

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TOBI safely and effectively. See full prescribing information for TOBI.

TOBI® (tobramycin inhalation solution), for oral inhalation use
Initial U.S. Approval: 1975

-----RECENT MAJOR CHANGES-----

Warnings and Precautions, Ototoxicity (5.2) 10/2018

-----INDICATIONS AND USAGE-----

TOBI is an aminoglycoside antibacterial indicated for the management of cystic fibrosis in adults and pediatric patients 6 years of age and older with *Pseudomonas aeruginosa*. (1)

Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with forced expiratory volume in 1 second (FEV₁) < 25% or > 75% predicted, or patients colonized with *Burkholderia cepacia*. (1)

-----DOSAGE AND ADMINISTRATION-----

- For oral inhalation only. (2.1)
- The recommended dosage for adults and pediatric patients 6 years of age and older is one single-dose ampoule (300 mg) twice daily by oral inhalation in alternating periods of 28 days on drug, followed by 28 days off drug. (2.1)
- Dosage is not adjusted by weight. (2.1)
- Take doses as close to 12 hours apart as possible; but not less than 6 hours apart. (2.1)
- Administer each 300 mg dose by inhalation using a hand-held PARI LC PLUS Reusable Nebulizer with a DeVilbiss Pulmo-Aide compressor. (2.2)

-----DOSAGE FORMS AND STRENGTHS-----

Inhalation Solution: 300 mg per 5 mL solution in a single-dose ampoule (3)

-----CONTRAINDICATIONS-----

Known hypersensitivity to any aminoglycoside (4)

-----WARNINGS AND PRECAUTIONS-----

- **Bronchospasm:** Can occur with inhalation of TOBI. Treat as medically appropriate, if it occurs. (5.1)

- **Ototoxicity:** Tinnitus and hearing loss have been reported in patients receiving TOBI. If noted, manage as medically appropriate, including potentially discontinuing TOBI. (5.2)
- **Nephrotoxicity:** Has been associated with aminoglycosides as a class. If nephrotoxicity develops, manage the patient as medically appropriate, including potentially discontinuing TOBI. (5.3)
- **Neuromuscular Disorders:** Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but mechanical assistance may be necessary. (5.4)
- **Embryo-fetal Toxicity:** Aminoglycosides can cause fetal harm (5.5, 8.1)

-----ADVERSE REACTIONS-----

Most common adverse reactions (incidence > 5%) are increased cough, pharyngitis, increased sputum, dyspnea, hemoptysis, decreased lung function, voice alteration, taste perversion and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Concurrent and/or sequential use of TOBI with other drugs with neurotoxic, nephrotoxic, or ototoxic potential should be avoided. (7.1)
- Concomitant administration with ethacrynic acid, furosemide, urea, or intravenous mannitol is not recommended due to possible enhancement of aminoglycoside toxicity. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TOBI is indicated for the management of cystic fibrosis in adults and pediatric patients 6 years of age and older with *Pseudomonas aeruginosa*.

Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with forced expiratory volume in 1 second (FEV₁) < 25% or > 75% predicted, or patients colonized with *Burkholderia cepacia* [see *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

TOBI is for oral inhalation only [see *Dosage and Administration (2.2)*]. The recommended dosage of TOBI for both adults and pediatric patients 6 years of age and older is one single-dose ampoule (300 mg) administered twice daily for 28 days. Dosage is not adjusted by weight. All patients should be administered 300 mg twice daily.

TOBI is administered twice daily 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. The doses should be taken as close to 12 hours apart as possible; they should not be taken less than 6 hours apart.

If patients miss a dose, they should take it as soon as possible anytime up to 6 hours prior to their next scheduled dose. If less than 6 hours remain before the next dose, wait until their next scheduled dose.

2.2 Administration Instructions

TOBI is administered by oral inhalation over an approximately 15-minute period, using a hand-held PARI LC PLUS Reusable Nebulizer with a DeVilbiss Pulmo-Aide compressor. TOBI should not be diluted or mixed with dornase alfa or other medications in the nebulizer. TOBI is *not* for subcutaneous, intravenous or intrathecal administration.

