

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

TOBRAMYCIN WOCKHARDT Tobramycin 300 mg/5 mL, Solution for inhalation.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL ampoule contains a sterile solution of tobramycin 300 mg
For the full list of excipients, see **Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

Solution for inhalation.

TOBRAMYCIN WOCKHARDT is a sterile, clear slightly yellow, non-pyrogenic, aqueous solution with the pH and salinity adjusted specifically for administration by a compressed air driven reusable nebuliser.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TOBRAMYCIN WOCKHARDT injection is indicated for the management of cystic fibrosis patients with *P. aeruginosa* infections. Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with FEV₁ <25% or >75% predicted, or patients colonised with *Burkholderia cepacia* (see Section 5.1 Pharmacodynamic properties: Clinical trials)

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults and paediatric patients 6 years of age and older

The recommended dosage for both adults and paediatric patients 6 years of age and older is one single-use ampoule (300 mg) administered twice daily for 28 days. Dosage is not adjusted by weight. All patients should be administered 300 mg twice daily. The doses should be taken as close to 12 hours apart as possible; they should not be taken less than six hours apart. tobramycin is inhaled while the patient is sitting or standing upright and breathing normally through the mouthpiece of the nebuliser. Nose clips may help the patient breathe through the mouth.

Tobramycin is administered twice daily in alternating periods of 28 days. After 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next 28 days on/28 days off cycle.

Method of administration

TOBRAMYCIN WOCKHARDT is supplied as a single-use ampoule and is administered by inhalation, over a 10 to 15 minute period, using a hand-help PARI LC PLUS reusable nebuliser with a DeVilbiss PulmoAide compressor. The use of TOBRAMYCIN WOCKHARDT with nebulizers other than the PARI LC PLUS has not been adequately studied.

TOBRAMYCIN WOCKHARDT is not for subcutaneous, intravenous or intrathecal administration.

TOBRAMYCIN WOCKHARDT should not be diluted or mixed with dornase alfa or other medications in the nebuliser.

During clinical studies, patients on multiple therapies were instructed to take them first, followed by tobramycin.

Detailed instructions for use are provided in the patient package insert supplied.

4.3 CONTRAINDICATIONS

Tobramycin is contraindicated in patients with a known hypersensitivity to any aminoglycoside.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Tobramycin is not for subcutaneous, intravenous or intrathecal administration.

Caution should be exercised when prescribing tobramycin to patients with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction. Patients receiving concomitant parenteral aminoglycoside therapy should be monitored as clinically appropriate.

Aminoglycosides can cause foetal harm when administered to a pregnant woman.

Aminoglycosides cross the placenta, and streptomycin has been associated with several reports of total, irreversible, bilateral congenital deafness in paediatric patients exposed in utero. Patients who use tobramycin during pregnancy, or become pregnant while taking tobramycin should be apprised of the potential hazard to the foetus.

Ototoxicity

In clinical studies 4 (1%) patients reported mild to moderate hearing loss in clinical studies of up to 9 treatment cycles. Hearing loss was transient for 3 patients and ongoing at the end of study for one patient. Three of these patients had received IV aminoglycosides concomitantly to receiving tobramycin. In postmarketing experience, some patients receiving tobramycin and extensive previous or concomitant parenteral aminoglycosides have reported hearing loss. Patients with hearing loss frequently reported tinnitus. Tinnitus is a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution (see section 4.8 UNDESIRABLE EFFECTS).

Ototoxicity, manifested as both auditory and vestibular toxicity, has been reported with parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness.

If a patient reports tinnitus or hearing loss during tobramycin therapy, the physician should refer them for audiological assessment.

If ototoxicity occurs in a patient receiving tobramycin tobramycin therapy should be discontinued until tobramycin serum concentrations fall below 2 µg/mL.

Also see SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Laboratory Tests: serum concentrations.

