AUSTRALIAN PRODUCT INFORMATION

TOBI® & TOBI® PODHALER®

(Tobramycin) conventional inhalation,

(Tobramycin) hard capsule

1 NAME OF THE MEDICINE

Tobramycin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TOBI solution for inhalation (TOBI solution) and TOBI PODHALER capsules for inhalation (TOBI PODHALER) are two different formulations of tobramycin specifically developed for administration by inhalation.

TOBI solution for inhalation

Each TOBI solution single-use 5 mL ampoule contains 300 mg tobramycin and 11.25 mg sodium chloride in sterile water for injections. Sulfuric acid and sodium hydroxide are added to adjust the pH to 6.0. Nitrogen is used for sparging. All ingredients meet USP requirements. The formulation contains no preservatives.

TOBI PODHALER

Each TOBI PODHALER capsule contains tobramycin 28 mg, distearoylphosphatidylcholine, calcium chloride dihydrate, and sulfuric acid. The hard capsule shell contains hypromellose, potassium chloride, carrageenan, carnauba wax, butan-1-ol, indigo carmine aluminium lake, isopropyl alcohol, propylene glycol, purified water, shellac, titanium dioxide.

Excipients with known effect: soya bean products

3 PHARMACEUTICAL FORM

TOBI solution for inhalation ampoule

TOBI solution 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.

TOBI PODHALER capsules for inhalation

TOBI PODHALER includes clear, colorless hypromellose capsules containing a white to almost-white powder for inhalation. The capsules have ”MYL TPH” in blue radial imprint on one part of the capsule and the Mylan logo in blue radial imprint on the other part of the capsule. The capsules must be administered specifically with a Podhaler® device provided in the same pack.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TOBI solution and TOBI PODHALER are 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 FEV_1 < 25 % or > 80 % predicted at screening, or patients colonized with *Burkholderia cepacia* (see section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Dosage is not adjusted by age or weight. The doses should be taken as close to 12 hours apart as possible; they should not be taken less than six hours apart. In case of a missed dose with at least 6 hours until the next dose, the patient should take the dose as soon as possible. Otherwise, the patient should wait for the next dose and not inhale more medication to make up for the missed dose.

TOBI solution or TOBI PODHALER are administered twice daily in alternating periods of 28 days. After 28 days of therapy, patients should stop therapy for the next 28 days, and then resume therapy for the next 28 day on/28 day off cycle.

Therapy should be initiated by a physician experienced in the management of cystic fibrosis. Treatment with TOBI should be continued on a cyclical basis for as long as the physician considers that the patient is gaining clinical benefit from the inclusion of TOBI solution or TOBI PODHALER in their treatment regimen. If clinical deterioration of pulmonary status is evident, additional anti-pseudomonal therapy should be considered.

TOBI solution

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.

TOBI PODHALER

Adults and paediatric patients 6 years of age and older

The recommended dosage is four capsules (4 x 28 mg = 112 mg tobramycin) administered twice daily for 28 days.

Dosing in special populations

Paediatric population below 6 years

TOBI solution and TOBI PODHALER are not indicated for use in paediatric patients less than 6 years of age.

Elderly patients (≥ 65 years)

There are insufficient data in this population to support a recommendation for or against dose adjustment. Renal function in elderly patients should be taken into account while using TOBI Solution and TOBI PODHALER (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Patients with renal impairment

Patients with serum creatinine 176.8 micromoles per litre (0.18 mmol/L) or more and blood urea nitrogen (BUN) 14 mmol/L or more have not been included in clinical studies and there are no data in this population to support a recommendation for or against dose adjustment with TOBI. Also see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

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.

Patients after organ transplantation

Adequate data do not exist for the use in patients after organ transplantation.

Administration

Where patients are receiving several different inhaled medications and performing chest physiotherapy, it is recommended that TOBI is taken last.

TOBI solution

TOBI solution is supplied as a single-use, ready to use ampoule and is administered by inhalation, over an approximately 15 minute period, using a hand-held nebuliser and compressor. See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

TOBI solution should be inhaled whilst the patient is sitting or standing upright and breathing normally through the mouthpiece of the nebulizer. Nose clips may be used to help the patient breathe through the mouth.

TOBI should not be diluted or mixed with dornase alfa or other medications in the nebuliser. See section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

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

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

TOBI PODHALER

TOBI PODHALER capsules are for oral inhalation route only using a Podhaler device. The capsules must not be administered by any other route.

To ensure proper administration of the medicine, the physician or other healthcare professional should show the patient how to operate the Podhaler device. In addition, any caregivers must be advised to provide assistance to children starting TOBI PODHALER treatment, particularly those aged 10 years or younger, and that they should continue to supervise them until they are able to use the Podhaler device without help.

Studies under high humidity conditions (25ºC/75% relative humidity) during product use showed some accumulation of powder (drug) in the inhaler. Patients should be made aware of the need to store the product in the original package when not in use and to avoid using the product in humid environments (see section 6.4 SPECIAL PRECAUTIONS FOR STORAGE).

Basic instructions for TOBI PODHALER use

1. Wash and fully dry hands.

2. Just before use, remove the Podhaler device from its case by holding the base and twisting off the top of the case in a counter-clockwise direction. Set the top of the case aside. Briefly inspect the inhaler to make sure it is not damaged or dirty, and then stand it in the base of the case.

3. Holding the body of the inhaler, unscrew and remove the mouthpiece from the inhaler body. Set the mouthpiece aside on a clean, dry surface.

4. Separate the morning and evening doses from the capsule card.

5. Peel back the foil from the capsule card to reveal one TOBI PODHALER capsule and remove it from the card.

6. Immediately insert the capsule into the inhaler chamber. Replace the mouthpiece and screw it on firmly until it stops. Do not over tighten.

7. To puncture the capsule, hold the inhaler with the mouthpiece down, press the button firmly with your thumb as far as it will go, then release the button. The medication is now ready for inhalation.

8. Fully exhale away from the inhaler.

9. Position the inhaler with the mouthpiece facing towards you. Place mouth over the mouthpiece creating a tight seal. Inhale the powder deeply with a single continuous inhalation.

10. Remove inhaler from mouth, and hold breath for a count of approximately 5 seconds, then exhale normally away from the inhaler.

11. After a few normal breaths away from the inhaler, perform a second inhalation from the same capsule, repeating steps 8 - 10.

12. Unscrew mouthpiece and remove the capsule from the chamber. Inspect the used capsule. It should appear punctured and empty.

13. If the capsule is punctured but still contains some powder, place it back into the chamber with the punctured side of the capsule inserted first, replace the mouthpiece and take another two inhalations from the capsule (repeat step 6, then steps 8-12). Reinspect the capsule.

14. If the capsule appears to be unpunctured, place it back into the chamber, replace the mouthpiece, press the button firmly as far as it goes and take another two inhalations from the capsule (repeat steps 6-12). If the capsule is still full and appears to be unpunctured, replace the inhaler with the reserve inhaler and try again (repeat steps 2, 3, and 6-12).

15. Discard the empty capsule.

16. Repeat, starting at step 5, for the remaining 3 capsules of the dose.

17. Replace the mouthpiece and screw it on firmly until it stops. When the full dose (4 capsules) has been inhaled, wipe the mouthpiece with a clean, dry cloth.

18. Place inhaler back in storage case and close tightly. The inhaler should never be washed with water.

19. TOBI PODHALER should be kept out of sight and reach of children, except when administered therapeutically under appropriate adult supervision.