Prior to administration of TOBI, read the Patient Information/Instructions for Use for TOBI for detailed information on how to use TOBI, and follow the manufacturer's instructions for use and care of the PARI LC PLUS Reusable Nebulizer and DeVilbiss Pulmo-Aide air compressor. 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.

Instruct patients on multiple therapies to take their medications, prior to inhaling TOBI or as directed by their physician.

TOBI should not be used if it is cloudy, if there are particles in the solution, or if it has been stored at room temperature for more than 28 days.

3 DOSAGE FORMS AND STRENGTHS

TOBI is supplied as a sterile inhalational solution for nebulization in single-dose 5 mL ampoules. Each 5 mL ampoule contains 300 mg of tobramycin.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Bronchospasm

Bronchospasm can occur with inhalation of TOBI. In clinical studies with TOBI, changes in FEV₁ measured after the inhaled dose were similar in tobramycin inhalation solution and placebo groups. Bronchospasm that occurs during the use of TOBI should be treated as medically appropriate.

5.2 Ototoxicity

Ototoxicity, manifested as both auditory and vestibular toxicity, has been reported with parenteral aminoglycosides.

Transient tinnitus occurred in eight TOBI treated patients versus no placebo patients in the clinical studies. Tinnitus may be a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants further clinical investigation.

Ototoxicity, as measured by complaints of hearing loss or by audiometric evaluations, did not occur with TOBI therapy during clinical studies, however in postmarketing experience, patients receiving TOBI have reported hearing loss.

Vestibular toxicity may be manifested by vertigo, ataxia or dizziness. Patients with known or suspected auditory or vestibular dysfunction should be closely monitored when taking TOBI. Monitoring might include obtaining audiometric evaluations and serum tobramycin levels. If ototoxicity is noted, the patient should be managed as medically appropriate, including potentially discontinuing TOBI.

5.3 Nephrotoxicity

Nephrotoxicity was not seen during clinical studies with TOBI but has been associated with aminoglycosides as a class. Patients with known or suspected renal dysfunction or taking concomitant nephrotoxic drugs along with TOBI should have serum concentrations of tobramycin and laboratory measurements of renal function obtained at the discretion of the treating physician. If nephrotoxicity develops, the patient should be managed as medically appropriate, including potentially discontinuing TOBI.

5.4 Neuromuscular Disorders

Aminoglycosides, including tobramycin, may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function. Neuromuscular blockade, respiratory failure, and prolonged respiratory paralysis may occur more commonly in patients with underlying neuromuscular disorders, such as myasthenia gravis or Parkinson's disease. Prolonged respiratory paralysis may also occur in patients receiving concomitant neuromuscular blocking agents. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but mechanical assistance may be necessary.

5.5 Embryo-fetal Toxicity

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*. However, systemic absorption of tobramycin following inhaled administration is expected to be minimal [see *Clinical Pharmacology* (12.3)]. Patients who use TOBI during pregnancy, or become pregnant while taking TOBI should be apprised of the potential hazard to the fetus [see *Use in Specific Populations* (8.1)].

5.6 Concomitant Use of Systemic Aminoglycosides

Patients receiving concomitant TOBI and parenteral aminoglycoside therapy should be monitored as clinically appropriate for toxicities associated with aminoglycosides as a class. Serum tobramycin levels should be monitored.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Bronchospasm [see *Warnings and Precautions* (5.1)]
- Ototoxicity [see *Warnings and Precautions* (5.2)]
- Nephrotoxicity [see *Warnings and Precautions* (5.3)]
- Neuromuscular Disorders [see *Warnings and Precautions* (5.4)]
- Embryo-fetal Toxicity [see *Warnings and Precautions* (5.5)]
- Concomitant Use of Systemic Aminoglycosides [see *Warnings and Precautions* (5.6)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

TOBI was studied in two Phase 3 clinical studies involving 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.

Table 1 lists the percent of patients with selected adverse reactions that occurred in > 5% of TOBI patients during the two Phase 3 studies.