Nephrotoxicity

Nephrotoxicity was not seen during tobramycin clinical studies but has been associated with aminoglycosides as a class. Nephrotoxicity has been reported with the use of parenteral aminoglycosides. If nephrotoxicity occurs in a patient receiving tobramycin, tobramycin therapy should be discontinued until serum concentrations fall below 2 mcg/ml.

Also see SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Laboratory Tests: serum concentrations.

Laboratory tests of renal function should be monitored as clinically appropriate.

Muscular Disorders

Tobramycin should be used cautiously in patients with muscular disorders, such as myasthenia gravis or Parkinson's disease, since aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.

Bronchospasm

Bronchospasm can occur with inhalation of medicinal products and has been reported with tobramycin. In clinical studies of tobramycin, changes in FEV measured after the inhaled dose were similar in the tobramycin and placebo groups. Bronchospasm should be treated as medically appropriate.

Laboratory Tests

Audiograms

Clinical studies of tobramycin did not identify hearing loss using audiometric tests which evaluated hearing up to 8000 Hz. Tinnitus may be a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution. Physicians should consider an audiogram for patients who show any evidence of auditory dysfunction, or who are at increased risk for auditory dysfunction.

Serum Concentrations

In patients with normal renal function treated with tobramycin, serum tobramycin concentrations are approximately 1 mcg/mL one hour after dose administration and do not require routine monitoring. Serum concentrations of tobramycin should be monitored in patients with known or suspected auditory or renal dysfunction. Patients treated with concomitant parenteral tobramycin should be monitored at the discretion of the treating physician. The serum concentration of tobramycin should only be monitored through venipuncture and not finger prick blood sampling. Contamination of the skin of the fingers with tobramycin may lead to falsely increased measurements of serum levels of the drug. This contamination cannot be completely avoided by hand washing before testing.

Renal Function

The clinical studies of tobramycin did not reveal any imbalance in the percentage of patients in the tobramycin and placebo groups who experienced at least a 50% rise in serum creatinine from baseline (see Section 4.8 Undesirable effects). Laboratory tests of urine and renal function should be conducted at the discretion of the treating physician.

Animal Toxicology

Bronchoepithelial hyperplasia and chronic interstitial inflammation around terminal bronchioles occurred in studies in rats after daily inhalational exposures to tobramycin for 6 months. Progression of the hyperplastic lesions is currently uncertain and this will be assessed further in a 2 year inhalational study in progress.

Carcinogenesis

A two-year rat inhalation toxicology study to assess the carcinogenic potential of tobramycin has been completed. Rats were exposed to tobramycin for up to 1.5 hours per day for 95 weeks. Serum levels of tobramycin of up to 35 µg/mL were measured in rats. There was no drug-related increase in the incidence of any variety of tumour.

Mutagenicity

Tobramycin has been evaluated for genotoxicity in a battery of assays for gene mutations and chromosomal damage. Tobramycin was negative in the bacterial reverse mutation and the mouse lymphoma forward mutation assays. Tobramycin did not induce chromosomal aberrations in Chinese hamster ovary cells, and was negative in the mouse micronucleus test.

Characteristics in special population

Paediatric Use

The safety and efficacy of tobramycin have not been studied in paediatric patients under 6 years of age.

Patients with renal impairment

Tobramycin is primarily excreted unchanged in the urine and renal function is expected to affect the exposure to tobramycin. See PRECAUTIONS - Nephrotoxicity.

Patients with hepatic impairment

No studies have been performed on patients with hepatic impairment. As tobramycin is not metabolized, an effect of hepatic impairment on the exposure to tobramycin is not expected.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No clinical drug interaction studies have been performed with tobramycin. However, in clinical studies of tobramycin, patients taking tobramycin concomitantly with dornase alfa, β -agonists, inhaled corticosteroids, other anti-pseudomonal antibiotics, or parenteral aminoglycosides

demonstrated adverse experience profiles similar to the study population as a whole.