20. Caregivers should provide assistance to children starting TOBI PODHALER treatment, particularly those aged 10 years or younger, and should continue to supervise them until they are able to use the Podhaler inhaler properly without help.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

TOBI solution and TOBI PODHALER are for oral inhalation only.

TOBI solution is not for subcutaneous, intravenous or intrathecal administration.

TOBI PODHALER capsules must not be swallowed.

The use of TOBI solution with nebulisers other than the PARI LC PLUS reusable nebuliser or PARI Pro-neb system with a DeVilbiss Pulmo-Aide compressor has not been adequately studied.

Caution should be exercised when prescribing TOBI solution or TOBI PODHALER 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 TOBI solution or TOBI PODHALER during pregnancy, or become pregnant while taking one of these products should be apprised of the potential hazard to the foetus.

Ototoxicity

In clinical studies, 4 patients (1 %) reported mild to moderate hearing loss in clinical studies of up to 9 treatment cycles of TOBI solution. 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 TOBI solution.

Hearing loss and tinnitus were reported by patients in the TOBI PODHALER clinical trials (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

In postmarketing experience, some patients receiving TOBI solution and extensive previous or concomitant parenteral aminoglycosides have reported hearing loss. Some of these reports occurred in patients with previous or concomitant treatment with systemic aminoglycosides. 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 ADVERSE EFFECTS (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.

Caution should be exercised when prescribing TOBI solution or TOBI PODHALER to patients with known or suspected auditory or vestibular dysfunction. Physicians should consider an audiogram before initiating TOBI therapy for patients who show any evidence of auditory dysfunction, or who are at increased risk for auditory dysfunction.

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

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

Risk of Ototoxicity Due to Mitochondrial DNA Variants

Cases of ototoxicity with aminoglycosides have been observed in patients with certain variants in the mitochondrially encoded 12S rRNA gene (MT-RNR1), particularly the m.1555A>G variant. Ototoxicity occurred in some patients even when their aminoglycoside serum levels were within the recommended range. Mitochondrial DNA variants are present in less than 1% of the general US population, and the proportion of the variant carriers who may develop ototoxicity as well as the severity of ototoxicity is unknown. In case of known maternal history of ototoxicity due to aminoglycoside use or a known mitochondrial DNA variant in the patient, consider alternative treatments other than aminoglycosides unless the increased risk of permanent hearing loss is outweighed by the severity of infection and lack of safe and effective alternative therapies.

Nephrotoxicity

Nephrotoxicity was not seen during TOBI solution or TOBI PODHALER clinical studies but has been associated with aminoglycosides as a class. Nephrotoxicity has been reported with the use of parenteral aminoglycosides. Caution should be exercised when prescribing TOBI solution or TOBI PODHALER to patients with known or suspected renal dysfunction.

If nephrotoxicity occurs in a patient receiving TOBI solution or TOBI PODHALER, 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 of renal function should be monitored as clinically appropriate. Urea and creatinine levels should be reassessed after every 6 complete cycles of therapy.

Neuromuscular dysfunction

TOBI solution or TOBI PODHALER 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 TOBI solution or TOBI PODHALER. Bronchospasm should be treated as medically appropriate. If an allergic response is suspected, TOBI solution or TOBI PODHALER should be discontinued.

In clinical studies of TOBI, changes in FEV_1 measured after the inhaled doses were similar in the TOBI and placebo groups.

The first dose of TOBI PODHALER should be given under supervision. FEV_1 should be measured before and after inhalation of the first dose of TOBI PODHALER. If there is evidence of therapy-induced bronchospasm, the physician should carefully evaluate whether the benefits of continued use of TOBI PODHALER outweigh the risks to the patient.

Cough

Cough was the most commonly reported adverse event considered treatment related for both TOBI solution and TOBI PODHALER, but was reported more frequently in patients treated with TOBI PODHALER. If there is evidence of continued therapy-induced cough, the physician should consider the use of alternative therapeutic options.

Haemoptysis

Haemoptysis is a complication in cystic fibrosis and is more frequent in adults. Patients with clinically significant haemoptysis (> 60 mL) were excluded from the clinical studies so no data exist on the use of TOBI solution or TOBI PODHALER in these patients. The use of TOBI solution or TOBI PODHALER in such patients should be undertaken only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.

Concomitant antibiotic therapy

Serum concentrations of tobramycin should be monitored in patients receiving concomitant parenteral aminoglycoside therapy (or other medications that can affect renal excretion). These patients should be monitored as clinically appropriate, taking into account the risk of cumulative toxicity. See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Decrease in susceptibility to tobramycin

In clinical studies, some patients on TOBI PODHALER therapy showed an increase in aminoglycoside MICs for *P. aeruginosa* isolates tested. There is a theoretical risk that patients being treated with TOBI PODHALER may develop *P. aeruginosa* isolates resistant to tobramycin. The *in vitro* antimicrobial susceptibility test methods used for parenteral tobramycin therapy can be used to monitor the susceptibility of *P. aeruginosa* isolated from CF patients. Also see section 5.1 PHARMACODYNAMIC PROPERTIES.

Clostridium difficile-associated disease

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including tobramycin. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Use in 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.

Use in renal impairment

Tobramycin is primarily excreted unchanged in the urine and renal function is expected to affect the exposure to tobramycin. See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Use in the elderly

See section 5.2 Pharmacokinetics in special patient groups – Elderly patients.

Paediatric use

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

Effects on laboratory tests

Audiograms:

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 TOBI solution or TOBI PODHALER, serum tobramycin concentrations are approximately 1 μg/mL one hour after dose administration and do not require routine monitoring.

Serum concentrations of tobramycin should be monitored in patients receiving concomitant parenteral aminoglycoside therapy (or other medications that can affect renal excretion). These patients should be monitored as clinically appropriate, taking into account the risk of cumulative toxicity.

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 with TOBI solution and TOBI PODHALER did not reveal any imbalance in the percentage of patients in the TOBI and placebo groups who experienced at least a 50 % rise in serum creatinine from baseline (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Laboratory tests of urine and renal function should be conducted at the discretion of the treating physician.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinical drug interaction studies have been performed with TOBI solution or TOBI PODHALER.

Some diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. TOBI should not be administered concomitantly with etacrynic acid, furosemide, urea, or intravenous mannitol.

Based on the interaction profile for tobramycin following intravenous and aerosolized administration, concurrent and/or sequential use of TOBI with other drugs with neurotoxic, nephrotoxic, or ototoxic potential should be avoided.

In patients with a predisposing risk due to previous prolonged, systemic aminoglycoside therapy, it may be necessary to consider renal and audiological assessment before initiating TOBI therapy.

Other medicinal products that have been reported to increase the potential toxicity of parenterally administered aminoglycosides include: amphotericin B, cefalotin, ciclosporin, tacrolimus, polymyxins (risk of increased nephrotoxicity); platinum compounds (risk of increased nephrotoxicity and ototoxicity); anticholinesterases, and botulinum toxin (neuromuscular effects).

Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.

Absence of interactions

In clinical studies of TOBI solution, patients taking TOBI solution concomitantly with domase alfa, β2-agonists, inhaled corticosteroids, other anti-pseudomonal antibiotics, or parenteral aminoglycosides demonstrated adverse experience profiles similar to the study population as a whole.

In a clinical study with TOBI PODHALER, similar proportions of patients receiving TOBI PODHALER and TOBI solution continued to take dornase alfa, bronchodilators, inhaled corticosteroids and macrolides.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No reproduction toxicology studies have been conducted with TOBI administered by inhalation.

Subcutaneous administration of up to 600 mg/m^2/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

Pregnancy Category D

There are no adequate data from the use of tobramycin administered by inhalation in pregnant women.

