBRAMYCIN 80 mg/2 ml FRESENIUS is indicated for treatment of potentially life-threatening infections usually in combination with another antibiotic with Gram-negative activity, in the following infections, caused by susceptible organisms:

- complicated or recurrent urinary tract infections
- respiratory tract infections
- various nosocomial infections.

Sensitivity testing of the various organisms should always be undertaken whenever possible.

4.2 Posology and method of administration

Posology

Adults with serious infections: 3 mg/kg/day, administered once daily or in three equally divided doses every 8 hours (see Table 1).

Adults with life-threatening infections: Up to 5 mg/kg/day may be administered once daily or in three or four equally divided doses. The dosage should be reduced to 3 mg/kg/day as soon as clinically indicated.

To prevent increased toxicity due to excessive blood levels dosage should not exceed 5 mg/kg/day unless serum levels are monitored.

Treatment should generally continue for not longer than 7 to 10 days.

Table 1: Dosage schedule guide for adults with normal renal function

Patient mass	**Usual dose for serious infections** **1 mg/kg 8 hourly** **(total: 3 mg/kg/day)**		**Maximum dose for life-threatening infections** **(reduce as soon as possible)** **1,66 mg/kg 8 hourly** **(total: 5 mg/kg/day)**	
	mg/dose	**ml/dose** **40 mg/ml**	**mg/dose**	**ml/dose** **40 mg/ml**
120 kg	120 mg	3,0 ml	200 mg	5,0 ml
100 kg	100 mg	2,5 ml	155 mg	4,0 ml
80 kg	80 mg	2,0 ml	133 mg	3,0 ml
60 kg	60 mg	1,5 ml	100 mg	2,5 ml
40 kg	40 mg	1,0 ml	66 mg	1,6 ml

Special populations

Paediatric population

Children: 6 mg/kg/day to 7,5 mg/kg/day in three or four equally divided doses (2,0 mg/kg to 2,5 mg/kg every 8 hours or 1,5 mg/kg to 1,9 mg/kg every 6 hours).

Premature or full-term neonates 1 week of age or less:

Up to 4 mg/kg/day may be administered in two equally divided doses every 12 hours.

TOBRAMYCIN 80 mg/2 ml FRESENIUS should not be physically premixed with other medicines, but should be administered separately.

Note: The dosing interval of TOBRAMYCIN 80 mg/2 ml FRESENIUS in paediatric patients may vary from every four hours to every twenty-four hours, depending on the medical condition of the patient (cystic fibrosis, burns, renal dysfunction); serum levels must be monitored.

Method of administration

TOBRAMYCIN 80 mg/2 ml FRESENIUS may be given intramuscularly or intravenously over 20 to 60 minutes in 50 to 100 ml of sterile sodium chloride or glucose solutions. Proportionately less fluid should be given to children. It is recommended that a needle not larger than 21 gauge is used to reduce fragmentation of the rubber stopper.

4.7 Contraindications

- A history of allergy to tobramycin, other aminoglycosides or to any of the excipients listed in section 6.1.
- Pregnancy and lactation.
- Myasthenia gravis, parkinsonism and other conditions characterised by muscular weakness.

4.7 Special warnings and precautions for use

TOBRAMYCIN 80 mg/2 ml FRESENIUS contains sodium metabisulphite 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 sulphite sensitivity in the general population is unknown and probably low, but it occurs more frequently in asthmatic patients.

Concurrent and sequential use of other aminoglycosides and other potentially neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cefaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin and amikacin should be avoided (see section 4.5).

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, are usually bilateral, and may be partial or total. Eighth cranial nerve impairment may develop in patients with pre-existing renal damage and if TOBRAMYCIN 80 mg/2 ml FRESENIUS 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 8th nerve toxicity, and partial or total irreversible bilateral deafness may continue to develop after TOBRAMYCIN 80 mg/2 ml FRESENIUS 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 8th cranial nerve function should be closely monitored in patients with known or suspected renal impairment and 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 TOBRAMYCIN 80 mg/2 ml FRESENIUS 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.

A serum sample should be drawn about 30 minutes following intravenous infusion or at one hour after intramuscular injection in order to measure the peak level. Trough levels are measured by obtaining serum samples at 8 hours or just prior to the next TOBRAMYCIN 80 mg/2 ml FRESENIUS dose.

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 80 mg/2 ml FRESENIUS in higher doses or for longer periods of time than those recommended.