Concurrent and/or sequential use of tobramycin with other drugs with neurotoxic, nephrotoxic, or ototoxic potential should be avoided. Some diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. Tobramycin should not be administered concomitantly with ethacrynic acid, frusemide, urea, or intravenous mannitol.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No reproduction toxicology studies have been conducted with tobramycin administered by inhalation. Data in animals from subcutaneous administration of tobramycin did not reveal a problem or potential problem concerning fertility in either males or females. Subcutaneous administration of up to 600 mg/m² /day of tobramycin did not affect mating behaviour or cause impairment of fertility in male or female rats, although fertility of the offspring was not examined.

Use in pregnancy

Category D. There are no adequate data from the use of tobramycin administered by inhalation in pregnant women. No reproduction toxicology studies have been conducted with tobramycin. However, subcutaneous administration of tobramycin at doses of 600 or 220 mg/m²/day during organogenesis was not teratogenic in rats or rabbits, respectively. Doses of tobramycin = 440 mg/m²/day were severely maternally toxic to rabbits and precluded the

evaluation of teratogenicity. Aminoglycosides can cause foetal harm (eg. congenital deafness) when administered to a pregnant woman and high systemic concentrations are achieved. Ototoxicity was not evaluated in offspring during nonclinical reproduction toxicity studies with tobramycin.

Treatment with tobramycin during pregnancy should be undertaken only if the benefits to the mother outweigh the risks to the foetus or baby. If tobramycin is used during pregnancy, or if the patient becomes pregnant while taking tobramycin, the patient should be apprised of the potential hazard to the foetus. Aminoglycosides can cross the placenta. There is evidence of selective uptake of aminoglycosides by foetal kidney resulting in damage (probably reversible) to immature nephrons. Eighth cranial nerve damage has also been reported following in utero exposure to some of the aminoglycosides. Because of their chemical similarity, all aminoglycosides must be considered potentially nephrotoxic and ototoxic to the foetus. It should also be noted that therapeutic blood concentrations in the mother do not equate with safety to the foetus.

Use in Lactation

It is not known if tobramycin will reach sufficient concentrations after administration by inhalation to be excreted in human breast milk. Because of the potential for ototoxicity and nephrotoxicity in infants, a decision should be made whether to terminate nursing or discontinue treatment with tobramycin, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tobramycin has minor influence on the ability to drive and use machines.

Patients should be warned about the potential for nervous system such as dizziness and somnolence, and advised not to drive or operate machinery if these symptoms occur or until their individual susceptibility is known.

4.8 UNDESIRABLE EFFECTS

Tobramycin was generally well tolerated during two placebo-controlled clinical studies in 258 cystic fibrosis patients ranging in age from 6 to 48 years. Patients received tobramycin in alternating periods of 28 days on and 28 days off drug in addition to their standard cystic fibrosis therapy for a total of 24 weeks.

Voice alteration and tinnitus were the only adverse experiences reported by significantly more tobramycin-treated patients. Thirty-three patients (13%) treated with tobramycin complained of voice alteration compared to 17 (7%) placebo patients. Voice alteration was more common in the on-drug periods. Eight patients from the tobramycin group (3%) reported tinnitus compared to no placebo patients.

All episodes were transient, resolved without discontinuation of the tobramycin treatment regimen, and were not associated with loss of hearing in audiograms. Tinnitus is one of the sentinel symptoms of cochlear toxicity, and patients with this symptom should be carefully monitored for high frequency hearing loss. The numbers of patients reporting vestibular adverse experiences such as dizziness were similar in the tobramycin and placebo groups. Nine (3%) patients in the tobramycin group and nine (3%) patients in the placebo group had increases in serum creatinine of at least 50% over baseline. In all nine patients in the tobramycin group, creatinine decreased at the next visit.

Table 1 lists the percent of patients with treatment-emergent adverse experiences that occurred in $\geq 5\%$ of patients during the 48 weeks of the open label extension. The table also presents the corresponding data from the 24-week placebo controlled studies, where one group of patients received placebo and the other group received tobramycin during the first three cycles of therapy.

