PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**TOBI®**

Tobramycin Inhalation Solution

Solution, 300 mg / 5mL tobramycin (as sulfate), Inhalation

USP

RESPIRATORY ANTIBIOTIC

BGP Pharma ULC

85 Advance Road

Etobicoke, Ontario

M8Z 2S6

Date of Initial Authorization:
FEB 16, 1999

Date of Revision:
DEC 5, 2023

Submission Control Number: 275742

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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions, Ear/Nose/Throat: Ototoxicity	12/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TOBI (Tobramycin Inhalation Solution, USP) is indicated for:

- the management of cystic fibrosis patients with chronic pulmonary *Pseudomonas aeruginosa* (*P. aeruginosa*) infections.

Demonstration of safety and efficacy of TOBI is limited to clinical trial data obtained over 3 cycles (6 months) of therapy for efficacy and up to 6 cycles (12 months) of therapy for safety.

Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with Forced Expiratory Volume in 1 second (FEV_1) < 25% or > 75% predicted, or patients colonized with *Burkholderia cepacia*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of TOBI and other antibacterial drugs, TOBI should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

Culture and sensitivity testing performed periodically will provide information on changing microbial flora and the possible emergence of bacterial resistance (see 14.1 Clinical Trials by Indication and 15 MICROBIOLOGY).

1.1 Pediatrics

Pediatrics (≥ 6 years to < 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of TOBI in pediatric patients 6 years of age and older has been established. Therefore, Health Canada has authorized an indication for this patient population.

Pediatrics (< 6 years of age): The safety and efficacy of TOBI has not been studied in pediatric patients under 6 years of age. Therefore, Health Canada has not authorized an indication for this patient population.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

TOBI is contraindicated in:

- patients with a known hypersensitivity to any aminoglycoside or who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- TOBI (Tobramycin Inhalation Solution) should be administered by oral inhalation and using a hand-held PARI LC PLUS™ reusable nebulizer with a DeVilbiss Pulmo-Aide® compressor. TOBI is not for subcutaneous, intravenous or intrathecal administration.
- The dose of TOBI is the same for all patients within the approved age range regardless of age or weight.
- Safety and efficacy have not been demonstrated in patients with Forced Expiratory Volume in 1 second (FEV_1) < 25% or > 75% predicted, or patients colonized with *Burkholderia cepacia*.

4.2 Recommended Dose and Dosage Adjustment

- The recommended dosage for both adults and pediatric patients 6 years of age and older is one single-use ampoule (300 mg) administered twice a day (BID) for 28 days. The doses should be taken as close to 12 hours apart as possible; they should not be taken less than six hours apart.

  TOBI is administered BID in alternating periods of 28 days. After 28 days of therapy, patients should stop TOBI therapy for the next 28 days, and then resume therapy for the next 28 day on / 28 day off cycle.

  Dosage is not adjusted by weight. All patients should be administered 300 mg BID.

- **Dosing in special populations**
  - **Pediatrics (< 6 years of age)**

    TOBI is not indicated for use in this age group. Safety, efficacy and pharmacokinetic studies have not been conducted in patients under the age of 6 years.
  - **Geriatrics (≥ 65 years of age)**

    Use of TOBI has not been studied in geriatric patients.
  - **Patients with renal impairment**

    Tobramycin is primarily excreted unchanged in the urine and renal function is expected to affect the exposure to tobramycin. A dosing recommendation cannot be supported (see 7 WARNINGS AND PRECAUTIONS, Renal: Nephrotoxicity).
  - **Patients with hepatic impairment**

    Use of TOBI has not been studied in patients with hepatic impairment.
  - **Patients after organ transplantation**

    Use of TOBI has not been studied in patients after organ transplantation.

4.4 Administration

TOBI is supplied as a single-use ampoule and is administered by inhalation. TOBI is not for subcutaneous, intravenous or intrathecal administration.

TOBI is administered using a hand-held PARI LC PLUS™ reusable nebulizer with a DeVilbiss Pulmo-Aide® compressor over a 15 minute period on average. TOBI is inhaled while the patient is sitting or standing upright and breathing normally through the mouthpiece of the nebulizer. Nose clips may help the

patient breathe through the mouth.

TOBI should not be diluted or mixed with dornase alfa (PULMOZYME®) in the nebulizer.

TOBI must be kept out of the sight and reach of children other than when administered therapeutically under appropriate adult supervision.

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

4.5 Missed Dose

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 to make up for the missed dose.

5 OVERDOSAGE

Signs and symptoms of acute toxicity from overdosage of intravenous (IV) tobramycin might include dizziness, tinnitus, vertigo, loss of high-tone hearing acuity, respiratory failure, neuromuscular blockade and renal impairment. Administration by inhalation results in low systemic bioavailability of tobramycin. Tobramycin is not significantly absorbed following oral administration. Tobramycin serum concentrations may be helpful in monitoring overdose.

Acute toxicity should be treated with immediate withdrawal of TOBI, and baseline tests of renal function should be undertaken.

In all cases of suspected overdosage, physicians should contact the regional poison control center for information about effective treatment. In the case of any overdosage, the possibility of drug interactions with alterations in drug disposition should be considered.

Hemodialysis may be helpful in removing tobramycin from the body.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral Inhalation	Solution 300 mg / 5mL tobramycin (as sulfate)	nitrogen, sodium chloride, sodium hydroxide, sulfuric acid and water for injection

Composition

TOBI is a tobramycin solution for inhalation. It 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 nebulizer. Each single-use 5 mL ampoule contains 300 mg tobramycin and 11.25 mg sodium chloride in sterile water for injection. Sulfuric acid and sodium hydroxide are added to adjust the pH to 6.0, forming the sulfate salt of tobramycin in solution. Nitrogen is used for sparging. All

ingredients meet USP requirements. The formulation contains no preservatives.

Availability of Dosage Forms

TOBI is supplied in single-use, low-density polyethylene plastic 5 mL ampoules. TOBI is packaged in boxes of 56 ampoules (14 flexible, laminated foil over-pouches, each containing 4 ampoules).

7 WARNINGS AND PRECAUTIONS

General

Caution should be exercised when prescribing TOBI to patients with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction.

Patients receiving concomitant parenteral aminoglycoside therapy should be monitored as clinically appropriate (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Concurrent and/or sequential use of TOBI with other drugs with neurotoxic, nephrotoxic, or ototoxic potential should be avoided (see 9 DRUG INTERACTIONS).

Aminoglycosides can cause fetal 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 pediatric patients exposed *in utero*. Patients who use TOBI during pregnancy, or become pregnant while taking TOBI should be apprised of the potential hazard to the fetus (see 7.1.1 Pregnant Women).

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Ear/Nose/Throat

- **Ototoxicity**

Caution should be exercised when TOBI is prescribed to patients with known or suspected auditory or vestibular dysfunction. In these patients and those who are at increased risk for auditory dysfunction, it may be necessary to consider audiological assessment before initiating TOBI therapy.

Ototoxicity, manifested as both auditory and vestibular toxicity, has been reported with aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness. Tinnitus is a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution.

In clinical studies, transient tinnitus occurred in eight TOBI treated patients versus no placebo patients.

In post marketing experience, severe hearing loss has been reported in some patients who received TOBI therapy in association with either previous or concomitant parenteral aminoglycoside use (see 8 ADVERSE REACTIONS).

If a patient reports tinnitus or hearing loss during TOBI therapy, the physician should refer them for audiological assessment. If ototoxicity occurs in a patient receiving TOBI, tobramycin therapy should be discontinued until serum concentrations fall below 2 µg/mL (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests: Serum Concentrations).

- **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. These

patients may be at increased risk for ototoxicity. Ototoxicity occurred in some patients even when their aminoglycoside serum levels were within the recommended range. 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.

Gastrointestinal

- ***Clostridium difficile*-Associated Disease**

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including tobramycin. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases.

Immune

- **Allergic Reactions**

Severe hypersensitivity (allergic) reactions have been reported following administration of tobramycin for injection to patients.

TOBI is contraindicated in patients with a known history of hypersensitivity to any aminoglycoside. If an allergic reaction to TOBI does occur, stop administration of the drug and initiate treatment as appropriate (see 2 CONTRAINDICATIONS).

Monitoring and Laboratory Tests

- **Audiograms**

For patients with known or suspected auditory or vestibular dysfunction and those who are at increased risk for auditory dysfunction, it may be necessary to consider audiological assessment before initiating TOBI therapy. Tinnitus may be a sentinel symptom of ototoxicity and therefore the onset of this symptom warrants caution. If a patient reports tinnitus or hearing loss during TOBI therapy, the physician should refer them for audiological assessment.

Clinical studies of 4-6 cycles duration of TOBI therapy did not identify hearing loss using audiometric tests which used as criteria a bilateral, high frequency decrease of ≥ 15 dB at two consecutive

frequencies, evaluating frequencies up to 8000 Hz. However, tinnitus was documented in a small number of TOBI patients, and there have been occasional reports of severe hearing loss in post marketing experience where patients received TOBI in association with previous or concomitant parenteral aminoglycoside use (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

- **Serum Concentrations**

Serum tobramycin concentrations should be monitored in patients with known or suspected auditory or renal dysfunction. Serum concentrations of tobramycin should be monitored in patients receiving concomitant parenteral aminoglycoside therapy. These patients should be monitored as clinically appropriate, taking into account the risk of cumulative toxicity.

If oto- or nephrotoxicity occurs in a patient receiving TOBI, tobramycin therapy should be discontinued until trough serum concentration falls below 2 µg/mL.