Because TOBRAMYCIN 80 mg/2 ml FRESENIUS has the inherent potential for causing oto- and nephrotoxicity, patients under treatment, especially at high dosage levels and with long duration of treatment, in infants and the elderly, should be monitored. Obese patients and those with cystic fibrosis should also be monitored. Impaired hepatic function or auditory function, bacteraemia, fever and exposure to loud noises have been reported to increase the risk of ototoxicity, while volume depletion or hypotension, liver disease, or female sex have been reported as additional risk factors for nephrotoxicity.

Use of TOBRAMYCIN 80 mg/2 ml FRESENIUS during pregnancy may damage the 8th cranial nerve of the fetus (see section 4.6).

Care should be exerted when it is given to patients receiving other medicines with a neuromuscular blocking activity or which are ototoxic or nephrotoxic. Anti-emetics may mask ototoxic symptoms.

Patients with reduced renal function, however, are particularly prone to the potential ototoxic and nephrotoxic effects of TOBRAMYCIN 80 mg/2 ml FRESENIUS, so dosage should be adjusted carefully based on regular monitoring of serum drug concentrations and of renal function.

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 tobramycin, as in TOBRAMYCIN 80 mg/2 ml FRESENIUS. In such patients treated with TOBRAMYCIN 80 mg/2 ml FRESENIUS, measurement of serum concentration is especially recommended as a basis for determination of appropriate dosage.

Tobramycin, as in TOBRAMYCIN 80 mg/2 ml FRESENIUS, may be absorbed in significant quantities from body surfaces after local irrigation or application and may cause neurotoxicity and nephrotoxicity.

TOBRAMYCIN 80 mg/2 ml FRESENIUS should not be used in patients with muscular disorders, such as myasthenia gravis or parkinsonism, since these medicines may aggravate muscle weakness because of their potential curare-like effect on neuromuscular function.

Neuromuscular blockade or respiratory paralysis may occur following rapid intravenous administration of many aminoglycosides, including TOBRAMYCIN 80 mg/2 ml FRESENIUS.

The possibility of prolonged secondary apnoea should be considered if TOBRAMYCIN 80 mg/2 ml FRESENIUS is administered to anaesthetised patients who are also receiving neuromuscular blocking medicines 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 80 mg/2 ml FRESENIUS 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 medicines are administered by separate routes.

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

TOBRAMYCIN 80 mg/2 ml FRESENIUS may rarely cause severe hypersensitivity reactions and bronchospasm.

Prolonged concentrations above 12 µg/ml should be avoided. Rising trough levels (above 2 µg/ml) may indicate tissue accumulation.

Contains sodium

Contains less than 1 mmol (23 mg) sodium per dosage, that is to say essentially sodium-free.

Paediatric population:

Use in neonates: TOBRAMYCIN 80 mg/2 ml FRESENIUS should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of tobramycin.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of TOBRAMYCIN 80 mg/2 ml FRESENIUS with:

- Pyridostigmine: TOBRAMYCIN 80 mg/2 ml FRESENIUS may antagonise the effect of pyridostigmine on skeletal muscles in patients with myasthenia gravis.
- Neostigmine: TOBRAMYCIN 80 mg/2 ml FRESENIUS may antagonise the effect of neostigmine.
- Neuromuscular blocking agents: The effect of neuromuscular blocking agents (e.g. anaesthetics) resulting in skeletal muscle weakness and possible respiratory depression or paralysis may be enhanced by TOBRAMYCIN 80 mg/2 ml FRESENIUS.
- Other neurotoxic/nephrotoxic medicines: Concurrent and sequential use of other aminoglycosides and other potentially neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cefaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin and amikacin should be avoided (see section

4.4).

- Potent diuretics: TOBRAMYCIN 80 mg/2 ml FRESENIUS 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: When TOBRAMYCIN 80 mg/2 ml FRESENIUS is used in conjunction with other antibacterials, such as cephalosporins notably cephalothin, there is an increased risk of nephrotoxicity.
- Cytotoxics and ciclosporins: There is increased risk of nephrotoxicity and possibly ototoxicity with cisplatin as well as increased risk of nephrotoxicity with ciclosporins.
- Tobramycin, as in TOBRAMYCIN 80 mg/2 ml FRESENIUS, has been known to potentiate warfarin and phenindione.

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation have not been established. Use of TOBRAMYCIN 80 mg/2 ml FRESENIUS during pregnancy may damage the 8th cranial nerve of the fetus (see section 4.4).

Pregnancy

TOBRAMYCIN 80 mg/2 ml FRESENIUS is containdicated during pregnancy**.**

Aminoglycosides can cause fetal 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, fetus, or newborn have not been reported in the treatment of pregnant women with other aminoglycosides.