Subcutaneous administration of tobramycin at doses of 600 or 220 mg/m^2/day during organogenesis was not teratogenic in rats or rabbits, respectively. Doses of tobramycin ≥440 mg/m^2/day were severely maternally toxic to rabbits and precluded the evaluation of teratogenicity.

Aminoglycosides can cause foetal harm (e.g., 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 TOBI during pregnancy should be undertaken only if the benefits to the mother outweigh the risks to the foetus or baby. If TOBI is used during pregnancy, or if the patient becomes pregnant while taking TOBI, 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 TOBI 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 TOBI, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse Events in Clinical Trials

TOBI solution

TOBI solution 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 TOBI solution 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 TOBI solution-treated patients. Thirty-three patients (13 %) treated with TOBI solution complained of voice alteration compared to 17 (7 %) placebo patients. Voice alteration was more common in the on-drug periods.

Eight patients from the TOBI solution group (3 %) reported tinnitus compared to no placebo patients. All episodes were transient, resolved without discontinuation of the TOBI solution 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 TOBI solution and placebo groups.

Nine (3%) patients in the TOBI solution 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 TOBI group, creatinine decreased at the next visit.

Table 1 lists the percent of patients with treatment-emergent adverse experiences that occurred in 25 % 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 TOBI solution during the first three cycles of therapy.

Table 1: Percent of patients treated with TOBI solution or placebo with treatment-emergent adverse events occurring in ≥ 5 % of patients in any group

	During the Open Label Extension [a]		**During the Placebo-Controlled Studies**	
Adverse Event	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	28	22	14	22
Nausea	16	19	11	16
Diarrhea	17	13	6	10
Dyspepsia	5	5	4	4
Oral Moniliasis	6	3	2	1
Metabolic and 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
Haemic and Lymphatic System				
Lymphadenopathy	8	7	4	2
Nervous System				
Dizziness	6	6	6	8
Somnolence	6	6	2	4
Musculoskeletal				
Myalgia	6	5	5	3

[a] Patients 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 TOBI solution during both the controlled study and the open label extension.

TOBI PODHALER

TOBI PODHALER has been evaluated for safety in 395 CF patients exposed to at least one dose of TOBI PODHALER, including 273 who were exposed across three cycles (6 months) of treatment. Each cycle consisted of 28 days on-treatment (with 112 mg administered twice daily) and 28 days off treatment. The majority of patients evaluated for safety were entered into Study C2302 which included an active-treatment control group administered TOBI solution. The TOBI PODHALER group included 308 patients; the TOBI solution group numbered 209 patients (see section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

The primary safety population, randomized in a planned 3:2 ratio, consisted of the 308 patients treated with Podhaler capsules and 209 patients treated with TOBI solution 300 mg/5 mL tobramycin nebulizer solution) in Study C2302, an open-label study comparing Podhaler capsules with TOBI solution over 3 treatment cycles. For both treatment groups, mean exposure to medication for each cycle was 28-29 days.

The supportive safety population considered an additional 87 patients treated with Podhaler capsules and 49 treated with placebo in Study C2301, which was double-blind for the first treatment cycle, followed by all patients receiving Podhaler capsules for 2 additional cycles. At these exposures, Podhaler capsules were generally well tolerated.

In Study C2302, the most frequently occurring adverse drug reactions (ADRs) related to the respiratory, thoracic and mediastinal system organ class. The most commonly occurring ADRs (by preferred term) were cough and lung disorder in both the Podhaler capsules and TOBI solution treatment groups.

During the placebo-controlled cycle of Study C2301, the overall incidence of ADRs was lower in the Podhaler treatment group than in the placebo group, with the exceptions of pharyngolaryngeal pain, dysphonia, and dysgeusia.

In Study C2301, no patients reported adverse events related to hearing loss. Two patients were found during planned audiology testing to have significant decreases in hearing (defined as 10-15 dB in at least two consecutive frequencies, or 20 dB or more at a single frequency). In Study C2302, hearing complaints such as tinnitus were reported in approximately 2 % of patients overall. Of a subset of patients in Study C2302 who received serial audiology testing, 25.6 % (Podhaler capsules) and 15.6% (TOBI solution) showed decreases from baseline at any visit (80 % of the subset had normal hearing assessments at baseline). However, the majority of such changes was transient and had resolved by the end of the study. Four patients in the Podhaler capsules treatment group experienced significant decreases in hearing which were transient in three patients and persistent in one case. Less than 3 % of patients in either group showed evidence of significant hearing loss. Using the criteria for either ear of 10 dB loss at 3 consecutive frequencies, 15 dB loss at two consecutive frequencies and 20 dB loss at any frequency, three Podhaler capsules patients and two TOBI solution patients (matching the randomization ratio) were judged to have ototoxicity.

Adverse drug reactions reported in Study C2302 regardless of relationship to study medication are listed in Table 2. Adverse reactions considered at least possibly related to study medication are summarized in Table 3. Overall the most frequently reported adverse event was cough which was reported in 48 % of the TOBI PODHALER group compared with 31 % of the TOBI solution group. Discontinuations due to cough were reported by 3.9 % of the TOBI PODHALER group and 1.0 % of the TOBI solution group. Adverse drug reactions from Study C2302 are listed according to MedDRA system organ class in Table 2. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first, and by database. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse reaction: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

Bronchospasm was reported for 1.6 % of the TOBI PODHALER group and 0.5 % of the TOBI solution group.

In Study C2302, hearing complaints such as tinnitus were reported in 1.9 % of patients overall. Of the subsets of patients in this study who underwent serial audiology testing, 25.6 % of the TOBI PODHALER group and 15.6 % of the TOBI solution group showed decreases from baseline at any visit; however, the majority of such changes were transient. Using the criteria of 10 dB loss at 3 consecutive frequencies, 15 dB loss at two consecutive frequencies and 20 dB loss at any one frequency for either ear, three TOBI capsule patients and two TOBI solution patients were judged to have ototoxicity. Deafness including deafness unilateral (reported as mild to moderate hearing loss or increased hearing loss) was reported in 1.0 % of patients receiving TOBI PODHALER and 0.5 % of patients receiving TOBI solution. Aphonia was reported in 1.0% of the TOBI PODHALER group and 0% of the TOBI solution group.

In the placebo-controlled Cycle 1 of Study C2301, which included 46 TOBI PODHALER patients and 49 placebo patients, ADRs included: pharyngolaryngeal pain (10.9 % TOBI PODHALER vs. 0 % placebo, very common) and dysphonia (4.3 % TOBI PODHALER vs. 0 % placebo, common) in the System Organ Class (SOC) Respiratory, Thoracic, and Mediastinal Disorders; and dysgeusia (6.5 % TOBI PODHALER vs. 2.0 % placebo, common) in the SOC Gastrointestinal Disorders.