In patients with normal renal function treated with TOBI, serum tobramycin concentrations are approximately 1 µg/mL one hour after dose administration. Peak serum concentrations greater than 12 µg/mL and trough serum concentrations > 2 µg/mL are associated with tobramycin toxicity. All tobramycin treatment should be discontinued if concentrations exceed these levels.

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**

Laboratory tests of urine and renal function should be conducted at the discretion of the treating physician.

The clinical studies of TOBI 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 through 3 cycles of therapy (see 8 ADVERSE REACTIONS).

Neurologic

- **Neuromuscular Disorders**

Caution should be exercised when TOBI is prescribed to patients with known or suspected neuromuscular disorders such as myasthenia gravis or Parkinson's disease. Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.

Renal

- **Nephrotoxicity**

Caution should be exercised when TOBI is prescribed to patients with known or suspected renal dysfunction and serum concentrations of tobramycin should be monitored (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Nephrotoxicity was not seen during 4-6 cycles of TOBI therapy in clinical studies but has been associated with aminoglycosides as a class. If nephrotoxicity occurs in a patient receiving TOBI, tobramycin therapy should be discontinued until serum concentrations fall below 2 µg/mL.

Respiratory

- **Bronchospasm**

Bronchospasm can occur with inhalation of TOBI. In clinical studies of 3 cycles of TOBI therapy, acute changes in FEV_1 % predicted, measured 30 minutes after the inhaled dose, documented decreases of ≥ 20% FEV_1 % predicted in 12 TOBI patients (4.7%) and 2 placebo patients (0.8%). Bronchospasm should be treated as medically appropriate (see 8 ADVERSE REACTIONS).

If there is evidence of therapy-induced bronchospasm, the physician should carefully evaluate whether the benefits of continued use of TOBI outweigh the risks to the patient. If an allergic response is suspected, TOBI should be discontinued.

Sensitivity/Resistance

- **Development of Drug-Resistant Bacteria**

Prescribing TOBI in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

- **Potential for Microbial Overgrowth**

The prevalence of *Aspergillus* sp. and C. *albicans* increased in a clinical trial over three cycles of therapy with TOBI.

The use of TOBI may promote the selection of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

7.1 Special Populations

7.1.1 Pregnant Women

The use of tobramycin administered by inhalation in pregnant women has not been evaluated.

Aminoglycosides can cause fetal harm (e.g., congenital deafness) when administered to a pregnant woman. When administered to humans intravenously, tobramycin has been shown to cross the placenta and to distribute to fetal circulation and amniotic fluid.

No reproduction toxicology studies have been conducted with TOBI. However, subcutaneous administration of tobramycin at doses of 100 or 20 mg/kg/day during organogenesis was not teratogenic in rats or rabbits, respectively. Doses of tobramycin ≥ 40 mg/kg/day were severely maternally toxic to rabbits and precluded the evaluation of teratogenicity. 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 fetus 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 fetus.

7.1.2 Breast-feeding

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 TOBI.

7.1.3 Pediatrics

Pediatrics (< 6 years of age): The safety and efficacy of TOBI has not been studied in pediatric patients under 6 years of age. Therefore, Health Canada has not authorized an indication for this patient population.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Use of TOBI has not been studied in geriatric patients.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

TOBI (Tobramycin Inhalation Solution, USP) was generally well tolerated during two clinical studies in 258 cystic fibrosis patients ranging in age from 6 to 48 years. Patients received TOBI 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-treated patients. Thirty-three patients (13%) treated with TOBI complained of voice alteration (dysphonia) compared to 17 (7%) placebo patients. Voice alteration (dysphonia) was more common in the on-drug periods. Episodes were transient and resolved during the off-drug period.

Eight patients from the TOBI group (3%) reported tinnitus compared to no placebo patients. All episodes were transient, resolved without discontinuation of the TOBI treatment regimen, and were not associated with loss of hearing in scheduled audiograms. (The audiogram schedule did not necessarily coincide with the tinnitus episode.) Tinnitus is one of the sentinel symptoms of cochlear toxicity, and patients with this symptom should be carefully monitored for high frequency hearing loss (see 7 WARNINGS AND PRECAUTIONS). The numbers of patients reporting vestibular adverse experiences such as dizziness were similar in the TOBI and placebo groups.

Nine (3%) patients in the TOBI 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.

Tabulated summary of adverse drug reactions from clinical trials

Table 2 compares the incidence of treatment-emergent adverse drug reactions reported with an incidence of > 1% in patients receiving TOBI.

Table 2 - Incidence of Treatment-emergent Adverse Drug Reactions Reported With an Incidence of >1% in Patients Receiving TOBI *

	TOBI Placebo-controlled parallel group studies (PC-TNDS-002 / PC-TNDS-003)	
	TOBI n = 258 (%)	**Placebo n = 262 (%)**
Respiratory, thoracic, and mediastinal disorders		
Cough	23.6%	21.0%
Pharyngitis	12.0%	12.2%
Rhinitis	10.5%	6.5%
Hemoptysis	6.6%	7.6%
Productive cough	6.6%	8.8%
Dysphonia	5.8%	3.1%
Lung Disorder	5.0%	4.6%
Asthma	4.7%	6.9%
Dyspnea	4.3%	8.8%
Sputum discolored	1.9%	0.8%
Bronchospasm	1.6%	1.9%
Laryngitis	1.2%	0.0%
Gastrointestinal disorders		
Abdominal pain	3.5%	3.4%
Vomiting	2.7%	2.7%
Nausea	1.6%	2.7%
General disorders and administration site conditions		
Chest pain	7.0%	6.9%
Asthenia	5.0%	5.0%
Pyrexia	2.3%	2.7%
Malaise	1.6%	0.8%
Pain	1.2%	1.9%

	TOBI Placebo-controlled parallel group studies (PC-TNDS-002 / PC-TNDS-003)	
	TOBI n = 258 (%)	**Placebo n = 262 (%)**
Metabolism and nutrition disorders		
Anorexia	1.6%	3.1%
Musculoskeletal and connective tissue disorders		
Back pain	1.2%	0.0%
Myalgia	1.2%	0.0%
Nervous system disorders		
Dysgeusia	6.2%	6.1%
Headache	4.3%	5.7%
Dizziness	1.6%	1.5%
Ear and labyrinth disorders		
Tinnitus	1.2%	0.0%
Investigations		
Pulmonary function test decreased	6.2%	5.0%

* Adverse drug reactions from clinical trials are listed according to Medical Dictionary for Regulatory Activities (MedDRA).

Table 3 lists the percent of patients with treatment-emergent adverse experiences (spontaneously reported and solicited) that occurred in > 5% of TOBI patients during the two Phase III studies, where patients received up to 3 cycles of therapy (see 14.1 Clinical Trials by Indication).

Table 3 - Percent of Patients With Treatment Emergent Adverse Experiences Occurring in > 5% of TOBI Patients During Phase III Studies (Up to 6 Months of Therapy)*

	TOBI n = 258 (%)	**Placebo n = 262 (%)**
Body as a Whole		
Asthenia	35.7	39.3
Fever[1]	32.9	43.5
Headache	26.7	32.1

	TOBI n = 258 (%)	Placebo n = 262 (%)
Chest pain	26.0	29.8
Abdominal pain	12.8	23.7
Pain	8.1	12.6
Back pain	7.0	8.0
Malaise	6.2	5.3
Digestive System		
Anorexia	18.6	27.9
Vomiting	14.0	22.1
Nausea	11.2	16.0
Diarrhea	6.2	10.3
Metabolic and Nutritional Disorders		
Weight loss	10.1	15.3
Nervous System		
Dizziness	5.8	7.6
Respiratory System		
Cough increased	46.1	47.3
Pharyngitis	38.0	39.3
Sputum increased	37.6	39.7
Rhinitis	34.5	33.6
Dyspnea	33.7	38.5
Lung disorder	31.4	31.3
Sputum discoloration	21.3	19.8
Hemoptysis	19.4	23.7
Lung Function decreased[2]	16.3	15.3
Asthma	15.9	20.2
Voice alteration	12.8	6.5
Sinusitis	8.1	9.2
Epistaxis	7.0	6.5
Lower Resp. Tract Infection	5.8	8.0
Hyperventilation	5.4	9.9

	TOBI n = 258 (%)	Placebo n = 262 (%)
Special Senses		
Ear pain	7.4	8.8
Taste perversion	6.6	6.9
Skin and Appendages		
Rash	5.4	6.1

[1] Includes subjective complaints of fever.
[2] Includes reported decreases in pulmonary function tests or decreased lung volume on chest radiograph associated with intercurrent illness or study drug administration.
* Adverse drug reactions from clinical trials are listed according to Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART).

In a follow-on study of TOBI, the following adverse experiences were observed at a higher frequency in patients who received 4 to 6 cycles (over 6 to 12 months) of TOBI therapy than that seen in patients who received ≤ 3 cycles (up to 6 months) (see Table 4). The role of chronic progression of disease on the increasing frequency of adverse experiences should be considered in the interpretation of these data.