Breastfeeding

TOBRAMYCIN 80 mg/2 ml FRESENIUS is excreted in human breast milk and should be avoided in nursing women.

4.7 Effects on ability to drive and use machines

TOBRAMYCIN 80 mg/2 ml FRESENIUS may cause dizziness and vertigo (see section 4.8). Patients should therefore be warned to be cautious when driving a vehicle or operating machinery.

4.8 Undesirable effects

Blood and lymphatic system disorders

Frequency unknown: anaemia, granulocytopenia, purpura, increased or decreased reticulocyte count, thrombocytopenia, leucopenia, leucocytosis, eosinophilia

Immune system disorders

Less frequent: hypersensitivity reactions

Frequency unknown: fever

Psychiatric disorders

Frequency unknown: encephalopathy, mental confusion, lethargy, hallucinations, mental depression, disorientation

Nervous system disorders

Frequent: neurotoxicity (muscle twitching, paraesthesia, convulsions)

Less frequent: neuromuscular blockade (respiratory depression, muscular paralysis)

Frequency unknown: meningeal irritation, arachnoiditis, polyradiculitis, ventriculitis following the intrathecal, intracisternal or intraventricular administration of aminoglycosides, headache, dizziness

Eye disorders

Frequency unknown: visual disturbances

Ear and labyrinth disorders

Frequent: ototoxicity, irreversible (previous exposure to other ototoxic medicines such as kanamycin, gentamycin, paromomycin, amikacin and others may be a contributing factor), vertigo, tinnitus, roaring in the ears, hearing loss (usually irreversible and is manifested initially by diminution of high tone acuity)

Gastrointestinal disorders

Frequency unknown: pseudomembranous colitis, nausea, vomiting, diarrhoea

Hepato-biliary disorders

Frequency unknown: increased serum aminotransferase (AST and ALT) and serum bilirubin levels

Skin and subcutaneous tissue disorders

Frequency unknown: rash, exfoliative dermatitis, itching, urticaria

Renal and urinary disorders

Frequency unknown: acute renal failure (often in association with concurrent administration of other nephrotoxic medicines), renal impairment is usually mild, although acute tubular necrosis and interstitial nephritis have occurred, renal function changes, as shown by rising blood urea and serum creatinine and by oliguria, cylindruria and increased proteinuria, may occur, 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), decreased glomerular filtration rate is usually seen only after several days, and may even occur after therapy has been discontinued

General disorders and administration site conditions

Frequency unknown: hypomagnesaemia, hypocalcaemia, hyponatraemia, hypokalaemia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of TOBRAMYCIN 80 mg/2 ml FRESENIUS is important. It allows continued monitoring of the benefit/risk balance of TOBRAMYCIN 80 mg/2 ml FRESENIUS. Health care providers are asked to report any

suspected adverse reactions via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Health care providers are asked to report any suspected Adverse Drug Reactions to the Holder of the Certificate of Registration at the following email address:

safety.fksa@fresenius-kabi.com, and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Signs and symptoms: Severity of the manifestations of TOBRAMYCIN 80 mg/2 ml FRESENIUS overdose depends on the dose, the patient's renal function, state of hydration, age and whether concurrent medicine with similar toxicities is being given. Toxicity may occur in patients treated for more than 10 days, given more than 5 mg/kg/day, children given more than 7,5 mg/kg/day, or patients with reduced renal function whose dose has not been appropriately adjusted.

Nephrotoxicity following the parenteral administration of an aminoglycoside is most closely related to the AUC of serum concentration versus time. Nephrotoxicity is more likely if trough levels fail to fall below 2 mg/l and is also proportional to the average blood concentration. Patients who are elderly, have renal impairment, are receiving other nephrotoxic or ototoxic medicines, or are volume depleted, are at greater risk for developing acute tubular necrosis. Auditory and vestibular toxicities have been associated with aminoglycoside overdose. These toxicities occur in patients treated longer than 10 days, in patients with abnormal renal function, in dehydrated patients, or in patients on other ototoxic medicines. 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 TOBRAMYCIN 80 mg/2 ml FRESENIUS 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, as in TOBRAMYCIN 80 mg/2 ml FRESENIUS, is unlikely because aminoglycosides are poorly absorbed from an intact gastrointestinal 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 2 mg/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

Category and class: A 20.1.1 Broad and medium spectrum antibiotics.

Pharmacotherapeutic group: Aminoglycoside antibacterials, ATC code: JO1GB01.

5.1 Pharmacodynamic properties

Tobramycin is an aminoglycoside antibiotic with bactericidal activity mainly against Gram-negative aerobic organisms which results mainly from inhibition of protein synthesis in susceptible microorganisms.