Table 2: Adverse drug reactions experienced[1] in two or more percent of TOBI PODHALER patients in Study C2302 (TOBI PODHALER vs. TOBI solution, open label), all randomized safety population

System Organ Class/MedDRA Preferred Term	TOBI PODHALER (N=308) % of patients	TOBI solution (N=209) % of patients
Respiratory,Thoracic, and Mediastinal Disorders		
Very Common		
Cough	48.4	31.1
Lung Disorder[2]	33.8	30.1
Productive Cough	18.2	19.6
Dyspnea	15.6	12.4
Oropharyngeal Pain	14.0	10.5
Dysphonia	13.6	3.8
Haemoptysis	13.0	12.4
Common		
Nasal Congestion	8.1	7.2
Rales	7.1	6.2
Wheezing	6.8	6.2
Chest Discomfort	6.5	2.9
Throat Irritation	4.5	1.9

1 Frequency category using CIOMS III

2 Most commonly reported as pulmonary exacerbation

System Organ Class/MedDRA Preferred Term	TOBI PODHALER (N=308) % of patients	TOBI solution (N=209) % of patients
Gastrointestinal Disorders		
Common		
Vomiting	6.2	5.7
Diarrhoea	4.2	1.9
Nausea	7.5	9.6
Dysgeusia	3.9	0.5
Infections and infestations		
Common		
Upper Respiratory Tract Infection	6.8	8.6
Investigations		
Common		
Pulmonary Function Test Decreased	6.8	8.1
Forced Expiratory Volume Decreased	3.9	1.0
Blood Glucose Increased	2.9	0.5
Vascular disorders		
Common		
Epistaxis	2.6	1.9
Nervous system disorders		
Very common		
Headache	11.4	12.0
General Disorders and Administration Site Conditions		
Very common		
Pyrexia	15.6	12.4
Musculoskeletal and Connective Tissue Disorders		
Common		
Musculoskeletal Chest Pain	4.5	4.8
Skin and Subcutaneous Tissue Disorders		
Common		
Rash	2.3	2.4

Events inclusive of all treatment cycles on and off treatment

Post-marketing Surveillance

Some patients receiving TOBI solution and extensive previous or concomitant parenteral aminoglycosides have reported hearing loss during postmarketing surveillance (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Adverse drug reactions derived from spontaneous reports for TOBI solution

The following adverse drug reactions have been derived from post marketing experience with TOBI 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.

Table 3:

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

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

The following adverse drug reactions have been derived from post marketing experience with TOBI PODHALER 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.

Malaise

Sputum discolored

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs and symptoms

In the event of inadvertent administration of tobramycin by the IV route, signs and symptoms of parenteral toxicity from 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, systemic toxicity is unlikely as tobramycin is poorly absorbed from an intact gastrointestinal tract.

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

Treatment

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia). 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 TOBI, 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

Mechanism of action

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 (P. aeruginosa)*. It is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Susceptibility Testing

A single sputum sample from a cystic fibrosis (CF) patient may contain multiple morphotypes of *P. aeruginosa* and each morphotype may have a different level of *in vitro* susceptibility to tobramycin. Treatment for 6 months with TOBI PODHALER 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 CF patients.

The *in vitro* antimicrobial susceptibility test methods used for parenteral tobramycin therapy can be used to monitor the susceptibility of *P. aeruginosa* isolated from CF 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 inhaled administration of TOBI. The relationship between *in vitro* susceptibility test results and clinical outcome with TOBI therapy is not clear.

Clinical trials

Placebo-controlled studies

TOBI solution

Management of pulmonary *Pseudonomas aeruginosa* infection

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 FEV_1% 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 TOBI

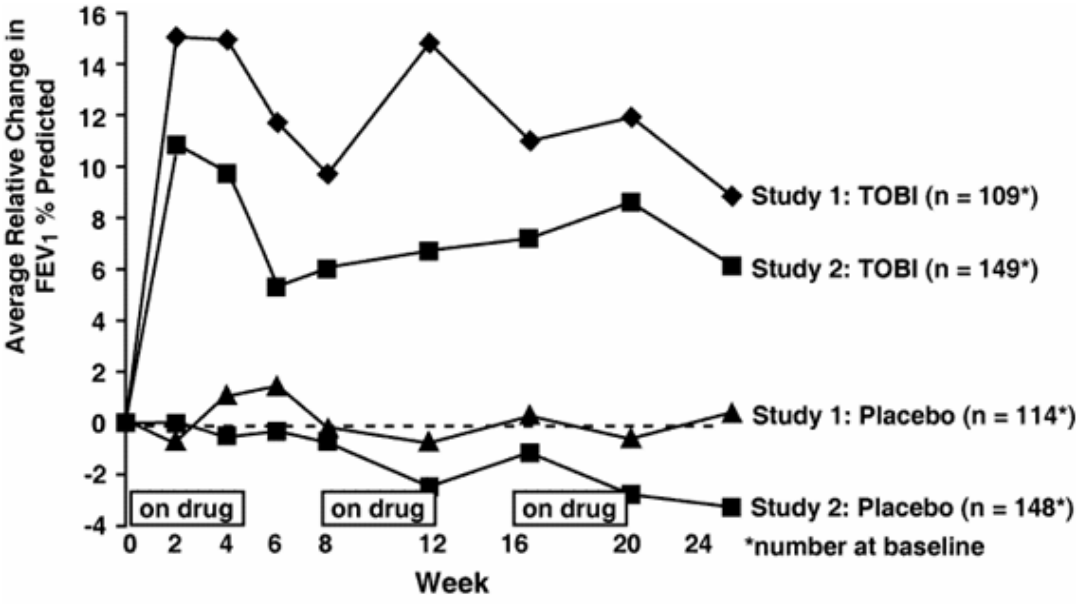
solution (300 mg) or placebo (saline with 1.25 mg quinine) twice daily, delivered by aerosol using a hand-held PARI LC PLUS Reusable Nebuliser with a DeVilbiss Pulmo-Aide Compressor.

All patients received study drug in addition to standard treatment recommended for cystic fibrosis patients, which included oral and parenteral anti-pseudomonal therapy, β_2-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 treatment with TOBI solution 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.

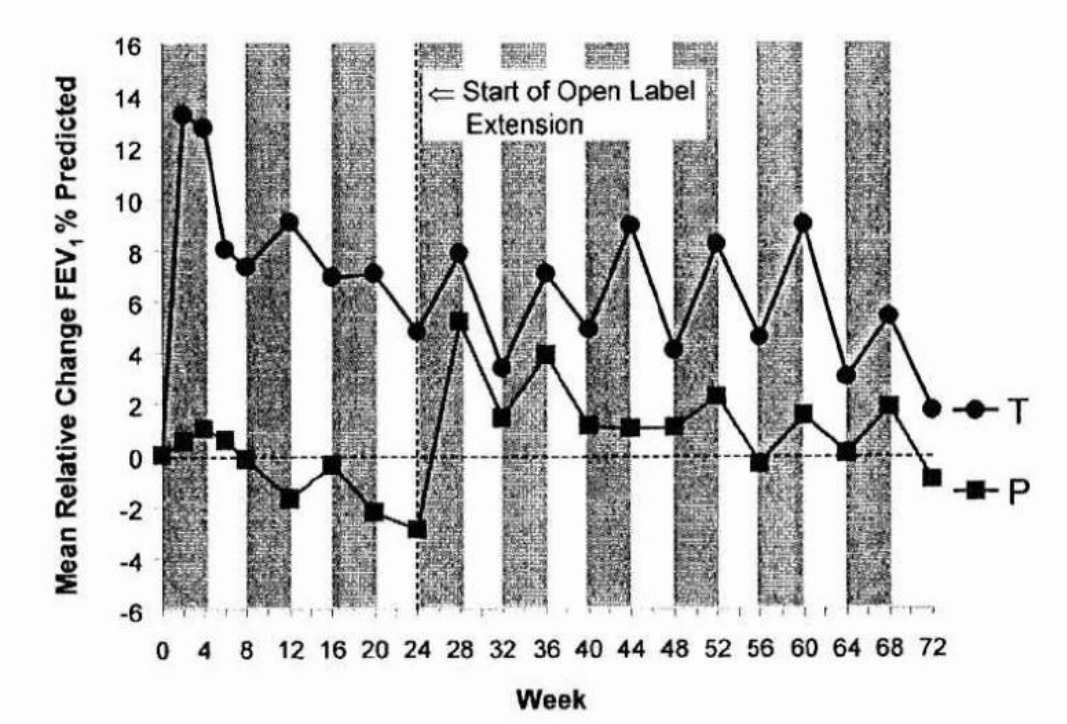
In each of the two placebo-controlled studies, TOBI solution-treated patients experienced significant improvement in pulmonary function. Improvement was demonstrated in the TOBI solution group in Study 1 by an average increase in FEV_1 % predicted of about 11 % relative to baseline (Week 0) during 24 weeks compared to no average change in placebo patients. In Study 2, TOBI solution treated patients had an average increase of about 7 % compared to an average decrease of about 1 % in placebo patients. Figure 1 shows the average relative change in FEV_1 % predicted over 24 weeks for both studies.