Table 4 - Treatment Emergent Adverse Experiences[1] Occurring at Higher Frequency During 6 to 12 Months of TOBI Therapy*

Adverse Event	4-6 Cycles n = 192 (%)	≤ 3 Cycles n = 204 (%)
Body as a Whole		
Asthenia	44.3	38.2
Chest pain	36.5	35.3
Back Pain	10.4	5.9
Lymphadenopathy	8.3	6.9
Chills	6.8	5.9
Sweating	5.7	4.9
Digestive System		
Anorexia	29.2	27.5
Diarrhea	16.7	12.7
Oral monoliasis	6.3	2.5
Dyspepsia	5.2	4.9
Musculoskeletal System		
Myalgia	5.7	5.4

Adverse Event	4-6 Cycles n = 192 (%)	≤ 3 Cycles n = 204 (%)
Respiratory System		
Cough increased	49.5	48.0
Pharyngitis	47.9	43.6
Sputum increased	43.8	38.2
Dyspnea	41.7	33.8
Rhinitis	37.5	33.3
Hemoptysis	31.3	27.0
Lung function decreased	28.6	23.0
Asthma	28.1	23.5
Sputum discoloration	24.5	19.1
Upper respiratory infection	13.5	9.8
Voice alteration	12.0	6.4
Hyperventilation	8.9	5.4
Laryngitis	5.2	3.4
Special Senses		
Otitis media	5.2	2.0

[1]Includes Adverse Experiences that were observed in > 5% of patients in the 4-6 Cycles group and at a higher frequency than in the ≤ 3 Cycles group. (The ≤ 3 Cycles group received placebo during Phase III studies.)
* Adverse drug reactions from clinical trials are listed according to Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART).

In open label follow-on clinical trials, the following additional adverse events have been reported infrequently in patients receiving TOBI concurrently with other medications: Fungal infection, hypoxia, mouth ulcerations, photosensitivity reaction.

8.5 Post-Market Adverse Reactions

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.

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

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

No clinical drug interaction studies have been performed with TOBI. In clinical studies of TOBI, patients taking TOBI concomitantly with dornase alfa (PULMOZYME®), β-agonists, inhaled corticosteroids, other anti-pseudomonal antibiotics, or parenteral aminoglycosides demonstrated adverse experience profiles similar to the study population as a whole. In post marketing experience, some patients receiving TOBI with previous or concomitant parenteral aminoglycosides have reported severe hearing loss.

Concurrent and/or sequential use of TOBI 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. TOBI should not be administered concomitantly with ethacrynic acid, furosemide, urea, or intravenous mannitol.

Other medicinal products that have been reported to increase the potential toxicity of parenterally administered aminoglycosides include:

Amphotericin B, cefalotin, cyclosporine, tacrolimus, polymyxins (risk of increased nephrotoxicity);

Platinum compounds (risk of increased nephrotoxicity and ototoxicity); and,

Anticholinesterases, botulinum toxin (neuromuscular effects).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

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 (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

TOBI (Tobramycin Inhalation Solution, USP) is a formulation of tobramycin designed specifically for administration by inhalation. When TOBI is inhaled, tobramycin can be detected at high concentration in the sputum of cystic fibrosis patients. The drug substance, tobramycin, is an aminoglycoside antibiotic derived from *Streptomyces tenebrarius*. Tobramycin, a cationic polar molecule that does not readily cross epithelial membranes, is chemically and pharmacologically related to the aminoglycoside class of antibiotics. The primary mode of action is bactericidal resulting from disruption of protein synthesis in susceptible bacteria.

10.2 Pharmacodynamics

See 15 MICROBIOLOGY.

10.3 Pharmacokinetics

Concentrations of tobramycin in the sputum vary widely. This variation may be explained by individual differences in nebulizer performance and airway pathology. Following administration of TOBI, tobramycin remains concentrated primarily in sputum in the airways.

- **Sputum Concentrations**

Ten minutes after inhalation of the first 300 mg dose of TOBI by cystic fibrosis patients, the mean (median) concentration of tobramycin in the sputum was 1237 µg/g (959 µg/g) with the range from 35 to 7417 µg/g. Tobramycin does not accumulate in sputum; after 20 weeks of therapy with the TOBI regimen, the mean (median) concentration of tobramycin at ten minutes after inhalation was 1154 µg/g (818 µg/g), ranging from below quantifiable limits to 8085 µg/g. High intra- and inter-subject variability of tobramycin concentrations in the sputum was observed. Two hours after inhalation, sputum tobramycin concentrations declined to approximately 14% of sputum tobramycin concentrations at ten minutes after inhalation.

- **Serum Concentrations**

The mean (median) serum concentration of tobramycin one hour after inhalation of a single 300 mg dose of TOBI by cystic fibrosis patients was 0.95 µg/mL (0.91 µg/mL), ranging from below quantifiable limits to 3.62 µg/mL. After 20 weeks of therapy on the TOBI regimen, the mean (median) serum tobramycin concentration one hour after dosing was 1.05 µg/mL (0.94 µg/mL), ranging from below quantifiable limits to 3.41 µg/mL.

- **Systemic Pharmacokinetics Following Aerosolized Administration**

The pharmacokinetics of tobramycin were examined in two Phase III studies and analyzed using a population modeling approach. Data from this analysis was compared to literature. These findings are summarized in Table 5.

Table 5 - Summary of Tobramycin Serum Pharmacokinetics Following Aerosol Administration

Patient Type[1]	N	Dose	Nebulizer	Ka (hr^{-1})	$T_{1/2\alpha}$ (hr)	$T_{½\beta}$ (hr)	Vdss (L)	Cl (L/h)	Analytical Method[2]	Reference
CF	247	300 mg	Pari LC Plus™				57.3[3,4]	5.79[4]	FPIA	BGP
HV MV	5 5	300 mg	Pneumatic Nebulizer			8.96 ± 0.47 11.23 ± 2.26			HPLC/ EMIT	Le Conte (1993); 147(5):1279-82
CF	6	600 mg	Ultrasonic Nebulizer	1.98 ± 1.40[5]	1.54 ± 0.97	13.0 ± 5.2	96.9 ± 49.6	6.98 ± 2.89	FPIA	Touw (1997); 41(1):184-7

[1] CF = cystic fibrosis; HV = healthy volunteer; MV = mechanically ventilated patients.
[2] HPLC = high performance liquid chromatography; FPIA = fluorescent polarization immunoassay; EMIT= enzyme immunoassay.
[3] Parameter was corrected by absolute bioavailability estimate.
[4] Parameter obtained from population pharmacokinetic analysis (Harris labs).
[5] Mean ± SD.

The systemic pharmacokinetics of tobramycin when administered by inhalation or parenterally are comparable both in terms of clearance and volume of distribution. Estimates of the terminal elimination half-life for tobramycin in serum following aerosol administration are quite variable, ranging from 1.3 to 13 hours. The systemic pharmacokinetics of tobramycin following aerosol administration are best described by a two-compartment model with biexponential elimination.

- **Serum and Sputum Concentrations Following Aerosolized Tobramycin**

In a Phase II study and two Phase III studies, serum and sputum concentrations were measured following tobramycin administration. Serum and sputum concentrations following aerosolized administration in clinical studies as well as from the literature are presented in Table 6.

Table 6 - Summary of the Serum and Bronchial Secretions/Sputum Concentrations of Tobramycin Following Aerosolized Administration

Patient Type[1]	N	Dose/ Regimen	Nebulizer	Serum (S)		Bronchial Secretion (BS)/ Sputum (SP)			Ratio S/SP[4]	Ref -erence
				Sampling (hr. Post)	Conc. (µg/mL)[2]	Sampling (hr. Post)	BS Conc. (µg/mL)	SP Conc. (µg/g)	(%)	
CF	61 61 61	300 mg/BID 300 mg/BID 600-1200 mg/BID	Pari LC Jet Sidestream Jet UltraNeb	1.0 1.0 1.0	0.57±0.38 0.74±0.43 0.79±0.76	1.0 1.0 1.0		139±56 116±183 388±451	1.2±1.3 1.9±1.9 0.70±1.3	BGP
CF	247	300 mg/BID 3 cycles of 28 days	Pari LC Plus Jet	1.0	1.01±0.57	0.167		1199.2± 1115.8	0.191	BGP

Patient Type[1]	N	Dose/ Regimen	Nebulizer	Serum (S)		Bronchial Secretion (BS)/ Sputum (SP)			Ratio S/SP[4]	Ref -erence
				Sampling (hr. Post)	Conc. (µg/mL)[2]	Sampling (hr. Post)	BS Conc. (µg/mL)	SP Conc. (µg/g)	(%)	
CF	6	10.2 mg/kg	Wisto Senior	1.0	1.27±1.07				NR	Touw (1997); 41(1):184-7
RD	20	80 mg/one dose	Unspecified Jet	1	<0.1-0.2	0.5	2.0± 2.26		NR	Baran (1990); 84(3):203-4
CF w/ RD	14	80 mg/BID	Unspecified Jet	1.0	<0.1-0.4					Gappa (1988); Suppl 143:74-6
HV MV LC/TS LC/TS	5 5 5 5	300 mg/ one dose	Atomeca Pneumatic	0.25-24 0.25-24 0.5 0.5	0.27±0.15 <0.1 0.43 0.55	4 12		5.57± 5.52[3] 3.61± 4.34[3]	NR	Le Conte (1993); 147(5):1279-82
CF w/ RD	27	120 mg/ one dose	Medix World Traveler-Intersurgical			0.25-1		401		Mukhopadhyay (1994); 88(3):203-11
CF w/ RD	22	666±195 mg/ TID	UltraNeb 100	NR	<0.1-1.5	immediate post aerosol		2300± 1900	NR	Smith (1989) & Weber (1989); 7(4):265-71
CF w/ RD	9 9 9 9	40 mg/ once for each device	Pulmo-Aide UltraNeb UltraNeb UltraNeb			0.05		0-629 16-1343 35-1980 94-3385		Weber (1994) : 17(5):331-9

[1] CF = cystic fibrosis; HV = healthy volunteer; MV = mechanically ventilated patients; LC/TS = lung cancer patient with thoracic surgery; RD = respiratory disease.
[2] Mean ± SD.
[3] Lung Tissue concentrations following biopsy.
[4] Mean ratio of individual serum/sputum results with N = 56, 59, 57 for the Pari LC, Sidestream, and UltraNeb, respectively.
BID = twice daily; TID = three times daily; NR = not reported.