EUCAST clinical MIC breakpoints

The non-species related breakpoints for susceptible (S) and resistant (R) species are:

S ≤ 2 mg/l and R > 4 mg/l

For Enterobacteriacaea	S < 2 mg/l and R > 4 mg/l
For Pseudomonas	S < 4 mg/l and R > 4 mg/l
For Acinetobacter	S < 4 mg/l and R > 4 mg/l
For Staphylococcus	S < 1 mg/l and R > 1 mg/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 medicine in at least some types of infections is questionable.

Bacterial resistance to tobramycin may rapidly occur and cross-resistance between aminoglycosides may exist.

Commonly susceptible species

Gram-positive aerobes

Staphylococcus aureus

Coagulase-negative staphylococci

Staphylococcus saprophyticus

Gram-negative aerobes

Citrobacter freundii

Citrobacter koseri

Enterobacter aerogenes

Enterobacter cloacae

Enterobacter sakazakii

Enterobacter spp.

Escherichia coli

Klebsiella oxytoca

Klebsiella pneumoniae

Klebsiella spp.

Morganella morganii

Proteus mirabilis

Proteus spp.

Proteus vulgaris

Pseudomonas aeruginosa.

Species for which acquired resistance may be a problem

Gram-positive aerobes

Staphylococcus capitis

Staphylococcus epidermidis

Staphylococcus haemolyticus

Staphylococcus hominis

Staphylococcus lugdunensis

Staphylococcus warnerii

Gram-negative aerobes

Citrobacter spp. – other

Klebsiella ozaenae

Serratia liquefaciens

Serratia marcescens

Serratia spp.

Inherently resistant organisms

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

Although most strains of enterococci demonstrate *in vitro* resistance, some strains are susceptible. *In vitro* studies have shown that an aminoglycoside combined with an antibiotic

that interferes with cell-wall synthesis affects some enterococcal strains synergistically. The combination of penicillin G and tobramycin results in a synergistic bactericidal effect *in vitro* against certain strains of *Enterococcus faecalis* (formerly *Streptococcus faecalis*).

However, this combination is not synergistic against other closely related organisms, e.g. *Enterococcus faecium* (formerly *Streptococcus faecium*). Speciation of enterococci alone cannot be used to predict susceptibility. Susceptibility testing and tests for antibiotic synergism are emphasised.

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

The combination of tobramycin, as in TOBRAMYCIN 80 mg/2 ml FRESENIUS, and carbenicillin is synergistic *in vitro* against most strains of *Pseudomonas aeruginosa*. Other Gram-negative organisms may be affected synergistically by the combination of tobramycin and a cephalosporin.

5.2 Pharmacokinetic properties

Absorption

It is poorly absorbed from the intestinal tract. 30 to 90 minutes following intramuscular injection, peak plasma concentrations are attained which are similar to those found 30 minutes following intravenous infusion.

Distribution

It has a half-life of 2,2 hours and is negligibly plasma protein bound. High concentrations are found only in the renal cortex and in the endolymph and perilymph of the inner ear. After repeated administration only, is it found in the pleural and synovial fluid at concentrations approximating plasma levels.

Tobramycin can be detected in tissues and body fluids after parenteral administration. Tobramycin has appeared in low concentration in the cerebrospinal fluid following parenteral administration and concentrations are dependent on dose, rate of penetration and degree of meningeal inflammation. It has also been found in sputum, peritoneal fluid, abscess fluids and it crosses the placental membranes.

Tobramycin levels may be somewhat lower than expected in adults with a large volume of extracellular fluid.

Probenecid does not affect the renal tubular transport of tobramycin.

Elimination

Excretion is almost entirely by glomerular filtration. Concentrations in bile and stools ordinarily have been low, which suggests minimum biliary excretion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol 0,9 % *v/v* (preservative)

Disodium edetate

Sodium metabisulphite 0,32 % *m/v* (antioxidant)

Sulphuric acid 10 % (for pH-adjustment)

Water for injection.

6.2 Incompatibilities

TOBRAMYCIN 80 mg/2 ml FRESENIUS may be given intramuscularly or intravenously over 20 to 60 minutes in 50 to 100 ml of sterile sodium chloride or glucose solutions.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

2 ml clear glass vials (Type I) sealed with bromobutyl rubber stoppers, in cartons of 10 vials.

6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd

6 Gibaud Road

Korsten 6020

Gqeberha

South Africa

8. REGISTRATION NUMBER

Z/20.1.1/287

9. DATE OF FIRST AUTHORISATION

05 July 1993

10. DATE OF REVISION OF THE TEXT

09 September 2022.