Table 1: Percent of Patients with Treatment-Emergent Adverse Events Occurring in $\geq 5\%$ of Patients in Any Group

Adverse Event	During the Open Label Extension ^a		During the Placebo-Controlled Studies	
	9 Cycles (n = 192)	6 Cycles (n = 204)	3 Cycles (n = 258)	Placebo (n = 262)
Respiratory System				
Cough Increased	50	48	46	47
Pharyngitis	48	44	38	39
Sputum Increased	44	38	38	40
Dyspnea	42	34	34	39
Rhinitis	38	33	35	34
Lung Disorder	34	36	31	31
Hemoptysis	31	27	19	24
Asthma	28	24	16	20
Lung Function Decreased	29	23	16	15
Sputum Discoloration	25	19	21	20
Upper Respiratory Tract Infection	14	10	5	8
Sinusitis	7	14	8	9
Voice Alteration	12	6	13	7
Epistaxis	8	8	7	7
Lower Respiratory Tract Infection	7	9	6	8
Respiratory Disorder	6	9	2	6
Hyperventilation	9	5	5	10
Hypoxia	6	6	5	4
Nasal Polyp	4	5	4	2
Laryngitis	5	3	4	3
Body as a Whole				
Fever	40	46	33	44
Asthenia	44	38	36	39
Chest pain	37	35	26	30
Headache	29	34	27	32
Abdominal Pain	21	27	13	24
Pain	18	24	8	13
Back Pain	10	6	7	8
Chills	7	6	3	2
Accidental Injury	5	6	4	3
Malaise	3	7	6	5
Flu Syndrome	4	5	1	2
Digestive System				

Anorexia	29	28	19	28
Vomiting	18	22	14	22
Nausea	16	19	11	16
Diarrhoea	17	13	6	10
Dyspepsis	5	5	4	4
Oral Moniliasis	6	3	2	1
Hemic and lymphatic system Lymphadenopathy	8	7	4	2
Metabolic & nutritional disorders				
Weight loss	16	20	10	15
Skin and Appendages				
Rash	10	12	5	6
Sweating	6	5	2	4
Special senses				
Ear pain	8	9	7	9
Ear disorder	4	7	2	4
Otitis media	5	2	3	3
Hemic and Lymphatic system				
Lymphadenopathy	8	7	4	2
Nervous system				
Dizziness	6	6	6	8
Somnolence	6	6	2	4
Musculoskeletal System				
Myalgia	6	5	5	3

^aPatients with newly-occurring or worsening adverse events since Week 24.

The 6-Cycle group received Placebo during the controlled study (first 3 cycles).

The 9-Cycle group received tobramycin during both the controlled study and the open label extension

Postmarketing Experience

Some patients receiving tobramycin and extensive previous or concomitant parenteral aminoglycosides have reported hearing loss during postmarketing surveillance (see PRECAUTIONS).

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post marketing experience with tobramycin via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Ear and labyrinth disorders

Hearing loss

Skin and subcutaneous tissue disorders

Hypersensitivity, pruritus, urticaria, rash

Nervous system disorders

Aphonia, dysgeusia

Respiratory, thoracic, and mediastinal disorders

Bronchospasm, oropharyngeal pain, sputum increased, chest pain

General disorders and administration site conditions

Decreased appetite

{Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions
<https://nzphvc.otago.ac.nz/reporting/>}

4.9 OVERDOSE

Signs and symptoms

In the event of inadvertent administration of tobramycin by the IV route, signs and symptoms of parenteral tobramycin overdosage may occur that include dizziness, tinnitus, vertigo, loss of high-tone hearing acuity, respiratory distress or failure, renal impairment, and neuromuscular blockade. Administration by inhalation results in low systemic bioavailability of tobramycin.

In the event of accidental oral ingestion of tobramycin, systemic toxicity is unlikely as tobramycin is not significantly absorbed following oral administration.