Serum concentrations from the clinical studies are comparable to those reported in the literature for cystic fibrosis patients following aerosolized administration of tobramycin, and less than those reported following therapeutic doses (1.7-4.0 mg/kg) administered parenterally. Using the Pari LC Plus™ nebulizer, the mean sputum concentration at ten minutes after dosing in the clinical studies was approximately 1200 µg/g (median = 959 µg/g; range = 35 to 7417 µg/g). Ninety-seven percent (97%) of patients had sputum concentrations in excess of the target 128 µg/g of sputum.

Absorption

- **Animal Pharmacology**
  - **Pharmacokinetics of Inhaled Tobramycin Solutions**

    Absorption of tobramycin into the systemic circulation after the delivery of aerosolized antibiotic to the lung was analyzed in three animal inhalation studies: a 14-day rat and guinea pig study, a 14-day rat study, and a 6-month rat study (Table 7).

    In general, after aerosol administration peak serum tobramycin concentrations increase in an approximate linear manner with increasing estimated inhaled doses up to about 15 mg/kg. At doses above 15 mg/kg, peak serum concentrations plateau in the range of 12-22 µg/mL (approximately 12 to 22 times higher than the peak serum concentration of 1 µg/mL following 300 mg twice daily dosing of TOBI in the two Phase III placebo-controlled studies).

    There was no evidence of accumulation over 14 days in rats and guinea pigs exposed daily by nose-only inhalation to aerosolized tobramycin. The mean serum concentrations also remained constant in the 6-month rat nose-only inhalation toxicity study indicating that long-term administration does not change the systemic absorption.

Table 7 - Animal Pharmacokinetic Data: Inhaled Tobramycin Solutions

Dose[a] (mg/kg/day)[b] [est. daily human dose][c]	**Cmax (µg/mL)**	**Comments**
Rat (Sprague Dawley) Duration: 14 days **Route of Administration: Nasal Inhalation**		
6% Solution 30 min \ 7.4 mg/kg/day; [6x] 60 min \ 14.5 mg/kg/day; [12x] 120 min \ 28.9 mg/kg/day; [24x] 30 min \ 6.0 mg/kg/day after 15 min Albuterol [5x]	Day 1/Day 14 7.2/4.5 11.4/7.8 15.8/11.4 6.4/4.8	Serum levels of drug generally increased with increasing aerosol dose. Levels were similar within dose groups after one and fourteen days of consecutive treatments, but were below detectable limits 24 hours after the last exposure. No indication of accumulation in serum with repeated aerosol administration. Pretreatment with Albuterol-Sulfate USP aerosols had no effect on serum drug levels.
Rat (Sprague Dawley) Duration: 14 days		

Dose[a] (mg/kg/day)[b] [est. daily human dose][c]	Cmax (µg/mL)	Comments
Route of Administration: Nasal Inhalation		
6% Solution 6 hours \ 97 mg/kg/day [81x] 10% Solution 6 hours \ 131 mg/kg/day [109x]	Day 1/Day 14 14.6/11.4 22.5/17.8	Serum levels of drug generally increased with increasing aerosol dose; though not in a dose proportionate manner. Levels were similar within dose groups after one and fourteen days of consecutive treatments, but were below detectable limits 24 hours after the last exposure. No indication of accumulation in serum with repeated aerosol administration.
Guinea Pig (Hartley) Duration: 14 days **Route of Administration: Nasal Inhalation**		
6% Solution 30 min \ 4.5 mg/kg/day [4x] 60 min \ 9.1 mg/kg/day [8x] 120 min \ 19.8 mg/kg/day [17x] 30 min \ 4.0 mg/kg/day after 15 min Albuterol [3x]	Day 1/Day 14 4.6/7.0 8.2/8.4 9.1/8.1 4.0/3.0	Serum levels of drug increased between low- (4.1 mg/kg) and mid-dose (9.1 mg/kg) groups, and were similar between mid- and high-dose (19.8 mg/kg) groups. Serum drug levels were similar within dose groups after Days 1 and 14, but were below detectable limits 24 hours after the last exposure. No indication of accumulation of tobramycin in the serum with repeated aerosol administration. Pretreatment with Albuterol Sulfate USP aerosols had no effect on serum drug levels.
Rat (Sprague Dawley) Duration: 6 months **Route of Administration: Nasal Inhalation**		
6% Solution 20 min \ 4.9 mg/kg/day [4x] 60 min \ 14.3 mg/kg/day [12x] 180 min \ 57.5 mg/kg/day [48x]	Day 1/Week 26 5.6/4.1 17.6/8.0 32.6/13.9	Mean serum concentrations were proportional to the total delivered dose for the low and mid-dose groups, but less for the high-dose group, indicating a rate-limiting absorption at higher doses. No evidence of accumulation, even though mean serum tobramycin values varied over the course of the study, particularly at the highest dose level. Generally, serum tobramycin values decreased with time. At ~58

Dose[a] (mg/kg/day)[b] [est. daily human dose][c]	Cmax (µg/mL)	Comments
		mg/kg/day there was considerable systemic exposure in this study.

[a] Control groups not included.

[b] Estimated dose deposited in the lungs. The doses administered to animals were estimated according to the equation:

$$\text{Daily Dose (mg/kg)} = \frac{\text{Exposure Conc. (mg/L)} \times \text{Inhaled Volume (L)} \times \%\ \text{Deposition}}{\text{Animal Body Weight (Kg)}}$$

Where: Exposure Conc. = Analytically determined tobramycin concentration; Inhaled Volume = 250 mL/min x exposure time (min) for rats, 300 mL/min for guinea pigs; Body weights = 250 and 300 grams for female and male rats, respectively, and 500 and 600 grams for female and male guinea pigs, respectively. % Deposition = 50 % for aerosols in the 2 to 3 µm MMAD range (Mass median aerodynamic diameter).

[c] The variable dose estimates from animal treatments are expressed as multiples of the estimated daily deposited clinical dose of 2 x 5 mL doses of 6% tobramycin solution (300 mg/dose) administered using a PARI LC nebulizer with 10% efficiency, to CF patients weighing ~50 kg; (1.2 mg/kg/day) who were enrolled in pharmacokinetic trials. Note that pivotal clinical trials for TOBI used the same dose of tobramycin but with the more efficient PARI LC PLUS™ nebulizer. The PARI LC PLUS™ is estimated to deposit about twice the amount of tobramycin as the PARI LC used in animal studies.

Elimination

The apparent terminal half-life of tobramycin in serum after inhalation of a 300 mg single dose of TOBI was 3 hours in cystic fibrosis patients. 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 administration, may be eliminated in expectorated sputum or via the gastrointestinal tract.

Special Populations and Conditions

- **Age:** There was a trend of increased sputum concentrations with increased age (range 6 to 48 years). However, due to the large variability within each of the stratified age groups, 6-<13 years, 13-<18 years and ≥ 18 years, these differences were not considered clinically significant.
- **Sex:** No significant differences were noted between males and females for either the sputum or serum concentrations.

11 STORAGE, STABILITY AND DISPOSAL

TOBI should be stored under refrigeration at 2-8°C/36-46°F. 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/77°F) for up to 28 days. TOBI should not be used beyond the expiration date stamped on the ampoule when stored under refrigeration (2-8°C/36-46°F) or beyond 28 days when stored at room temperature (25°C/77°F).

TOBI 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 color change does not indicate any change in the quality of the product as long as it is stored within the recommended storage conditions.

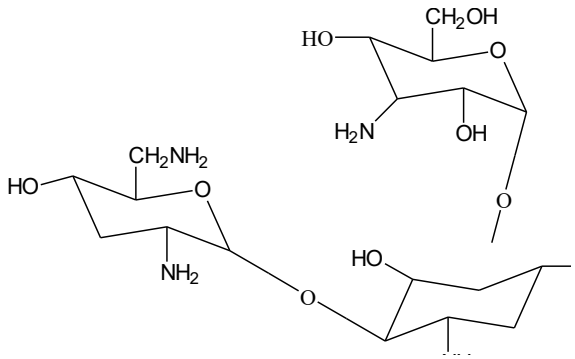
12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	tobramycin
Chemical name:	*O*-3-amino-3-deoxy-α-D-glucopyranosyl-(1→4)-*O*-[2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl-(1→6)]-2-deoxy-L-streptamine
Molecular formula and molecular mass:	$C_{18}H_{37}N_5O_9$ 467.52
Structural formula:	
Physicochemical properties:	Tobramycin is a white to off-white crystalline powder, soluble in 1.5 parts water, very slightly soluble in 95% ethanol, and practically insoluble in chloroform and ether. The pH of a 1 in 10 solution is 9-11. The melting point of tobramycin is 217°C.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Management of Cystic Fibrosis Patients with *Pseudomonas aeruginosa*

Two identically designed, double-blind, randomized, placebo-controlled, parallel group, 24-week clinical studies (Study 1 and Study 2) at a total of 69 cystic fibrosis centers in the United States were conducted in cystic fibrosis patients with *Pseudomonas aeruginosa* (*P. aeruginosa*). Subjects who were less than six years of age, had a baseline creatinine of > 2 mg/dL, or had *Burkholderia cepacia* isolated from sputum were excluded. All subjects had baseline FEV_1 % predicted between 25% and 75%. In these clinical studies, 258 patients received TOBI therapy on an outpatient basis (see Table 8) using a hand-held PARI LC PLUS™ reusable nebulizer with a DeVilbiss Pulmo-Aide® compressor.