Table 1: Percent of Patients With Selected Adverse Reactions Occurring in > 5% of TOBI Patients

| Adverse Reaction | Tobramycin Inhalation Solution (n = 258) % | Placebo (n = 262) % |
|--|---|------------------------------------|
| Cough Increased | 46.1 | 47.3 |
| Pharyngitis | 38.0 | 39.3 |
| Sputum Increased | 37.6 | 39.7 |
| Dyspnea | 33.7 | 38.5 |
| Hemoptysis | 19.4 | 23.7 |
| Lung Function Decreased¹ | 16.3 | 15.3 |
| Voice Alteration | 12.8 | 6.5 |
| Taste Perversion | 6.6 | 6.9 |
| Rash | 5.4 | 6.1 |

¹ Includes reported decreases in pulmonary function tests or decreased lung volume on chest radiograph associated with intercurrent illness or study drug administration.

Selected adverse reactions that occurred in less than or equal to 5% of patients treated with TOBI:

Ear and Labyrinth Disorders: Tinnitus

Musculoskeletal and Connective Tissue Disorders: Myalgia

Infections and Infestations: Laryngitis

Voice Alteration and Tinnitus

Voice alteration and tinnitus were the only adverse reactions reported by significantly more TOBI-treated patients. Thirty-three patients (13%) treated with TOBI 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 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 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 and placebo groups.

Changes in Serum Creatinine

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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of TOBI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Ear and Labyrinth Disorders

Hearing loss: Some of these reports occurred in patients with previous or concomitant treatment with systemic aminoglycosides. Patients with hearing loss frequently reported tinnitus [*see Warnings and Precautions (5.2)*].

Skin and Subcutaneous Tissue Disorders

Hypersensitivity, pruritus, urticaria, rash

Nervous System Disorders

Aphonia, dysgeusia

Respiratory, Thoracic, and Mediastinal Disorders

Bronchospasm [*see Warnings and Precautions (5.1)*] oropharyngeal pain

Metabolism and Nutrition Disorders

Decreased appetite

7 DRUG INTERACTIONS

7.1 Drugs with Neurotoxic, Nephrotoxic or Ototoxic Potential

Concurrent and/or sequential use of TOBI with other drugs with neurotoxic, nephrotoxic, or ototoxic potential should be avoided.

7.2 Diuretics

Some diuretics can enhance aminoglycoside toxicity by altering aminoglycoside concentrations in serum and tissue. TOBI should not be administered concomitantly with ethacrynic acid, furosemide, urea, or intravenous mannitol. The interaction between inhaled mannitol and TOBI has not been evaluated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Aminoglycosides can cause fetal harm. Published literature reports that use of streptomycin, an aminoglycoside, can cause total, irreversible, bilateral congenital deafness when administered to a pregnant woman [*see Warnings and Precautions (5.5)*]. Although there are no available data on TOBI use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes, systemic absorption of tobramycin following inhaled administration is expected to be minimal [*see Clinical Pharmacology (12.3)*]. There are risks to the mother associated with cystic fibrosis in pregnancy (*see Clinical Considerations*). In animal reproduction studies with subcutaneous administration of tobramycin in pregnant rats and rabbits during organogenesis, there were no adverse developmental outcomes; however, ototoxicity was not evaluated in the offspring from these studies (*see Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Cystic fibrosis may increase the risk for preterm delivery.

Data

Animal Data

No reproductive toxicity studies have been conducted with TOBI (tobramycin administered by inhalation). However, subcutaneous administration of tobramycin at doses of up to 100 (rat) or 20 (rabbit) mg/kg/day during organogenesis was not associated with adverse developmental outcomes. Doses of tobramycin \geq 40 mg/kg/day were severely maternally toxic to rabbits and precluded the evaluation of adverse developmental outcomes. Ototoxicity was not evaluated in offspring during non-clinical reproductive toxicity studies with tobramycin.

8.2 Lactation

Risk Summary

There are no data on the presence of TOBI in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. Limited published data on other formulations of tobramycin in lactating women indicate that tobramycin is present in human milk. However, systemic absorption of tobramycin following inhaled administration is

expected to be minimal [see *Clinical Pharmacology (12.3)*]. Tobramycin may cause alteration in the intestinal flora of the breastfeeding infant (see *Clinical Considerations*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TOBI and any potential adverse effects on the breastfed infant from TOBI or from the underlying maternal condition.

Clinical Considerations

Tobramycin may cause intestinal flora alteration. Advise a woman to monitor the breastfed infant for loose or bloody stools and candidiasis (thrush, diaper rash).