Figure 1: Relative change from baseline in FEV_1 % predicted for TOBI solution 300 mg or placebo (saline with 1.25 mg quinine) twice daily



Three hundred 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 TOBI solution, 3 cycles during the controlled studies and 6 cycles during the open label extension. At the end of cycle 9, in these patients FEV_1 % 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 TOBI solution. Whilst on placebo, these patients experienced a mean 2.9 % decrease in FEV_1 % predicted from baseline. After 6 cycles of TOBI solution, FEV_1 % predicted had improved to 1 % below baseline (see Figure 2).

Figure 2: Relative change from baseline in FEV_1 % predicted (Open label extension TOBI solution 300 mg twice daily)

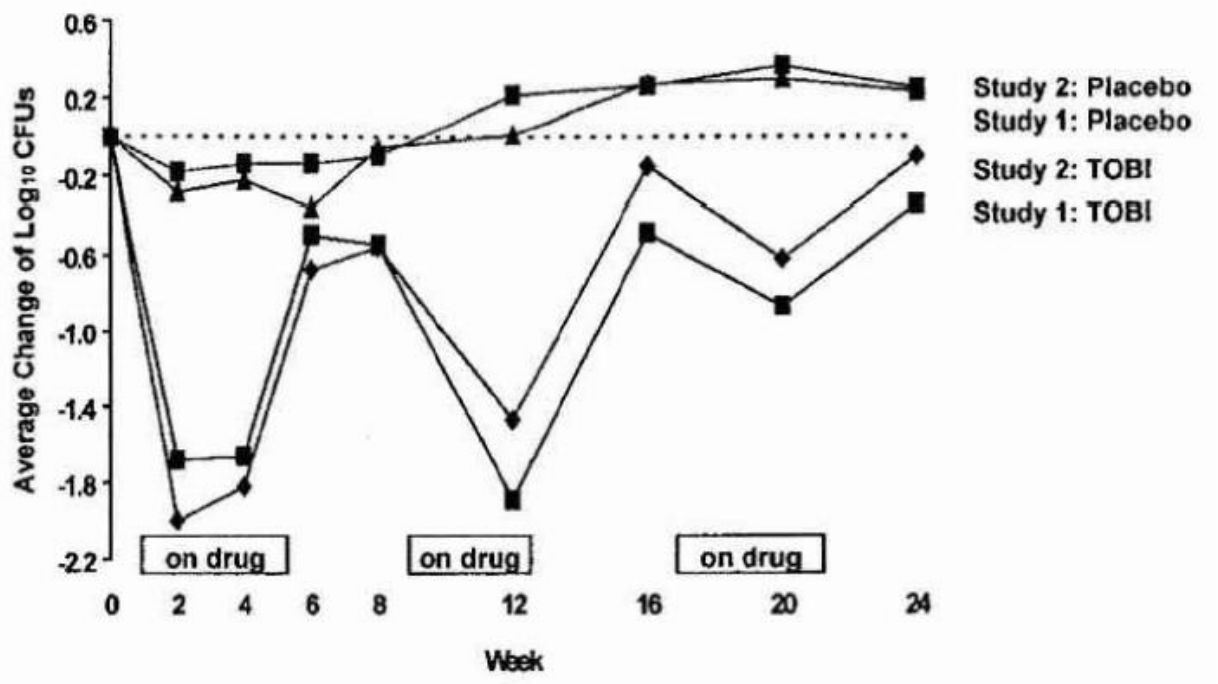


T = 9 Cycles of TOBI solution;
P = 3 Cycles of placebo followed by 6 cycles of TOBI solution
Shaded areas represent On-Drug periods

P. aeruginosa density in sputum was measured during the 24-week placebo-controlled studies. Treatment with TOBI solution 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 see Figure 3. *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 TOBI solution were hospitalised for an average of 5.1 days compared to 8.1 days for placebo patients. Patients treated with TOBI solution 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 TOBI solution 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 anti-pseudomonal antibiotics.

Figure 3: Absolute Change in Log_{10} CFUs for TOBI solution 300 mg or placebo (saline with 1.25 mg quinine) twice daily



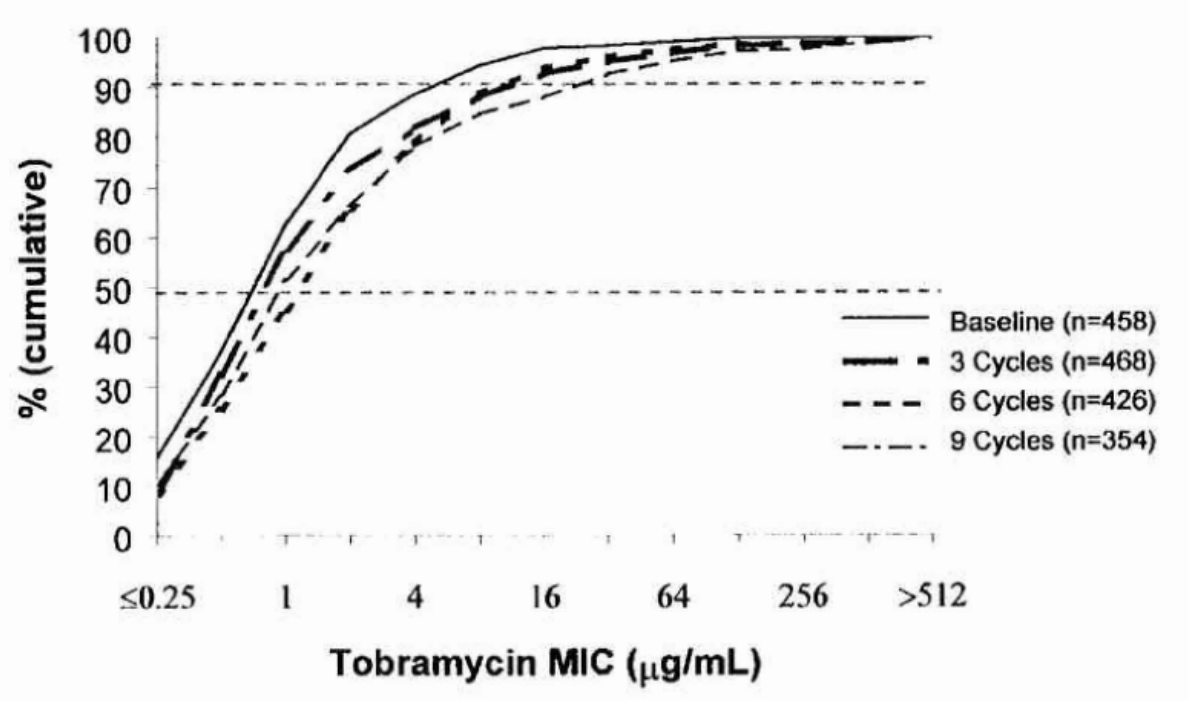
The relationship between *in vitro* susceptibility test results and clinical outcome with TOBI therapy is not clear. However, four TOBI solution patients who began the clinical trial with *P. aeruginosa* isolates having MIC values ≥128 µg/mL did not experience an improvement in FEV_1 or a decrease in 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.