Table 8 - Dosing Regimens in Clinical Studies

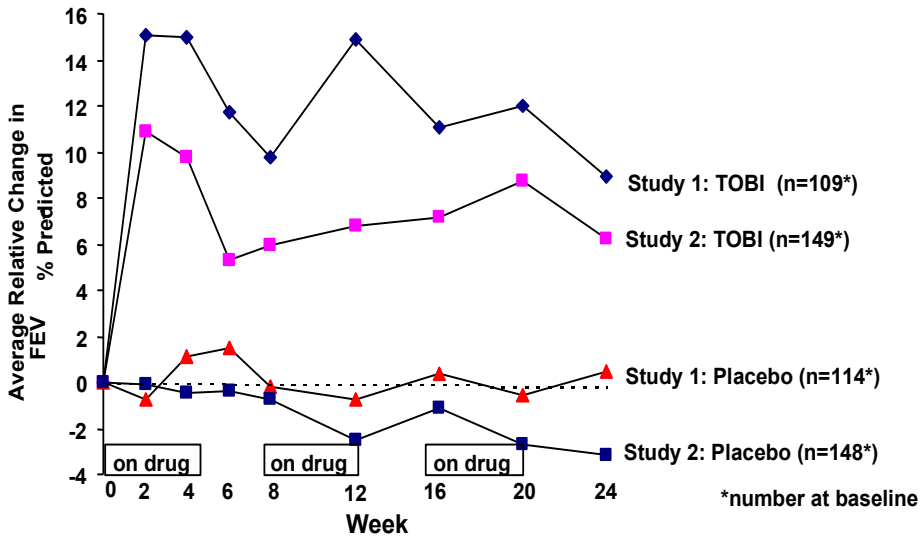
	Cycle 1		Cycle 2		Cycle 3	
	28 Days	**28 Days**	**28 Days**	**28 Days**	**28 Days**	**28 Days**
TOBI regimen n = 258	**TOBI** 300 mg BID	no drug	**TOBI** 300 mg BID	no drug	**TOBI** 300 mg BID	no drug
Placebo regimen n = 262	placebo BID	no drug	Placebo BID	no drug	placebo BID	no drug

BID = twice daily.

All patients received either TOBI or placebo (saline with 1.25 mg quinine for flavoring) in addition to standard treatment recommended for cystic fibrosis patients, which included oral and parenteral anti-pseudomonal therapy, β_2-agonists, cromolyn, inhaled steroids, and airway clearance techniques. In addition, approximately 77% of patients were concurrently treated with dornase alfa (PULMOZYME®).

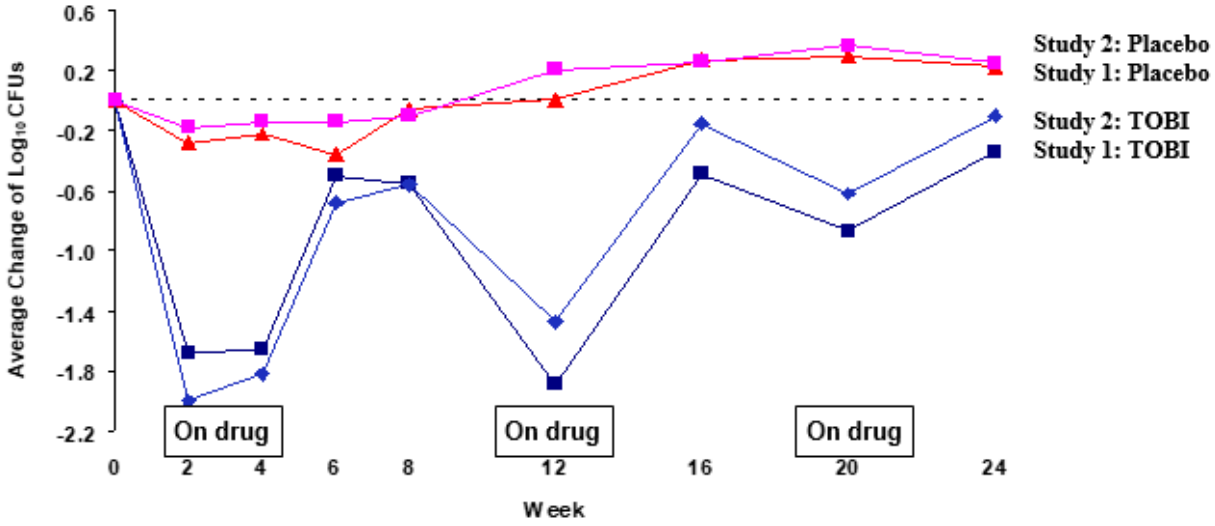
In each study, TOBI-treated patients experienced significant improvement in pulmonary function. Improvement was demonstrated in the TOBI group in Study 1 by an average increase in FEV_1 % predicted of about 11% relative to baseline (Week 0) during 24 weeks compared to no average change in placebo patients. In Study 2, TOBI 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 - Mean Relative Change From Baseline in FEV_1 % Predicted



In each study, TOBI therapy resulted in a significant reduction of approximately 1 log 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 2).

Figure 2 - Mean Absolute Change From Baseline in Log_{10} CFUs



Patients treated with TOBI were hospitalized for an average 5.1 days compared to 8.1 days for placebo patients. Patients treated with TOBI required an average of 9.6 days of parenteral anti-pseudomonal antibiotic treatment compared to 14.1 days for placebo patients. During the six months of treatment, 40% of TOBI patients and 53% of placebo patients were treated with parenteral anti-pseudomonal antibiotics.

Treatment with TOBI for three cycles was associated with a decline in the *in vitro* susceptibility of *P. aeruginosa* isolates to tobramycin compared to placebo. The percentage of patients with *P. aeruginosa* isolates with tobramycin MICs ≥ 16 µg/mL was 13% at the beginning, and 23% at the end of six months of the TOBI regimen, compared to 10% and 8% in the placebo group.

The relationship between *in vitro* susceptibility test results and clinical outcome with TOBI therapy is not clear. However, four TOBI patients who began the clinical study 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.

Over three cycles of therapy with TOBI, the prevalence of *S. aureus* in sputum tended to decline while that of *Aspergillus* sp. and *C. albicans* increased.

15 MICROBIOLOGY

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

- **Susceptibility Testing**

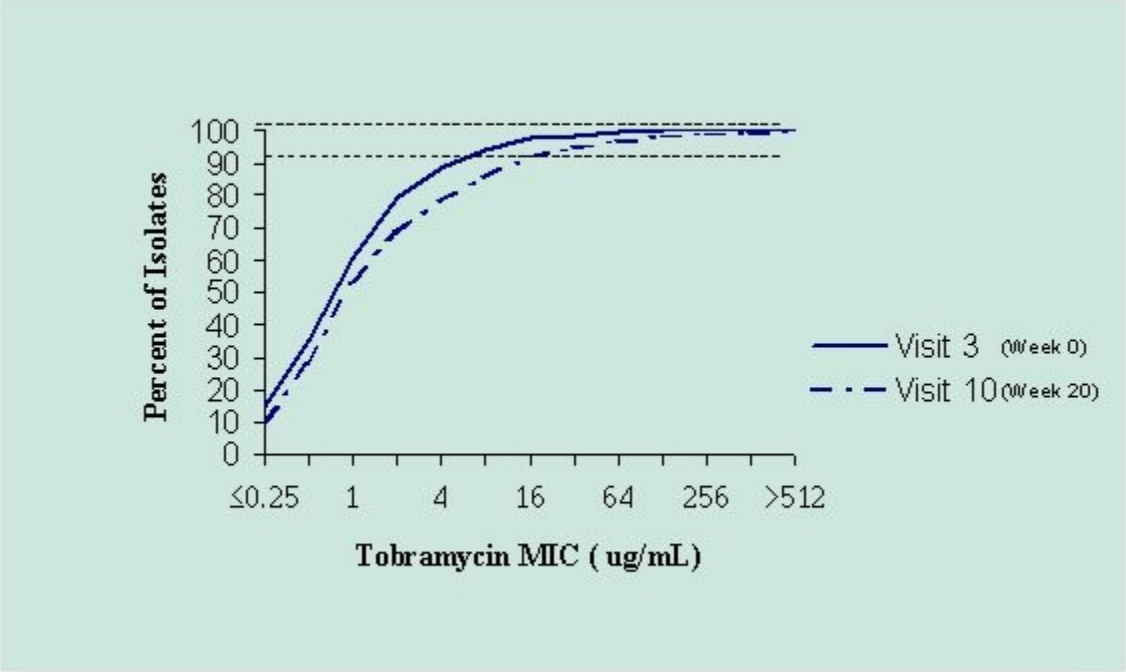
A single sputum sample from a cystic fibrosis patient may contain multiple morphotypes of *P. aeruginosa*, and each morphotype may have a different level of *in vitro* susceptibility to tobramycin.