The maximum tolerated daily dose of tobramycin has not been established. Tobramycin serum concentrations may be helpful in monitoring overdose.

Treatment

In all cases of suspected overdosage, physicians should contact the National Poisons Information Centre on telephone 0800 POISON or 0800 764 766 for information about advice on management. In the case of any overdosage, the possibility of drug interactions with alterations in drug disposition should be considered. Acute toxicity should be treated with immediate withdrawal of tobramycin, and baseline tests of renal function should be undertaken. Haemodialysis may be helpful in removing tobramycin from the body.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Aminoglycoside antibacterials, ATC code: J01GB01

Microbiology

Tobramycin is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. It acts primarily by disrupting protein synthesis, leading to altered cell membrane permeability, progressive disruption of the cell envelope, and eventual cell death.

Tobramycin has in vitro activity against a wide range of gram-negative organisms including *Pseudomonas aeruginosa*. It is bactericidal at concentrations equal to-or slightly greater than inhibitory concentrations.

Susceptibility Testing

A single sputum sample from a cystic fibrosis patient may contain multiple morphotypes of *Pseudomonas aeruginosa* and each morphotype may have a different level of *in vitro* susceptibility to tobramycin. Treatment for 6 months with tobramycin in two clinical studies did not affect the susceptibility of the majority of *P. aeruginosa* isolates tested; however, increased MICs were noted in some patients. The clinical significance of this information has not been clearly established in the treatment of *P. aeruginosa* in cystic fibrosis patients. For additional information regarding the effects of tobramycin on *P. aeruginosa* MIC values and bacterial sputum density, please refer to the CLINICAL TRIALS section.

The *in vitro* antimicrobial susceptibility test methods used for parenteral tobramycin therapy can be used to monitor the susceptibility of *P. aeruginosa* isolated from cystic fibrosis patients. If decreased susceptibility is noted, the results should be reported to the clinician. Susceptibility breakpoints established for parenteral administration of tobramycin do not apply to aerosolised administration of tobramycin. The relationship between *in vitro* susceptibility test results and clinical outcome with tobramycin therapy is not clear.

Clinical trials

Two identically designed, double-blind, randomised, placebo-controlled, parallel group, 24-week clinical studies were conducted in 520 cystic fibrosis patients aged ≥ 6 years who had Baseline FEV₁ % predicted between 25% and 75% and were positive for *P. aeruginosa*. Patients with a baseline creatinine of > 0.18 mmol/L or who had *Burkholderia cepacia* isolated from sputum were excluded. A cyclical treatment regimen consisting of 28 days on therapy followed by 28 days off therapy was used in these studies. This cycle was repeated twice for a total of three cycles. Patients received either tobramycin (300 mg) or placebo (saline with 1.25 mg quinine) twice daily, delivered by aerosol using a hand-held PARI LC PLUS Reusable Nebuliser with a DeVilbiss Pulmo-Aide Compressor. All patients received study drug in addition to standard treatment recommended for cystic fibrosis patients, which included oral and parenteral anti-pseudomonal therapy, 132-agonists, sodium cromoglycate, inhaled steroids, and airway clearance techniques. In addition, approximately 77% of patients were concurrently treated with dornase alfa. The randomised clinical studies were followed by a 48-week open label extension where all patients who chose to continue received up to 6 cycles of tobramycin therapy following the same regimen of 28 days on and 28 days off. Thus, patients who continued into the open label extension received a total exposure of either up to 9 cycles or up to 6 cycles, depending on their original assignment in the controlled studies. In each of the two placebo-controlled studies, tobramycin treated patients experienced significant improvement in pulmonary function. Improvement was demonstrated in the tobramycin group in Study 1 by an average increase in FEV₁% predicted of about 11% relative to baseline (Week 0) during 24 weeks compared to no average change in placebo patients. In Study tobramycin treated patients had an average increase of about 7% compared to an average decrease of about 1% in placebo patients. Three hundred and ninety-six (396) patients from the controlled studies participated in the open label extension. Of these, a total of 192 patients received up to 9 cycles of tobramycin, 3 cycles during the controlled studies and 6 cycles during the open label extension. At the end of cycle 9, in these patients FEV₁% predicted was 1.7% above baseline (measured at the start of the controlled trials). A total of 204 patients received placebo for 3 cycles followed by 6 cycles of tobramycin. Whilst on placebo, these patients experienced a mean 2.9% decrease in % predicted had improved to 1% below baseline.