8.4 Pediatric Use

The safety and efficacy of TOBI in pediatric patients under 6 years of age has not been established. The use of TOBI is not indicated in children < 6 years of age [see *Indications and Usage (1) and Dosage and Administration (2)*].

8.5 Geriatric Use

Clinical studies of TOBI did not include patients aged 65 years and over. Tobramycin is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function [see *Warnings and Precautions (5.3)*].

10 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 overdosage.

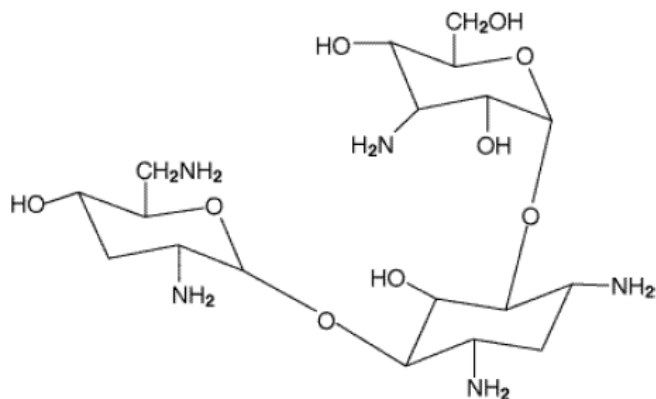
Acute toxicity should be treated with immediate withdrawal of TOBI, and baseline tests of renal function should be undertaken.

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.

11 DESCRIPTION

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. The chemical formula for tobramycin is $C_{18}H_{37}N_5O_9$ and the molecular weight is 467.52 g/mol. Tobramycin is O-3-amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 4)-O-[2,6-diamino-2,3,6-trideoxy- α -D-ribo-hexopyranosyl-(1 \rightarrow 6)]-2-deoxy-L-streptamine. The structural formula for tobramycin is:



Each single-dose 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. Nitrogen is used for sparging. All ingredients meet USP requirements. The formulation contains no preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tobramycin is an aminoglycoside antibacterial [see *Microbiology (12.4)*].

12.3 Pharmacokinetics

Absorption

TOBI contains tobramycin, a cationic polar molecule that does not readily cross epithelial membranes. ⁽¹⁾The bioavailability of TOBI may vary because of individual differences in nebulizer performance and airway pathology. ⁽²⁾Following administration of TOBI, tobramycin remains concentrated primarily in the airways.

Serum Concentrations

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

Sputum Concentrations

Ten minutes after inhalation of the first 300-mg dose of TOBI by cystic fibrosis patients, the average concentration of tobramycin was 1237 mcg/g (range 35 to 7417 mcg/g) in sputum. Tobramycin does not accumulate in sputum; after 20 weeks of therapy with the TOBI regimen, the average concentration of tobramycin at ten minutes after inhalation was 1154 mcg/g (range 39 to 8085 mcg/g) in sputum. Two hours after inhalation, sputum concentrations declined to approximately 14% of tobramycin levels at ten minutes after inhalation.

Distribution

Following administration of TOBI, tobramycin remains concentrated primarily in the airways. Binding of tobramycin to serum proteins is negligible.

Elimination

Metabolism

Tobramycin is not metabolized.

Excretion

The elimination half-life of tobramycin from serum is approximately 2 and 3 hours after intravenous (IV) administration and inhalation, respectively. Systemically absorbed tobramycin is primarily excreted unchanged in the urine principally by glomerular filtration. Unabsorbed tobramycin, following TOBI administration, is probably eliminated primarily in expectorated sputum.

12.4 Microbiology

Mechanism of Action

Tobramycin is an aminoglycoside antibacterial produced by *Streptomyces tenebrarius*. ⁽¹⁾It acts primarily by disrupting protein synthesis, leading to altered cell membrane permeability, progressive disruption of the cell envelope, and eventual cell death. ⁽³⁾

Tobramycin has *in vitro* activity against gram-negative bacteria including *Pseudomonas aeruginosa*. It is bactericidal *in vitro* at concentrations equal to or slightly greater than the minimum inhibitory concentration (MIC).