The *in vitro* antimicrobial susceptibility test methods used for parenteral tobramycin therapy can be used to monitor the susceptibility of *P. aeruginosa* isolated from cystic fibrosis patients.

Susceptibility breakpoints established for parenteral administration of tobramycin do not apply to aerosolized administration of TOBI. The relationship between *in vitro* susceptibility test results and clinical outcome with TOBI therapy is not clear (see 14.1 Clinical Trials by Indication).

As noted in Figure 3, treatment for six months (3 cycles) with TOBI in two clinical studies demonstrated a trend to decreasing *in vitro* susceptibility of *P. aeruginosa* isolates which was not observed in the placebo group. The clinical significance of this information has not been clearly established in the treatment of *P. aeruginosa* in cystic fibrosis patients (see 14.1 Clinical Trials by Indication). Similar decreases in amikacin susceptibility were noted in patients treated with TOBI for three cycles.

Figure 3 - Cumulative Frequency Distribution of Tobramycin MIC Values for All *P. aeruginosa* Isolates (3 Cycles of TOBI)



- **Effects on Respiratory Flora Testing**

There was no indication that treatment with TOBI for up to three cycles was associated with increased superinfection with *B. cepacia* or *A. xylosoxidans* (see Table 9). From Visit 3 to Visit 10 (Weeks 0 and 20), the number of TOBI patients infected with *H. influenzae* and *S. aureus* decreased. There was no apparent change in the number of patients infected with *S. pneumoniae*. The number of patients in the TOBI group infected with either *Aspergillus* sp. or *C. albicans* increased from Visit 3 to Visit 10 (Weeks 0 and 20). The clinical relevance of this finding is not clear (see Table 10).

Table 9 - Number of Patients with Treatment Emergent Infections with Intrinsically Tobramycin Resistant Organisms in Placebo-Controlled Studies

Pathogen	TOBI	Placebo
	N = 258 (%)	N = 262 (%)
B. cepacia	0 (0.0)	1 (0.4)
S. maltophilia	6 (2.3)	10 (3.8)
A. xylosoxidans	1(0.4)	3 (1.1)

Table 10 - Number of Patients From Whom Gram-Positive and Fungal Pathogens Were Recovered (Visits 3 and 10, Weeks 0 and 20) in Placebo-Controlled Studies

Pathogen	TOBI		Placebo	
	Visit 3 N = 258 (%)	Visit 10 N = 234 (%)	Visit 3 N = 262 (%)	Visit 10 N = 234 (%)
H. influenzae	11 (4.3)	0 (0.0)	12 (4.6)	7 (3.0)
S. aureus	109 (42.2)	78 (33.3)	91 (34.7)	93 (39.7)
S. pneumoniae	6 (2.3)	3 (1.3)	10 (3.8)	7 (3.0)
Aspergillus sp.	52 (20.2)	70 (29.9)	62 (23.7)	47 (20.1)
C. albicans	110 (42.6)	134 (57.3)	109 (41.6)	110 (47.0)
Other fungal pathogens	14 (5.4)	12 (5.1)	8 (3.0)	5 (2.1)

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

- **Inhalation Toxicity Studies**

To support administration of aerosolized tobramycin to humans, three inhalation studies were conducted: a 14-day rat and guinea pig study, a 14-day rat only study, and a 6-month rat study. Exposure conditions were designed to mimic as closely as possible the clinical setting with respect to daily dosing and aerosol characteristics. It was not possible to determine a classical maximum tolerated dose for TOBI, because guinea pigs and rats could not be held in the exposure system for greater than 3 or 6 hours, respectively, without risking death due to non drug-related phenomena such as dehydration or hypothermia.

Tobramycin aerosols were well tolerated by both rats and guinea pigs, with no overt clinical signs of toxicity nor lethality resulting from treatments up to the highest doses tested (see Tables 11, 12 and 13).

Table 11 - 14-Day Inhalation Toxicity (Rat and Guinea Pig)

STUDY CHARACTERISTICS	RESULTS
Species: Sprague-Dawley rat Hartley guinea pig (male and female, 10/sex/dose) Route: Nasal inhalation Duration: Up to 2 hours/day 14 consecutive days Dosing Solutions Tobramycin: 6% in 0.225% saline, pH 6.0 Control: 0.225% saline, pH 6.0 Doses: mg/kg/day (Multiple of daily human dose) Rats Group 1: 120 min Control Group 2: 30 min \ 7.4 mg/kg/day (6X) Group 3: 60 min \ 14.5 mg/kg/day (12X) Group 4: 120 min \ 28.9 mg/kg/day (24X) Group 5: 15 min Albuterol pretreatment then 30 min \ 6.0 mg/kg/day (5X) Guinea Pig Group 1: 120 min Control Group 2: 30 min \ 4.5 mg/kg/day (4X) Group 3: 60 min \ 9.1 mg/kg/day (8X) Group 4: 120 min \ 19.8 mg/kg/day (17X) Group 5: 15 min Albuterol pretreatment then 30 min \ 3.9 mg/kg/day (3X)	This study evaluated local and systemic responses of two species to inhalation of tobramycin aerosols and the effects of bronchodilator pretreatment on those responses. The No Observed Adverse Effect Level (NOAEL) was approximately 12X (rats) and 4X (guinea pigs) higher than the estimated daily deposited clinical dose of 1.2 mg/kg/day. Rats demonstrated no overt clinical signs of toxicity, no gross pathology findings, or treatment-related microscopic pathology. Pretreatment with albuterol had no demonstrable effect on any parameters examined. Guinea pigs also exhibited no overt clinical signs of toxicity. Tobramycin-related increases in organ weights were observed (lungs in male rats, kidneys in guinea pigs of both sexes at the higher dose levels). There were no histopathologic findings in these organs, nor in the cochlea of guinea pigs. Non-specific, aerosol-related histologic effects in larynx and tracheal endothelia were observed in both male and female guinea pigs at the higher doses.

Table 12 - 14-Day Inhalation Toxicity (Rat)

STUDY CHARACTERISTICS	RESULTS
Species: Sprague-Dawley rat (male and female, 10/sex/dose) Route: Nasal inhalation Duration: 6 hours/day 14 consecutive days Dosing Solutions 6% Tobramycin in 0.225% saline, pH 6.0 10% Tobramycin in 0.225% saline, pH 6.0 Control: 0.225% saline, pH 6.0 Doses: mg/kg/day (Multiple of daily human dose) Group 1: Control Group 2: 97 mg/kg/day (81X) (6% sol'n) Group 3: 131 mg/kg/day (109X) (10% sol'n)	This study evaluated local and systemic responses of rats to aerosolized tobramycin at doses significantly higher than clinical doses (81 and 109 times the estimated human dose) and exposure durations (6 hours). Tobramycin-related increases in lung weight and in kidney weight in females were noted, particularly at the higher dose. Non-specific, aerosol-related histologic effects in nasal and tracheal epithelia were observed with an increase in lung macrophages. The NOAEL could not be identified, because tobramycin-related hyperplasia of bronchoalveolar epithelia was noted at both doses tested.

Table 13 - Six Month Inhalation Toxicity (Rat)

STUDY CHARACTERISTICS	RESULTS
Species: Sprague-Dawley rat (male and female, 20/sex/dose) Route: Nasal inhalation Duration: Up to 3 hours/day Daily for 6 months, 28 day recovery Dosing Solutions 6% Tobramycin in 0.225% saline, pH 6.0 Control: 0.225% saline, pH 6.0 Doses: mg/kg/day (Multiple of daily human dose) Group 1: Control Group 2: 20 min \ 4.9 mg/kg/day (4X) Group 3: 60 min \ 14.3 mg/kg/day (12X) Group 4: 180 min \ 57.5 mg/kg/day (48X)	This study evaluated potential toxic effects and characterized the dose response to aerosolized tobramycin in rats. A four-week recovery period, equivalent to that used in human clinical trials, evaluated the potential for reversal or progression of any toxicity following six months of daily exposure. No overt clinical signs of toxicity were noted. No treatment-related gross lesions were observed on necropsy. Respiratory lesions similar to those seen in the 14-day rat study resolved almost completely after the 4-week recovery period. Increases in lung and kidney weights also reversed in the recovery period. Chronic nephropathy, characterized by renal tubular degeneration, mineralization, compensatory tubular regeneration, and protein casts, occurred in all groups, including controls. Incidence was greater in the high dose group,

STUDY CHARACTERISTICS	RESULTS
	indicating that tobramycin treatment accelerated the process. Mild hyperplastic changes observed in mucosal epithelia of the respiratory system were most likely adaptive responses to continuous exposure to aerosols, since the changes resolved spontaneously with cessation of dosing.

Carcinogenicity:

A two-year inhalation study in rats to assess the carcinogenic potential of TOBI has been completed. Rats were exposed to TOBI 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, in contrast to the maximum 3.62 µg/mL level observed in cystic fibrosis patients in clinical trials. There was no drug-related increase in the incidence of any variety of tumor.

Genotoxicity:

No mutagenicity studies have been conducted with TOBI. Tobramycin has been evaluated for genotoxicity in a battery of *in vitro* and *in vivo* tests. The Ames bacterial reversion test, conducted with five tester strains, failed to show a significant increase in revertants with or without metabolic activation in all strains. Tobramycin was negative in the mouse lymphoma forward mutation assay, both with or without S9 metabolic activation, at doses up to 5000 µg/mL. Tobramycin did not induce chromosomal aberrations in Chinese hamster ovary cells, with or without metabolic activation, and was negative in the *in vivo* mouse micronucleus test.