P. aeruginosa density in sputum was measured during the 24-week placebo-controlled studies. tobramycin therapy resulted in a significant reduction in the number of *P. aeruginosa* colony forming units (CFUs) in sputum during the on-drug periods. Sputum bacterial density returned to baseline during the off-drug periods. Reductions in sputum bacterial density were smaller in each successive cycle. *P. aeruginosa* density in sputum was not measured during the open label extension. During the 24 weeks of the placebo-controlled studies, patients treated with

tobramycin were hospitalised for an average of 5.1 days compared to 8.1 days for placebo patients. Patients treated with tobramycin required an average of 9.7 days of parenteral anti-pseudomonal antibiotic treatment compared to 14.1 days for placebo patients. During the 24 weeks of treatment, 40% of tobramycin patients and 53% of placebo patients were treated with parenteral anti-pseudomonal antibiotics. Over the subsequent 48 weeks of the open label extension, patients were hospitalised for a mean of 11.1 days. Patients were treated with parenteral anti-pseudomonal antibiotics for a mean of 22.4 days and 60.6% of patients were treated with parenteral antipseudomonal antibiotics.

The relationship between in vitro susceptibility test results and clinical outcome with tobramycin therapy is not clear. However, four tobramycin patients who began the clinical trial with *P.aeruginosa* isolates having MIC values 2:128 I-Ig/mL did not experience an improvement in FEV₁, or a decrease in sputum bacterial density during the first 24 weeks of therapy. For patients given 9 cycles of active treatment the proportion of patients with isolates of *P.aeruginosa* with an MIC = 16 µg/mL increased from 13.7% at baseline to 29.8% at the end of cycle 9. The proportion of patients with isolates of *P. aeruginosa* with MIC = 128 µg/mL increased from 2.1% at baseline to 9.2% at the end of cycle 9. During the open-label extension, susceptibility testing of other aminoglycosides (amikacin and gentamicin) indicated a shift toward increasing MIC values similar in magnitude to that seen for tobramycin. The MIC values for ciprofloxacin, aztreonam, ceftazidime and ticarcillin remained unchanged.

Treatment for 18 months (9 cycles) with tobramycin in clinical studies demonstrated a trend to decreasing in vitro susceptibility of *P. aeruginosa* isolates. The clinical significance of this information has not been clearly established in the treatment of *P. aeruginosa* in cystic fibrosis patients.

The safety and efficacy of tobramycin have not been studied in paediatric patients under 6 years of age.

5.2 PHARMACOKINETIC PROPERTIES

TOBRAMYCIN WOCKHARDT contains tobramycin, a cationic polar molecule that does not readily cross epithelial membranes. The bioavailability of tobramycin may vary because of individual differences in nebuliser performance and airway pathology. Following administration of tobramycin, tobramycin remains concentrated primarily in the airways.

Sputum Concentrations

Ten minutes after inhalation of the first 300 mg dose of tobramycin, the average concentration of tobramycin was 1237 mcg/g (ranging from 35 to 7414 mcg/g) in sputum. Tobramycin does not accumulate in sputum. After 20 weeks of therapy with the tobramycin regimen, the average concentration of tobramycin at ten minutes after inhalation was 1154 mcg/g (ranging from 39 to 8085 mcg/g) in sputum. High variability of tobramycin concentration in sputum was observed. Two hours after inhalation, sputum concentrations declined to approximately 14% of tobramycin levels at ten minutes after inhalation.