As noted in Figure 4, treatment for 18 months (9 cycles) with TOBI solution in clinical studies demonstrated a trend to decreasing *in vitro* susceptibility of *P. aeruginosa* isolates. The clinical significance of changes in Minimum inhibitory concentrations (MICs) for *P. aeruginosa* has not been clearly established in the treatment of CF patients.

Figure 4: Cumulative Frequency Distribution of tobramycin MIC values all *P. aeruginosa* (n = number of isolates)



Paediatric clinical study

In a double-blind, randomized, placebo-controlled trial, 51 patients aged 3 months to less than 7 years with a confirmed diagnosis of CF and an early colonization with P. aeruginosa (defined as: either first positive culture overall or first positive culture after at least a 1-year history of negative cultures) were treated with TOBI 300 mg/5 mL or placebo, both inhaled via a nebulizer (PARI LC Plus®) twice daily for 28 days. Patients who were treated with anti-pseudomonal therapy in the previous year were excluded.

This was a crossover trial in which 26 patients were allocated to the group receiving TOBI in the first treatment period and placebo in the crossover treatment period, and 25 patients were allocated to the group receiving placebo in the first treatment period and TOBI in the crossover treatment period.

The primary outcome was the proportion of patients free from P. aeruginosa colonization assessed by sputum/throat swab culture after completion of a 28-day treatment period which was 84.6% and 24% ($p<0.001$) for the TOBI and placebo groups, respectively.

The safety and efficacy of TOBI in children <6 years of age is not established. TOBI is not indicated for use in paediatric patients less than 6 years of age.

TOBI PODHALER (Study C2301)

TOBI PODHALER was studied in a randomized, placebo-controlled, multicentre, three-cycle, two treatment group trial in CF patients, aged between 6 and 21 years (mean age 13.3 years), with FEV_1 values from 25 % to 80 % (inclusive) predicted, who were infected with *P. aeruginosa*. Patients had no exposure to inhaled anti-pseudomonal antibiotics within 4 months prior to screening. The first cycle of this trial was conducted as a double-blind, randomized, placebo-controlled, parallel group trial. During the second and third cycles, all subjects were treated with TOBI PODHALER. Four capsules (112 mg tobramycin) were administered twice daily (each morning and evening), for three cycles of 28 days on-treatment and 28 days off-treatment (a total treatment period of 24 weeks).

TOBI PODHALER significantly improved lung function compared with placebo, as shown by the results for the primary endpoint: relative increase in percent predicted FEV_1 after 28 days of treatment (Table 4, and Figure 5). An analysis of covariance was employed for the efficacy analysis, with factors for treatment groups and regions and two continuous covariates (baseline FEV1% predicted and age). The sequential boundaries and stopping rules for the interim analysis were based on the Lan-DeMets procedure with an alpha-spending function that resembles the O'Brien-Fleming boundaries, to ensured control of the overall Type I error at the 0.5 level. A blinded review of the acceptability of spirometry data was conducted prior to study termination (recommended by an external Data Monitoring Committee) at the time of the interim analysis; all efficacy results below are derived from the sensitivity interim analysis after exclusion of technically unreliable spirometry data.

The improvements in lung function achieved during the first treatment cycle were maintained during the subsequent cycles of treatment with capsules. When patients in the placebo treatment group were switched from placebo to capsules at the start of the second treatment cycle, the relative change from baseline in percent predicted FEV_1 was the same as that seen during the first treatment cycle in the TOBI PODHALER treatment group and the improvements were also maintained over time during the third treatment cycle.

The distribution of tobramycin MICs of *P. aeruginosa* isolates was characterized by biotype: mucoid, dry, small colony variants, and overall. Sputum assessments in this study showed that at baseline, 91 % of TOBI PODHALER patients had *P. aeruginosa* isolates with an MIC at least 20 times lower than the mean sputum concentration observed within 30 minutes of dosing. At the end of the third 28 day dosing cycle, 86 % of TOBI PODHALER patients had *P. aeruginosa* with an MIC at least 30 times lower and 89 % of TOBI Podhaler patients had *P. aeruginosa* with a MIC at least 15 times lower than mean sputum concentration observed within 30 minutes of dosing. The sub-group of patients with MIC values > 8 µg/mL at baseline had an improvement in FEV_1 % predicted measurements after 3 cycles of treatment when treated with TOBI PODHALER.

Table 4: Relative change in percent predicted FEV_1 from baseline to end of dosing in Cycle 1 (Study C2301)

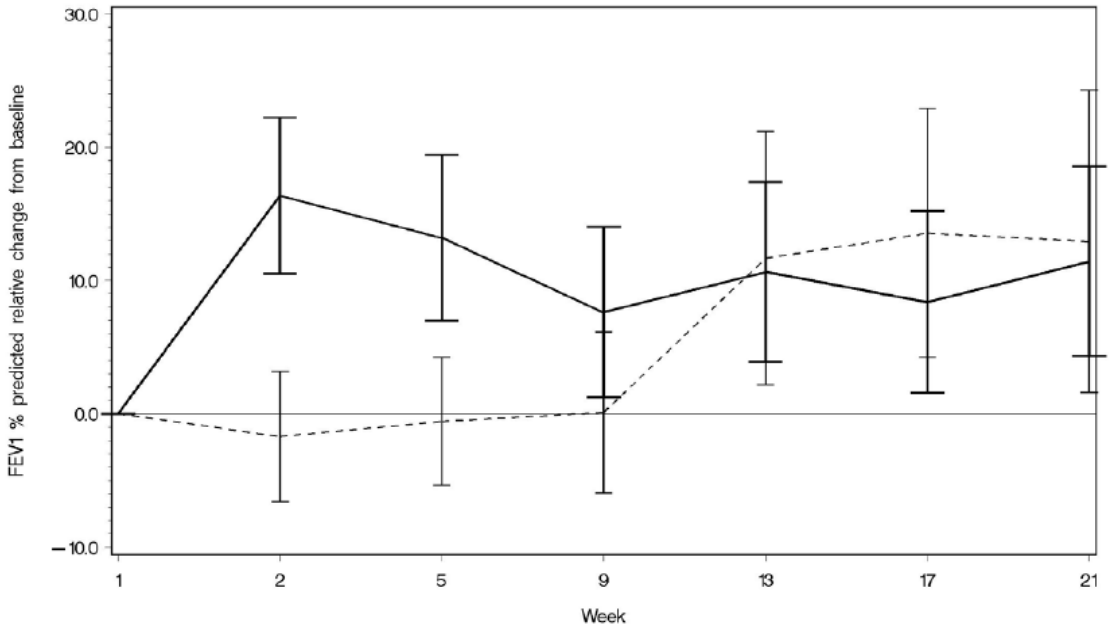
	TOBI PODHALER N=29	**Placebo N=32**	**Difference (SE)**	**95% CI of difference**	**P-value**
n	27	31			
Mean [(1)]	13.21	–0.57	13.79 (3.95)	(5.87,21.70)	0.0010
LS Mean [(2)]	13.97	0.68	13.29 (3.98)	(5.31,21.28)	0.0016

[(1)] Mean, p-value, mean difference, and its 95% confidence interval are calculated from ANOVA with treatment in the model.