Reproductive and Developmental Toxicology:

No reproduction studies have been conducted with TOBI. However, subcutaneous administration of up to 100 mg/kg tobramycin did not adversely affect mating behavior or cause impairment of fertility in male or female rats.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTOBI®

Tobramycin Inhalation Solution, USP

Read this carefully before you start taking **TOBI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TOBI**.

What is TOBI used for?

- TOBI is used to treat people (six years and older) with cystic fibrosis who have a bacterial lung infection with *Pseudomonas aeruginosa* (see "What is *Pseudomonas aeruginosa*?" section below).

Antibacterial drugs like TOBI treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, TOBI should be used exactly as directed. Misuse or overuse of TOBI could lead to the growth of bacteria that will not be killed by TOBI (resistance). This means that TOBI may not work for you in the future. Do not share your medicine.

How does TOBI work?

TOBI contains a medicine called tobramycin. Tobramycin belongs to the aminoglycoside class of antibiotics. TOBI is inhaled (breathe) directly into the lungs so that the antibiotic can kill the *Pseudomonas aeruginosa* bacteria causing the infection. This helps to fight lung infections and improve breathing in people with cystic fibrosis.

What is *Pseudomonas aeruginosa*?

It is a very common bacterium that infects the lung of nearly everyone with cystic fibrosis at some time during their lives. Some people do not get this infection until later on in their lives, while others get it very young. It is one of the most damaging bacteria for people with cystic fibrosis. If the infection is not properly fought, it will continue to damage your lungs causing further problems to your breathing.

What are the ingredients in TOBI?

Medicinal ingredients: Tobramycin

Non-medicinal ingredients: Nitrogen, sodium chloride, sodium hydroxide, sulfuric acid and water for injection.

TOBI comes in the following dosage forms:

Solution: 300 mg / 5 mL ampoule

Do not use TOBI if:

- you are allergic to tobramycin, or to any other aminoglycoside antibiotic such as amikacin, gentamycin, kanamycin, paromomycin, streptomycin,
- you are allergic to any of the other ingredients in TOBI (see What are the ingredients in TOBI?)

If this applies to you, **tell your healthcare professional without taking TOBI**.

If you think you may be allergic, ask your healthcare professional for advice.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TOBI. Talk about any health conditions or problems you may have, including if you:

- Have or have had hearing problems (including noises in the ears such as ringing or hissing, dizziness, or any changes in hearing).
- Your mother has had hearing problems after taking an antibiotic called an aminoglycoside.
- Have been told you have a certain genetic change related to hearing problems.
- Have vestibular problems (problems with your inner ear and brain) that can cause vertigo (loss of balance) and dizziness.
- Have kidney problems.
- Have unusual difficulty in breathing with wheezing or coughing and chest tightness.
- Have blood in your sputum (the substance you cough up).
- Have Parkinson's disease.
- Have a condition called myasthenia gravis which is a chronic disease that causes muscle weakness.
- Are breastfeeding or planning to breastfeed.
- Are receiving an antibiotic called an aminoglycoside by injection since this can cause hearing loss, kidney problems or dizziness.
- Are taking any other medicines.

Other warnings you should know about:

Pregnancy: Before taking TOBI, talk to your healthcare professional if you are pregnant or want to become pregnant. It is not known whether inhaling this medicine can harm an unborn baby. When given by injection, the medicine in TOBI can harm an unborn baby and cause deafness. Your healthcare professional will talk to you about whether you can take TOBI if you are pregnant.

Breastfeeding: When given by injection, the medicine in TOBI can be found in the breast milk. The quantity found in the breast milk after inhaling TOBI is not known. TOBI may cause problems to your baby's hearing or kidneys. Talk to your healthcare professional about whether you should stop breastfeeding or stop taking TOBI.

TOBI is in a class of antibiotics that may cause hearing loss, dizziness, or kidney problems. While you are using TOBI and if you have or are at risk of hearing or kidney problems, your healthcare professional may do bloodwork to check how your kidneys are working. You may also take a hearing test to check whether or not TOBI is affecting your hearing.

Children and adolescents: Caregivers should provide assistance to children when starting TOBI treatment, particularly those aged 10 years or younger, and should continue to supervise them throughout treatment.

TOBI can be taken by children and adolescents aged 6 years and older. TOBI should not be given to children less than 6 years old.

Driving and Operating Machinery: Give yourself time after taking TOBI to see how you feel before driving a vehicle or using machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TOBI:

You should not take the following medicines while you are taking TOBI:

- Furosemide or ethacrynic acid, a diuretic ("water pills")
- Urea or intravenous mannitol

You should not take the following medicines while you are taking TOBI, or soon after finishing TOBI treatment:

- Medicines (including tobramycin or another aminoglycoside antibiotic given by injection) that may harm your nervous system, kidneys or hearing. This interaction may cause hearing loss, dizziness, or kidney problems.

The following medicines can increase the chances of harmful effects occurring if they are given to you while receiving infusions of tobramycin or other aminoglycoside antibiotic. Talk to your healthcare professional if you are taking these medications:

- Amphotericin C, cefalotin, cyclosporine, tacrolimus, polymixins: these medicines may harm your kidneys.
- Platinum compounds (such as carboplastin and cisplatin): these medicines may harm your kidneys or hearing.
- Anticholinesterases (such as neostigmine and pyridostigmine) or botulinum toxin: these medicines may cause muscle weakness to appear or become worse.

Many other medications may also harm your nervous system, kidneys or hearing. Tell your healthcare professional about all the medications you are taking, even those that do not appear on this list.

How to take TOBI:

- TOBI is a solution specifically formulated for inhalation using a PARI LC PLUS™ reusable nebulizer and a DeVilbiss Pulmo-Aide® air compressor (see the step-by-step Instructions in the "**How To Administer TOBI**" section below).
- Take TOBI exactly as your healthcare professional tells you to. Ask your healthcare professional if you are not sure.
- Take TOBI at the same time each day. This will help you remember when to take TOBI.
- Do NOT mix TOBI with dornase alfa (PULMOZYME®) in the nebulizer.
- Please check the order of medications with your doctor. If you are taking several medications and have other therapies for cystic fibrosis, TOBI should always be taken last. Take your medicines in the following order:
  - 1st bronchodilator
  - 2nd chest physiotherapy
  - 3rd other inhaled medications
  - 4th TOBI.
- Continue taking TOBI as your healthcare professional tells you.
- If you have questions about how long to take TOBI, talk to your doctor or your pharmacist.

How To Administer TOBI:

This information is not intended to replace consultation with your healthcare professional, and cystic fibrosis care team about properly taking medication or using inhalation equipment.

TOBI is specifically formulated for inhalation using a PARI LC PLUS™ reusable nebulizer and a DeVilbiss Pulmo-Aide® air compressor. You can take TOBI at home, school, or at work. The following are instructions on how to use the DeVilbiss Pulmo-Aide® Compressor and PARI LC PLUS™ reusable nebulizer to administer TOBI.

You will need the following supplies:

- TOBI plastic ampoule (vial)
- DeVilbiss Pulmo-Aide® Compressor
- PARI LC PLUS™ Reusable Nebulizer
- Tubing to connect the nebulizer and compressor
- Clean paper or cloth towels
- Nose clips (optional)

It is important that your nebulizer and compressor function properly before starting your TOBI therapy.

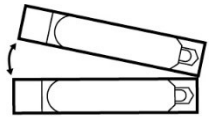
Note: Please refer to the manufacturers' care and use instructions for important information.

Preparing Your TOBI For Inhalation:

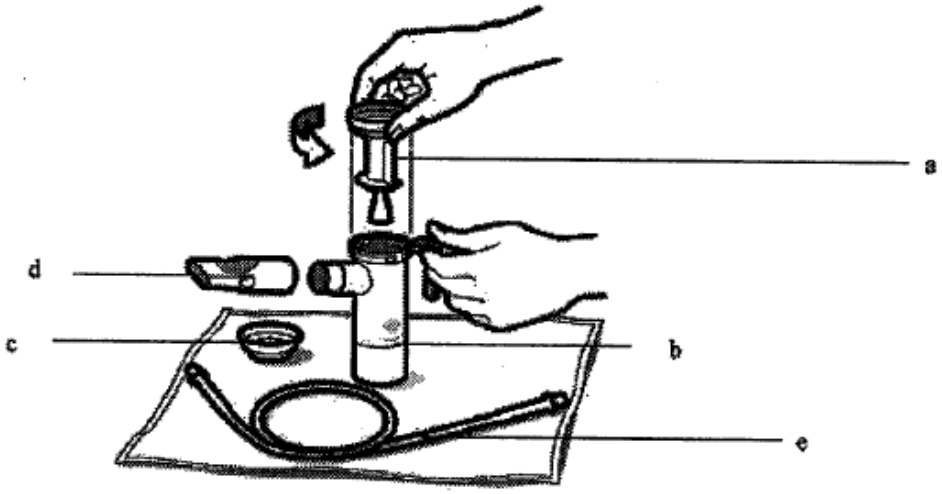
1. Wash your hands thoroughly with soap and water.

2a. TOBI is packaged with four ampoules per foil pouch.

2b. Separate one ampoule by gently pulling apart at the bottom tabs. Store all remaining ampoules in the refrigerator as directed.



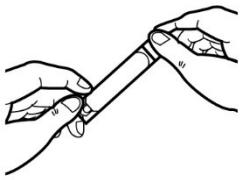
3. Lay out the contents of a PARI LC PLUS™ Reusable Nebulizer package on a clean, dry paper or cloth towel. You should have the following parts: nebulizer top (a), nebulizer bottom (b), inspiratory valve cap (c), mouthpiece with valve (d) and tubing (e) on a clean, dry paper or cloth towel.