Resistance

Treatment for 6 months with TOBI in two clinical studies did not affect the susceptibility of the majority of *P. aeruginosa* isolates tested; however, increased minimum inhibitory concentrations (MICs) were noted in some patients. The clinical

significance of this information has not been clearly established in the treatment of *P. aeruginosa* in cystic fibrosis patients [see *Clinical Studies (14)*].

Susceptibility Test Methods

Interpretive criteria for inhaled antibacterial products are not defined. The *in vitro* antimicrobial susceptibility test methods used for parenteral tobramycin therapy can be used to monitor the susceptibility of *P. aeruginosa* isolated from cystic fibrosis patients. If decreased susceptibility is noted, the results should be reported to the clinician.

Susceptibility breakpoints established for parenteral administration of tobramycin do not apply to aerosolized administration of TOBI. The relationship between *in vitro* susceptibility test results and clinical outcome with TOBI therapy is not clear.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year rat inhalation toxicology study to assess carcinogenic potential of TOBI has been completed. Rats were exposed to TOBI for up to 1.5 hours per day for 95 weeks. The clinical formulation of the drug was used for this carcinogenicity study. Serum levels of tobramycin of up to 35 mcg/mL were measured in rats, in contrast to the average 1 mcg/mL levels observed in cystic fibrosis patients in clinical trials. There was no drug-related increase in the incidence of any variety of tumor.

Additionally, tobramycin has been evaluated for genotoxicity in a battery of *in vitro* and *in vivo* tests. The Ames bacterial reversion test, conducted with 5 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, did not induce chromosomal aberrations in Chinese hamster ovary cells, and was negative in the mouse micronucleus test.

Subcutaneous administration of up to 100 mg/kg of tobramycin did not affect mating behavior or cause impairment of fertility in male or female rats.

14 CLINICAL STUDIES

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 *P. aeruginosa*. Subjects who were less than 6 years of age, had a baseline creatinine of > 2 mg/dL, or had *Burkholderia cepacia* isolated from sputum were excluded.

All subjects had baseline FEV₁% predicted between 25% and 75%. In these clinical studies, 258 patients received TOBI therapy on an outpatient basis (see Table 2) using a hand-held PARI LC PLUS Reusable Nebulizer with a DeVilbiss Pulmo-Aide compressor.

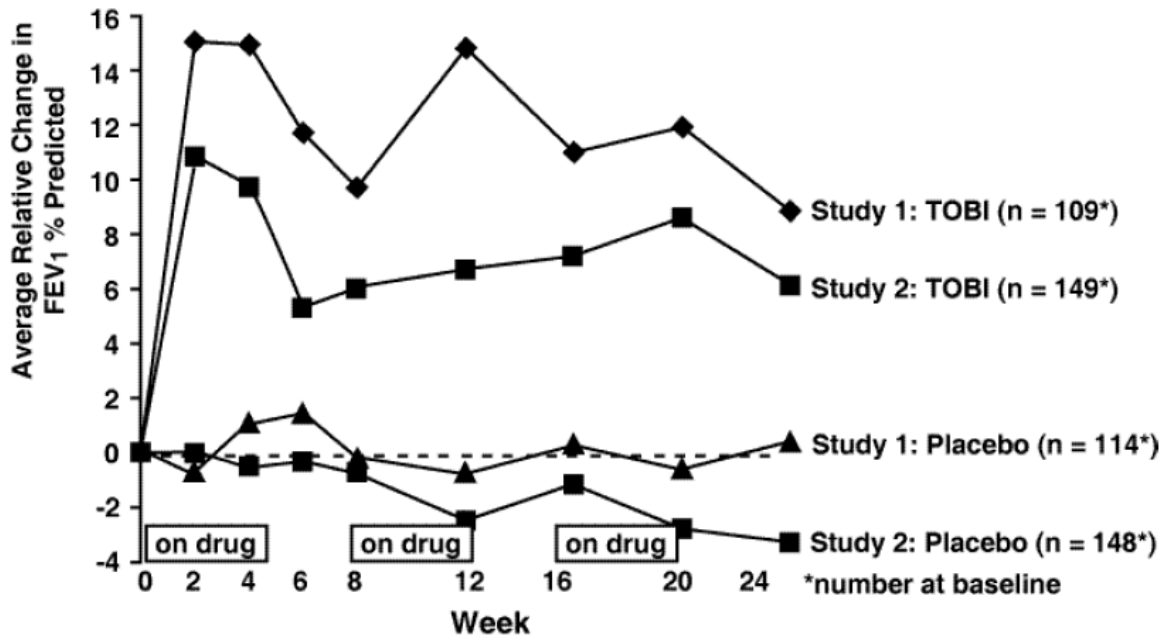
Table 2: Dosing Regimens in Clinical Studies