[(2)] Least square mean, p-value, least square mean difference, and its 95 % confidence interval are calculated from ANCOVA with treatment, baseline value, age and region in the model.

SE = standard error, n is number of subjects with value at baseline and Day 28. The analysis is based on observed data only; no imputation is performed for missing data.

Figure 5: Study C2301 FEV_1 percent predicted relative change in cycles 1-3 from baseline (on-treatment and off-treatment), by treatment group



Treatment code for cycle 1: Placebo - - - - Podhaler TOBI ---------

Note: Vertical bars show the 95% confidence interval.

Off-treatment phases: from week 5 to 9, week 13 to 17 and week 21 to 25.

X-axis is not linear between 1 to 5 weeks.

Active-controlled studies

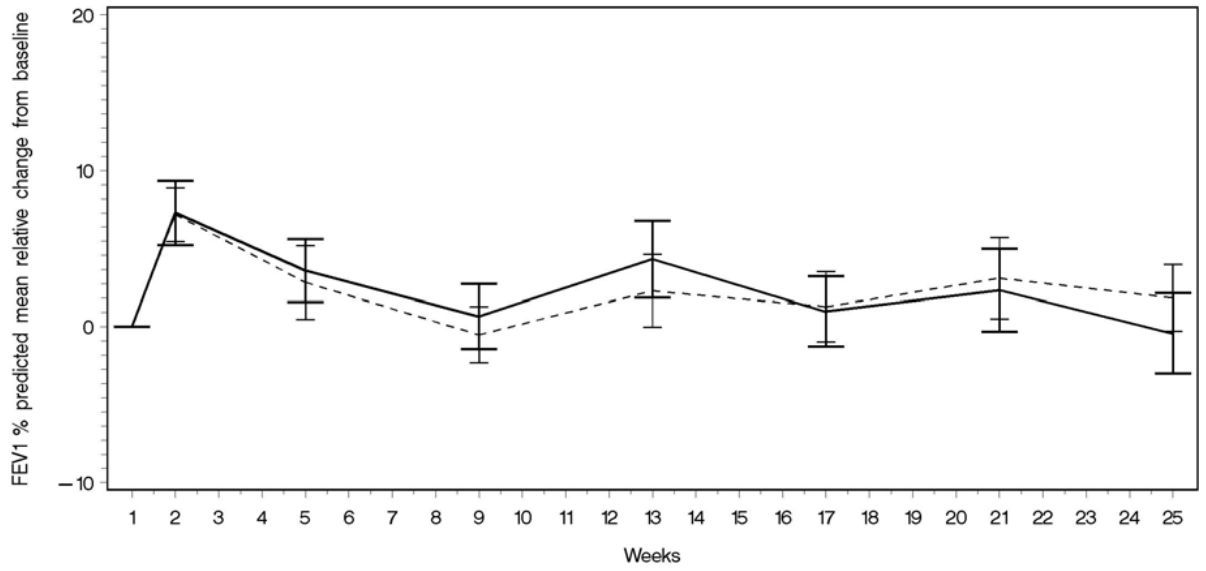
TOBI PODHALER and TOBI solution (Study C2302)

TOBI PODHALER and TOBI solution were studied in a randomized, open-label, multicentre, three-cycle, parallel-arm trial in 553 CF patients, aged between 6 and 66 years (mean age 25.6 years), with FEV_1 values from 25 % to 75 % (inclusive) predicted, who were infected with *P. aeruginosa*. Patients with no exposure to inhaled anti-pseudomonal antibiotics within 28 days prior to study drug administration were randomized in a 3:2 ratio to receive either TOBI PODHALER 112 mg (four 28 mg capsules) or TOBI solution 300 mg (one 300 mg/5 mL ampoule). The study medications were administered twice daily, at the same time each morning and evening, approximately 12 hours (but not less than 6 hours) apart, for three cycles of 28 days on-treatment and 28 days off-treatment (a total treatment period of 24 weeks). Blinding was not possible due to differences in study drug administration. Baseline demographics, disease characteristics and use of concomitant medications were similar between the two treatment groups.

The primary objective of the study was to assess the safety of TOBI PODHALER compared to TOBI solution. The main secondary objective was to assess the efficacy of TOBI PODHALER compared to TOBI solution, the key efficacy variable was the relative change in FEV_1 percent predicted at the end of Cycle 3 compared to baseline. A formal analysis of non-inferiority of TOBI PODHALER relative to TOBI solution was conducted based on a one-sided 85% confidence interval calculated from an analysis of covariance (ANCOVA) of relative change in FEV_1 % predicted from baseline to pre-dose Day 28 of Cycle 3. The non-inferiority margin of Δ = 6% was pre-defined. Treatment with both TOBI

PODHALER and TOBI solution resulted in relative increases from baseline to Day 28 of the third treatment cycle in percent predicted FEV_1 of 5.8 % and 4.7 % respectively (Figure 6).

Figure 6: Relative change from baseline in percent predicted FEV_1 in Cycles 1-3 (Study C2302)



- - - TOBI PODHALER —— TOBI solution

In Study C2302, at the end of the third active treatment period, there was a greater decrease in the mean change from baseline in log_{10} CFUs in both the TOBI PODHALER treatment group (–1.61 log_{10} CFUs) and TOBI solution treatment group (–0.77 log_{10} CFUs) especially during the third treatment cycle (a mean change of –1.61 log_{10} CFUs in the Podhaler capsule treatment group compared with –0.77 log_{10} CFUs in the TOBI solution treatment group. As in the previous study, there was a partial recovery of *P. aeruginosa* density at the end of the 28 day off-treatment phase in both treatment groups, but this was reversed during the on-treatment phase of each treatment cycle.

The mean time to administer a nebulised dose of TOBI solution was approximately 20 minutes, compared with 6 minutes to administer a dose of TOBI PODHALER through the dry powder inhaler. This time excludes any set up and breakdown time for the nebuliser used with TOBI solution.

In Study C2302, patients' satisfaction with treatment was assessed using a modified Treatment Satisfaction Questionnaire for Medication (TSQM) as part of the secondary objective. Patients consistently reported higher levels of satisfaction with treatment with TOBI PODHALER compared with TOBI solution, particularly for assessments of effectiveness, convenience and overall satisfaction.

In study C2302, the proportions of patients in the TOBI PODHALER and TOBI solution treatment groups requiring hospitalization for respiratory events was 24.4 % and 22.0 % respectively. The duration of hospitalizations was 15.6 days and 15.3 days respectively.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

TOBI solution and TOBI PODHALER contain tobramycin, a cationic polar molecule that does not readily cross epithelial membranes. Following inhalation of tobramycin, it is concentrated primarily in the airways. The systemic exposure to tobramycin after inhalation is expected to result from pulmonary

absorption of the dose fraction delivered to the lungs as tobramycin is not absorbed to any appreciable extent when administered via the oral route.

The bioavailability of TOBI solution may vary because of individual differences in nebuliser performance and airway pathology.

Sputum Concentrations

TOBI solution

Ten minutes after inhalation of the first 300 mg dose, the average concentration of tobramycin was 1237 µg/g (ranging from 35 to 7414 µg/g) in sputum. Tobramycin does not accumulate in sputum; after 20 weeks of therapy with the TOBI solution regimen, the average concentration of tobramycin at ten minutes after inhalation was 1154 µm/g (ranging from 39 to 8085 µm/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.