4. Remove the Nebulizer Top from the Nebulizer Cup by twisting the Nebulizer Top counter-clockwise, and then lifting off. Place the Nebulizer Top on the clean paper or cloth towel. Stand the Nebulizer Cup upright on the towel.

5. Connect one end of the tubing to the compressor air outlet. The tubing should fit snugly. Plug in your compressor to an electrical outlet.

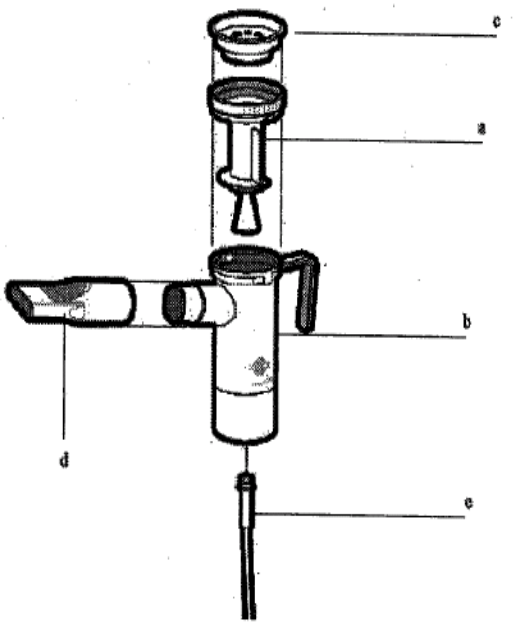
6. Open the TOBI ampoule by holding the bottom tab with one hand and twisting off the top of the ampoule with the other hand. Be careful not to squeeze the ampoule until you are ready to empty its contents into the Nebulizer Cup.



7. Squeeze **all** the contents of the ampoule into the Nebulizer Cup.

8. Replace the Nebulizer Top (a).

Note: In order to insert the Nebulizer Top into the Nebulizer Cup, the Semi-Circle halfway down the stem of the Nebulizer Top should face the Nebulizer Outlet (see illustration). Turn the Nebulizer Top clockwise until securely fastened to the Nebulizer Cup.



9. Attach the Mouthpiece (d) to the Nebulizer Outlet. Then firmly push the Inspiratory Valve Cap (c) in place on the Nebulizer Top. Note: the Inspiratory Valve Cap will fit snugly.

10. Connect the free end of the tubing (e) from the compressor to the Air Intake on the bottom of the nebulizer, making sure to keep the nebulizer upright. Press the tubing on the Air Intake firmly.

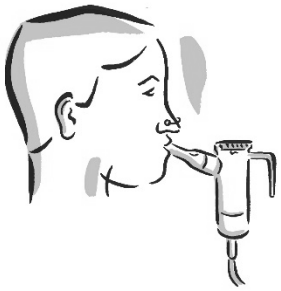
TOBI Treatment:

1. Turn on the compressor.

2. Check for a steady mist from the Mouthpiece. If there is no mist, check all tubing connections and confirm that the compressor is working properly.

3. Sit or stand in an upright position that will allow you to breathe normally.

4. Place mouthpiece between your teeth and on top of your tongue and breathe normally only through your mouth. Nose clips may help you breathe through your mouth and not through your nose. Do not block airflow with your tongue.



5. Continue treatment until all of your TOBI is gone and there is no longer any mist being produced. You may hear a sputtering sound when the Nebulizer Cup is empty. The entire TOBI treatment should take approximately 15 minutes to complete. Note: if you are interrupted, need to cough or rest during your TOBI treatment, turn off the compressor to save your medication. Turn the compressor back on when you are ready to resume your therapy.

6. Follow the nebulizer cleaning and disinfecting instructions after completing therapy.

Cleaning Your Nebulizer:

To reduce the risk of infection, illness or injury from contamination, you must thoroughly clean all parts of the nebulizer as instructed after each treatment. Never use a nebulizer with a clogged nozzle. If the nozzle is clogged, no aerosol mist is produced which will alter the effectiveness off the treatment. Replace the nebulizer if clogging occurs.

1. Remove tubing from nebulizer and disassemble nebulizer parts.

2. Wash all parts (except tubing) with warm water and liquid dish soap.

3. Rinse thoroughly with warm water and shake out water.

4. Air dry or hand dry nebulizer parts on a clean, lint-free cloth. Reassemble nebulizer when dry and store.

5. You can also wash all parts of the nebulizer in a dishwasher (except tubing). Place the nebulizer parts in a dishwasher basket, then place on the top rack of the dishwasher. Remove and dry the parts when the cycle is complete.

Disinfecting Your Nebulizer:

Your nebulizer is for your use only - Do not share your nebulizer with other people. You must regularly disinfect the nebulizer. Failure to do so could lead to serious or fatal illness.

Clean the nebulizer as described above. Every other treatment day, disinfect the nebulizer parts (except tubing) by boiling them in water for a full 10 minutes.

Dry parts on a clean, lint-free cloth.

Care And Use Of Your Pulmo-Aide Compressor:

Follow the manufacturer's instructions for care and use of your compressor.

Filter Change:

1. DeVilbiss Compressor filters should be changed every six months or sooner if filter turns completely grey in colour.

Compressor Cleaning:

1. With power switch in the "Off" position, unplug power cord from wall outlet.

2. Wipe outside of the compressor cabinet with a clean, damp cloth every few days to keep dust free.

Caution: Do not submerge in water; doing so will result in compressor damage.

Usual dose:

- Usual dose of TOBI in adults and children 6 years of age and older:
  - Inhale the content of one ampoule (with 300 milligrams (mg) of tobramycin) in the morning and one in the evening for 28 days using the nebulizer and a suitable compressor. Space the morning and evening doses as close as possible to 12 hours and not less than 6 hours apart.
- After taking TOBI for 28 days, stop using it and wait 28 days before starting another 28-days treatment cycle again.
- It is important that you keep using TOBI two times per day during your 28 days on treatment and that you keep to the 28-day on, 28-day off cycle (see picture below).

ON TOBI	OFF TOBI
Take TOBI twice a day, every day for 28 days	Do not take any TOBI for the next 28 days

Repeat cycle

Overdose:

If you think you, or a person you are caring for, have taken too much TOBI, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take TOBI and there are at least 6 hours to your next dose, take your dose as soon as you can. Otherwise, wait for your next dose. Do not double the dose to make up for the missed dose.

What are possible side effects from using TOBI?

These are not all the possible side effects you may have when taking TOBI. If you experience any side effects not listed here, tell your healthcare professional.

Some side effects are very common (these side effects may affect more than 1 in 10 patients):

- Runny or stuffy nose, sneezing
- Changes in your voice (hoarseness)
- Discoloration of the substance you cough up (sputum)
- Decreased results for the tests of lung function

Some side effects are common (these side effects may affect between 1 and 10 in every 100 patients):

- Generally feeling unwell
- Muscle pain
- Voice alteration with sore throat and difficulty swallowing (laryngitis)

The frequency of some side effects is not known (the frequency cannot be estimated from the available data):

- Increased quantity of the substance you cough up (sputum)
- Chest pain
- Reduced appetite
- Itching
- Itchy rash
- Rash
- Loss of voice
- Disturbed sense of taste
- Sore throat

If you experience symptoms such as severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness, you may have Clostridium difficile colitis (bowel inflammation). If this occurs, stop taking TOBI and contact your healthcare professional immediately.

Talk to your healthcare professional if the following occurs while taking TOBI:

- If you are not getting better. Strains of *Pseudomonas* can become resistant to treatment with the antibiotic over time. This can mean TOBI may not work as well over time.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Worsening of your underlying lung disease		X	
COMMON			
Unusual difficulty in breathing with wheezing or coughing and chest tightness (bronchospasm)			X
Hearing problems: • ringing in the ears (is a potential warning sign of hearing loss) • noises (such as hissing) in the ears • any changes in hearing			X
Shortness of breath, productive cough, sore throat, headache, fever	X		
Wheezing, rales (crackles), chest discomfort, chest pain from muscles and/or skeleton origins, decreased results for the tests of lung function, high level of sugar (glucose) in the blood	X		
NOT KNOWN			
Allergic reactions: • skin rash • hives • itching • difficulty breathing • throat tightness • facial swelling • flushing (warmth and redness of the skin)			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

TOBI ampoules are for single use only. Once opened, use immediately. Discard any unused solution.

Store TOBI ampoules in a refrigerator (2-8°C).

If you can't keep TOBI ampoules in the refrigerator store them in the foil pouches (opened or unopened) at room temperature (up to 25°C) for up to 28 days.

Store TOBI ampoules in the original package away from heat or direct light.

The solution in TOBI ampoule is normally slightly yellow. However unrefrigerated TOBI solution may darken with time. The colour change of unrefrigerated TOBI solution does not mean a change in the quality of TOBI provided that the foil pouches (opened or unopened) are stored at room temperature (up to 25°C) for a maximum of 28 days.

Do not use the unrefrigerated TOBI after 28 days.

Do not use TOBI:

- if the solution is cloudy or if there are particles in the solution,
- beyond the expiration date stamped on the ampoule.

Keep out of reach and sight of children.

If you want more information about TOBI:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.mylan.ca, or by calling 1-844-596-9526.

This leaflet was prepared by BGP Pharma ULC.

Last Revised DEC 5, 2023