Serum Concentrations

The average serum concentration of tobramycin one hour after inhalation of a single 300 mg dose of tobramycin by cystic fibrosis patients was 0.95 mcg/mL. After 20 weeks of therapy on the tobramycin regimen, the average serum tobramycin concentration one hour after dosing was 1.05 g/mL.

Elimination

The elimination half-life of tobramycin from serum is approximately 2 hours after intravenous (IV) administration. Assuming tobramycin absorbed following inhalation behaves similarly to tobramycin following IV administration, systemically absorbed tobramycin is eliminated principally by glomerular filtration. Unabsorbed tobramycin, following tobramycin administration, is probably eliminated primarily in expectorated sputum.

Microbiology

Tobramycin is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. It acts primarily by disrupting protein synthesis, leading to altered cell membrane permeability, progressive disruption of the cell envelope, and eventual cell death. Tobramycin has in vitro activity against a wide range of gram-negative organisms including *Pseudomonas aeruginosa*. It is bactericidal at concentrations equal to-or slightly greater than inhibitory concentrations.

5.3 PRECLINICAL SAFETY DATA

Animal Toxicology

Bronchoepithelial hyperplasia and chronic interstitial inflammation around terminal bronchioles occurred in studies in rats after daily inhalational exposures to tobramycin for 6 months. Progression of the hyperplastic lesions is currently uncertain and this will be assessed further in a 2 year inhalational study in progress.

Carcinogenesis

A two-year rat inhalation toxicology study to assess the carcinogenic potential of tobramycin has been completed. Rats were exposed to tobramycin for up to 1.5 hours per day for 95 weeks. Serum levels of tobramycin of up to 35 µg/mL were measured in rats. There was no drug-related increase in the incidence of any variety of tumour.

Mutagenicity

Tobramycin has been evaluated for genotoxicity in a battery of assays for gene mutations and chromosomal damage. Tobramycin was negative in the bacterial reverse mutation and the mouse lymphoma forward mutation assays. Tobramycin did not induce chromosomal aberrations in Chinese hamster ovary cells, and was negative in the mouse micronucleus test.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride, Sulfuric acid, Sodium hydroxide, Nitrogen, sterile water for injections

6.2 INCOMPATIBILITIES

Not Applicable.

6.3 SHELF LIFE

3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

TOBRAMYCIN WOCKHARDT should be stored under refrigeration at 2-8°C. Upon removal from the refrigerator, or if refrigeration is unavailable, TOBRAMYCIN WOCKHARDT pouches (opened or unopened) may be stored at room temperature (up to 25°C) for up to 28 days. TOBRAMYCIN WOCKHARDT should not be used beyond the expiration date stamped on the ampoule when stored under refrigeration (2-8°C) or beyond 28 days when stored at room temperature (up to 25°C). TOBRAMYCIN WOCKHARDT should not be used if it is cloudy or if there are particles in the solution.

Do not Freeze.

TOBRAMYCIN WOCKHARDT ampoules should not be exposed to intense light. The solution in the ampoule is slightly yellow, but may darken with age if not stored in the refrigerator; however, the colour change does not indicate any change in the quality of the product as long as it is stored within the recommended storage conditions. The contents of the whole ampoule should be used directly after opening; opened ampoules should never be stored for re-use.

Protect From Light.

6.5 NATURE AND CONTENTS OF CONTAINER

TOBRAMYCIN WOCKHARDT is supplied in single-use, low-density polyethylene plastic 5 mL ampoules, containing 300 mg tobramycin in 5 mL solution. TOBRAMYCIN WOCKHARDT is packaged in laminated foil over-pouches, each containing 7 ampoules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements for disposal.

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

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

Distributed in New Zealand by:

Healthcare Logistics
On behalf of InterPharma Pty Ltd
58 Richard Pearse Drive
Airport Oaks
Mangere 2022
Phone 09 9185100

9 DATE OF FIRST APPROVAL

9 Aug 2019

10 DATE OF REVISION OF THE TEXT

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	New Data Sheet