TOBI PODHALER

After inhalation of a single 112 mg dose (4 x 28 mg TOBI PODHALER capsules) in CF patients, sputum C_{max} of tobramycin was 1048 ± 1080 µg/g (mean ± SD). The variability in pharmaco- kinetic parameters was higher in sputum as compared to serum.

Serum Concentrations:

TOBI solution

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

TOBI PODHALER

After inhalation of a single 112 mg dose (4 capsules of 28 mg each) in CF patients, the maximum serum concentration (C_{max}) of tobramycin was 1.02 ± 0.53 µg/mL (mean ± SD) and the median time to reach the peak concentration (T_{max}) was one hour. At the end of a 4-week dosing cycle of TOBI PODHALER (112 mg twice daily), maximum average serum concentrations of tobramycin 1 hour after dosing was 1.99 ± 0.59 µg/mL.

Distribution

A population pharmacokinetic analysis for TOBI PODHALER in CF patients estimated the apparent volume of distribution of tobramycin in the central compartment to be 84.1 L for a typical CF patient. While the volume was shown to vary with body mass index (BMI) and lung function (as FEV_1% predicted), model-based simulations showed that peak (C_{max}) and trough (C_{trough}) concentrations were not impacted markedly with changes in BMI or lung function. Binding of tobramycin to serum proteins is negligible.

Metabolism

Tobramycin is not metabolized and is primarily excreted unchanged in the urine.

Excretion

The elimination half-life of tobramycin from serum is approximately 2 hours after intravenous (IV) administration. The apparent terminal half-life of tobramycin in serum after inhalation of a single 300mg dose of TOBI solution or a single 112 mg dose of TOBI PODHALER was approximately 3 hours in CF patients in both dosage forms.

Assuming tobramycin absorbed following inhalation behaves similarly to tobramycin following IV administration; systemically absorbed tobramycin is eliminated principally by glomerular filtration. Unabsorbed tobramycin, following TOBI solution or TOBI PODHALER administration, is probably eliminated primarily in expectorated sputum.

A population pharmacokinetic analysis for TOBI PODHALER in CF patients aged 6 to 66 years estimated the apparent serum clearance of tobramycin to be 14 L/h. This analysis did not show gender- or age-related pharmacokinetic differences.

Effect of food

Assessments of food-effect were not performed as TOBI solution and TOBI PODHALER are administered by oral inhalation.

Pharmacokinetics in special patient groups

Renal impairment

Tobramycin is primarily excreted unchanged in the urine and renal function is expected to affect the exposure to tobramycin. Patients with serum creatinine 176.8 micromoles per litre (0.18 mmol/L) or more and blood urea nitrogen (BUN) 14 mmol/L or more have not been included in clinical studies and there are no data in this population to support a recommendation for or against dose adjustment with TOBI solution or TOBI PODHALER. Refer to section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and section 4.2 DOSE AND METHOD OF ADMINISTRATION.

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.

Patients after organ transplantation

Adequate data do not exist for the use of TOBI solution or TOBI PODHALER in these patients.

Elderly patients

Renal function in elderly patients should be taken into account as systemically absorbed tobramycin is primarily excreted unchanged in the urine. Refer to section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric population below 6 years

No pharmacokinetic studies have been conducted in children below 6 years of age. Children 6 years and older have been included in clinical studies in which there was no dose adjustment made based on age or weight.

Race

Ethnic sensitivity studies have not been conducted. Since tobramycin is not metabolized, it is not expected that ethnic origin would influence exposure.

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 TOBI for 6 months.

Genotoxicity

TOBI 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.

Carcinogenicity

A two-year rat inhalation toxicology study to assess the carcinogenic potential of TOBI has been completed. Rats were exposed to tobramycin for up to 1.5 h/day for 95 weeks. Serum levels of tobramycin of up to 35 μg/mL were measured in rats, in contrast to the maximum 1.99 ± 0.59 μg/mL level observed in CF patients in clinical trials. At the highest doses in rats, the estimated dose of tobramycin deposited in the lungs and adjusted for body surface area, was similar to the human clinical dose. There was no drug-related increase in the incidence of any variety of tumour.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 – QUALITATIVE AND QUANTITATIVE COMPOSITION.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

TOBI solution

TOBI solution should be stored under refrigeration at 2°C-8°C. Upon removal from the refrigerator, or if refrigeration is unavailable, TOBI pouches (opened or unopened) may be stored at room temperature (up to 25°C) for up to 28 days.

TOBI solution should not be used beyond the expiration date stamped on the ampoule when stored under refrigeration (2 °C-8°C) or beyond 28 days when stored at room temperature (up to 25°C). TOBI solution should not be used if it is cloudy or if there are particles in the solution.

TOBI solution 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.

TOBI PODHALER

Do not store above 30°C. Protect from moisture. Store capsules in their original packaging and remove immediately before use only.

Podhaler device

Store the Podhaler device in its tightly closed case when not in use. Discard each Podhaler device after seven days use.

6.5 NATURE AND CONTENTS OF CONTAINER

TOBI solution

TOBI solution for inhalation is supplied in single-use, low-density polyethylene plastic 5 mL ampoules, containing 300 mg tobramycin. TOBI solution is packaged in laminated foil over-pouches, each containing 4 ampoules. Packs of 4*, 8*, or 56 ampoules.

TOBI PODHALER

Each TOBI PODHALER capsule contains a white to almost white powder in a clear, colourless capsule with "MYL TPH" in blue radial imprint on one part of the capsule and the Mylan logo in blue radial imprint on the other part of the capsule. Capsules are packed in blister strips, with each blister strip containing a daily dose of 8 capsules; 4 capsules taken in the morning and 4 capsules taken in the evening.

The Podhaler is a plastic inhalation device, used to puncture the capsules and deliver a tobramycin aerosol into the lungs. Each Podhaler device is housed in a sealed plastic case, which is used to protect the device during transport, storage, and the in-use period.

TOBI PODHALER is supplied in a monthly pack of 224 capsules with 5 Podhalers (4 boxes of 56 capsules with 1 Podhaler plus 1 spare Podhaler). The sample pack is supplied in a pack of 8 capsules with 1 Podhaler.

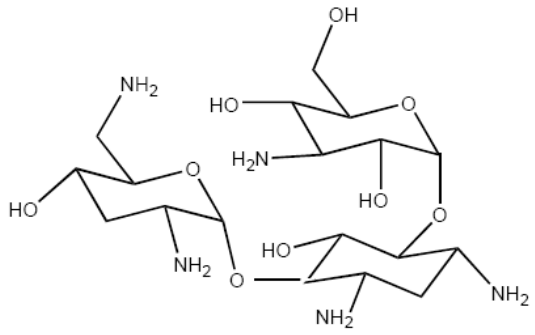
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

$C_{18}H_{37}N_5O_9$



CAS number

32986-56-4

Chemical name: *O*-3-amino-3-deoxy-α-D-glucopyranosyl-(l→4)-*O*-[2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl-(l → 6)]-2-deoxy-L-streptamine.

Molecular weight: 467.52

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

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Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

18 Feb 2000: TOBI tobramycin 300mg/5mL solution for inhalation ampoule (AUST R 73172)

06 Mar 2012: TOBI PODHALER tobramycin 28 mg hard capsule for inhalation blister pack with Podhaler device (AUST R 182302)

10 DATE OF REVISION

21/05/2024

Summary table of changes

Section Changed	Summary of new information
2	Update to schedule 1 declaration for TOBI PODHALER
All	Minor editorial changes

TOBI_TOBI PODHALER_pi\May24/00 (TOBI CCDS 27-Jan-2023; TOBI PODHALER CCDS 27-Jan-2023)