| | 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 twice daily | No drug | TOBI 300 mg twice daily | No drug | TOBI 300 mg twice daily | No drug |
| Placebo regimen n = 262 | placebo twice daily | No drug | placebo twice daily | No drug | placebo twice daily | No drug |

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 antipseudomonal therapy, β_2 -agonists, cromolyn, inhaled steroids, and airway clearance techniques. In addition, approximately 77% of patients were concurrently treated with dornase alfa (PULMOZYME, Genentech).

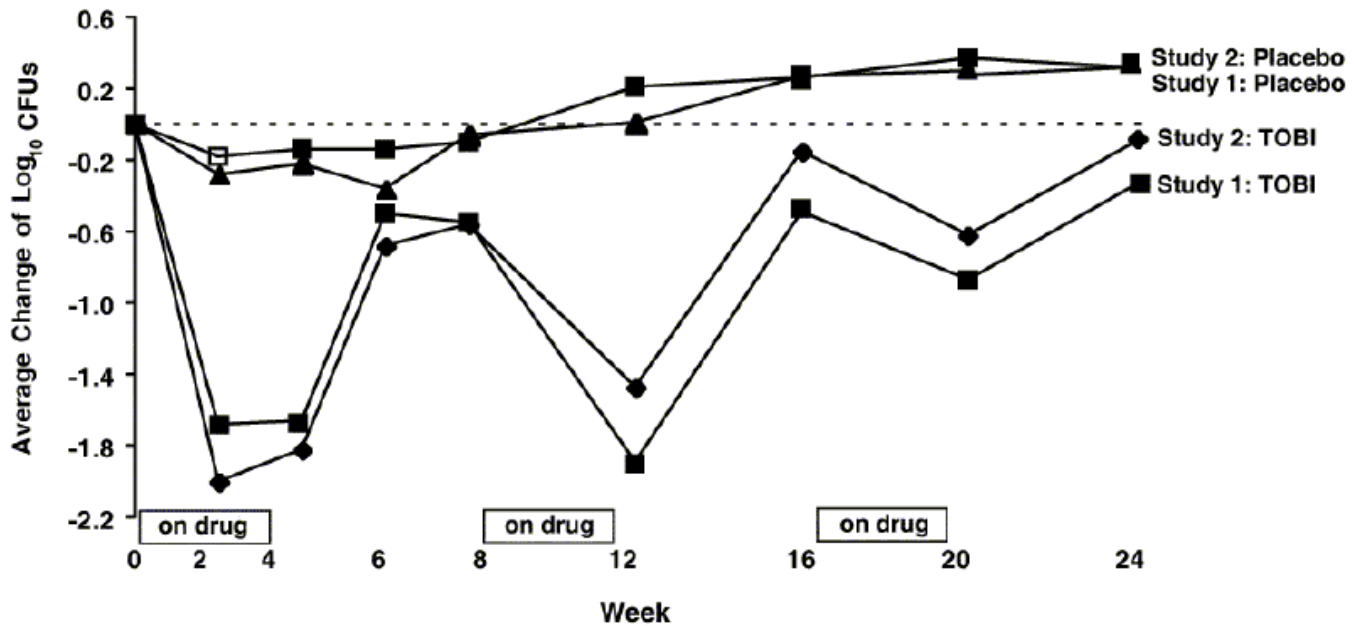
In each study, TOBI-treated patients experienced significant improvement in pulmonary function. Improvement was demonstrated in the TOBI group in Study 1 by an average increase in FEV₁% predicted of about 11% relative to baseline (Week 0) during 24 weeks compared to no average change in placebo patients. 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 FEV₁% predicted over 24 weeks for both studies.

Figure 1: Relative Change From Baseline in FEV₁% Predicted



In each study, TOBI therapy resulted in a significant reduction in the number of *P. aeruginosa* colony forming units (CFUs) in sputum during the on-drug periods. Sputum bacterial density returned to baseline during the off-drug periods. Reductions in sputum bacterial density were smaller in each successive cycle (see Figure 2).

Figure 2: Absolute Change From Baseline in Log₁₀ CFUs



Patients treated with TOBI were hospitalized for an average of 5.1 days compared to 8.1 days for placebo patients. Patients treated with TOBI required an average of 9.6 days of parenteral antipseudomonal, antibacterial treatment compared to 14.1 days for placebo patients. During the 6 months of treatment, 40% of TOBI patients and 53% of placebo patients were treated with parenteral antipseudomonal antibacterials.

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 trial with *P. aeruginosa* isolates having MIC values ≥ 128 mcg/mL did not experience an improvement in FEV₁ or a decrease in sputum bacterial density.

Treatment with TOBI did not affect the susceptibility of the majority of *P. aeruginosa* isolates during the 6-month studies. However, some *P. aeruginosa* isolates did exhibit increased tobramycin MICs. The percentage of patients with *P. aeruginosa* isolates with tobramycin MICs ≥ 16 mcg/mL was 13% at the beginning, and 23% at the end of 6 months of the TOBI regimen.

15 REFERENCES

1. Neu HC. Tobramycin: an overview. [Review]. J Infect Dis 1976; Suppl 134:S3-19.
2. Weber A, Smith A, Williams-Warren J et al. Nebulizer delivery of tobramycin to the lower respiratory tract. Pediatr Pulmonol 1994; 17 (5):331-9.
3. Bryan LE. Aminoglycoside resistance. Bryan LE, Ed. Antimicrobial drug resistance. Orlando, FL: Academic Press, 1984: 241-77.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TOBI is supplied as a sterile, clear, slightly yellow, non-pyrogenic, aqueous solution packaged in a 5 mL single-dose ampoule (300 mg tobramycin) for nebulization.

TOBI 300 mg is available as follows:

5 mL single-dose ampoule (carton of 56) NDC 0078-0494-71

16.2 Storage and Handling

TOBI should be stored under refrigeration at 2°C–8°C/36°F–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°C–8°C/36°F–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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Difficulty Breathing:

Advise patients to inform their physicians if they experience shortness of breath or wheezing after administration of tobramycin inhalation solution. Tobramycin inhalation solution can cause a narrowing of the airway [*see Warnings and Precautions (5.1)*].

Hearing Loss:

Advise patients to inform their physician if they experience ringing in the ears, dizziness, or any changes in hearing because tobramycin inhalation solution has been associated with hearing loss [*see Warnings and Precautions (5.2)*].

Kidney Damage:

Advise patients to inform their physician if they have any history of kidney problems because tobramycin inhalation solution is in a class of drugs that have caused kidney damage [*see Warnings and Precautions (5.3)*].

Embryo-fetal Toxicity:

Advise pregnant women that aminoglycosides can cause irreversible congenital deafness when administered to a pregnant woman [*see Warnings and Precautions (5.5) and Use in Specific Populations (8.1)*].

Lactation:

Advise a woman to monitor their breastfed infants for diarrhea and/or bloody stools [*see Use in Specific Populations (8.2)*].

Distributed by:

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PATIENT INFORMATION
TOBI (TOH-bee)
(tobramycin inhalation solution)
for oral inhalation use

What is TOBI?

TOBI is a prescription medicine that is used to treat people with cystic fibrosis who have a bacterial infection called *Pseudomonas aeruginosa*. TOBI contains an antibacterial medicine called tobramycin (an aminoglycoside).

It is not known if TOBI is safe and effective:

- in children under 6 years of age
- in people who have an FEV₁ less than 25% or greater than 75% predicted
- in people who are colonized with a bacterium called *Burkholderia cepacia*

Do not take TOBI if you are allergic to tobramycin, any of the ingredients in TOBI, or to any other aminoglycoside antibacterial.

See the end of this Patient Information for a complete list of ingredients in TOBI.

Before you take TOBI, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had hearing problems (including noises in your ears such as ringing or hissing)
- have dizziness
- have or have had kidney problems
- have or have had problems with muscle weakness such as myasthenia gravis or Parkinson's disease
- have or have had breathing problems such as wheezing, coughing, or chest tightness
- are pregnant or plan to become pregnant. TOBI is in a class of drugs that can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if TOBI passes into your breast milk.
- are receiving aminoglycoside therapy by injection or through a vein (intravenous) while taking TOBI. Your blood levels of tobramycin will be checked.

Tell your healthcare provider about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements.

How should I take TOBI?

- **See the step-by-step Instructions for Use** about the right way to take your TOBI.
- Take TOBI exactly as your healthcare provider tells you. **Do not** change your dose or stop taking TOBI unless your healthcare provider tells you to.
- The usual dose for adults and children over 6 years of age is:
 - 1 single-use ampule of TOBI inhaled 2 times each day using a hand-held PARI LC PLUS™ Reusable Nebulizer and a DeVilbiss® Pulmo-Aide® air compressor.
- Each dose of TOBI should be taken as close to 12 hours apart as possible.
- You should not take your dose less than 6 hours apart.
- TOBI is taken as a breathing treatment (inhalation) with a hand-held PARI LC PLUS Reusable Nebulizer with a DeVilbiss Pulmo-Aide compressor. **Do not** use any other nebulizer for your TOBI treatment.
- Do not mix or dilute TOBI with dornase alfa or other medicines in your nebulizer system.
- Each treatment should take about 15 minutes.
- TOBI should be inhaled while you are sitting or standing upright and breathing normally through the mouthpiece of the nebulizer. Nose clips may help you to breathe through your mouth.
- 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.
- After using TOBI for 28 days, you should stop using it and wait 28 days. After you have stopped using TOBI for 28 days, you should start using TOBI again for 28 days. Complete the full 28-day course even if you are feeling better. It is important that you keep to the 28-day on, 28-day off cycle.

If you are taking several medicines or treatments to treat your cystic fibrosis, you should take your medicines or other treatments before inhaling TOBI or as directed by your healthcare provider. Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter prescription medicines, vitamins, and herbal supplements.

Using TOBI with certain other medicines can cause serious side effects.

If you are using TOBI, you should discuss with your healthcare provider if you should take:

- other medicines that may harm your nervous system, kidneys, or hearing
- “water pills” (diuretics) such as ethacrynic acid, furosemide, or intravenous mannitol
- urea

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

What are the possible side effects of TOBI?

TOBI may cause serious side effects, including:

- severe breathing problems (bronchospasm). Tell your healthcare provider right away if you get any of these symptoms of bronchospasm with using TOBI:
 - shortness of breath with wheezing
 - coughing and chest tightness
- hearing loss or ringing in the ears (ototoxicity). Tell your healthcare provider right away if you have hearing loss or you hear noises in your ears such as ringing or hissing. Tell your healthcare provider if you develop vertigo, difficulty with balance or dizziness.
- worsening kidney problems (nephrotoxicity). TOBI is in a class of drugs which may cause worsening kidney problems, especially in people with known or suspected kidney problems. Your healthcare provider may do a blood test to check how your kidneys are working while you are using TOBI.
- worsening muscle weakness (neuromuscular disorder). TOBI is in a class of drugs which can cause muscle weakness to get worse in people who already have problems with muscle weakness (myasthenia gravis or Parkinson’s disease).

The most common side effects of TOBI include:

- | | | |
|---------------------|---------------------------|---------------------|
| ○ increased cough | ○ sore throat | ○ increased sputum |
| ○ coughing up blood | ○ decreased lung function | ○ trouble breathing |
| ○ voice changes | ○ loss or change in taste | ○ rash |

These are not all of the possible side effects of TOBI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TOBI

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TOBI for a condition for which it was not prescribed. Do not give it to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for more information about TOBI that is written for health professionals.

What are the ingredients in TOBI?

Active ingredient: tobramycin

Inactive ingredients: sodium chloride in sterile water for injection, sulfuric acid, sodium hydroxide, and nitrogen

What is *Pseudomonas aeruginosa*?

It is a very common bacterium that infects the lungs of nearly everyone with cystic fibrosis at some time during their lives. Some people do not get this infection until later 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 managed, it will continue to damage your lungs causing further problems to your breathing.

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For more information, go to www.pharma.us.novartis.com or call 1-888-669-6682.