PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr TOBI® PODHALER®

Tobramycin Inhalation Powder
(28 mg tobramycin per capsule)

Capsules to be used only with the supplied PODHALER inhalation device

RESPIRATORY ANTIBIOTIC

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral Inhalation	capsule, 28 mg tobramycin	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

TOBI PODHALER (Tobramycin Inhalation Powder) is indicated for the management of cystic fibrosis (CF) patients aged 6 years or older with chronic pulmonary *Pseudomonas aeruginosa (P. aeruginosa)* infections.

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

Safety and efficacy of TOBI PODHALER has been demonstrated in clinical trials over 3 cycles (6 months) of therapy.

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

Culture and susceptibility testing performed periodically will provide information on changing microbial flora and the possible emergence of bacterial resistance (See MICROBIOLOGY).

Geriatrics (≥ *65* years of age):
Clinical studies with TOBI PODHALER did not include sufficient number of patients aged 65 years old and over to determine whether they responded differently from younger patients (See WARNINGS AND PRECAUTIONS, Special populations).

Pediatrics (< 6 years of age):
Safety and efficacy for TOBI PODHALER have not been studied in patients under the age of 6 years (see CLINICAL TRIALS).

CONTRAINDICATIONS

TOBI PODHALER (Tobramycin Inhalation Powder) is contraindicated in patients with a known hypersensitivity to aminoglycosides or to any ingredient in the formulation or any components of the capsule or the container. For a complete listing see DOSAGE FORMS, COMPOSITION, AND PACKAGING section.

WARNINGS AND PRECAUTIONS

General

TOBI PODHALER (Tobramycin Inhalation Powder) is administered only by the oral inhalation route and only with the PODHALER device. It must not be administered by any other route or with any other device. TOBI PODHALER capsules must not be swallowed.

Caution should be exercised when TOBI PODHALER is prescribed to patients with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction. Systemic exposure with inhaled antibiotics is generally minimal.

Concurrent and/or sequential use of TOBI PODHALER with other drugs with neurotoxic, nephrotoxic, or ototoxic potential should be avoided. If parenteral aminoglycoside therapy is needed, patients should be monitored as clinically appropriate (See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and DRUG INTERACTIONS).

The prevalence of *P. aeruginosa* infection in cystic fibrosis patients increases with age. *P. aeruginosa* infection has been associated with poorer clinical outcomes, including more rapid decline in pulmonary function and higher mortality rates in CF patients.

Ear/Nose/Throat

Ototoxicity

Caution should be exercised when TOBI PODHALER 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 PODHALER therapy.

Ototoxicity, manifested as both auditory toxicity (hearing loss, tinnitus) and vestibular toxicity, has been reported with aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia, or dizziness. Tinnitus can have several causes but is a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution.

Hearing loss and tinnitus were reported by patients in the TOBI PODHALER clinical trials (see ADVERSE DRUG REACTIONS).

If a patient reports tinnitus or hearing loss during TOBI PODHALER therapy, the physician should refer them for audiological assessment. If ototoxicity occurs in a patient receiving TOBI PODHALER, all tobramycin therapy should be discontinued until trough

serum concentrations fall below 2 µg/mL (See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

In post marketing experience, severe hearing loss has been reported in some patients who received TOBI (Tobramycin Solution for Inhalation) therapy in association with either previous or concomitant parenteral aminoglycoside use.

Hepatic/Biliary/Pancreatic

Patients with hepatic impairment

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

Immune

Allergic Reactions

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

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

Neurologic

Neuromuscular dysfunction

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

Nephrotoxicity has been reported with the use of parenteral aminoglycosides. Nephrotoxicity was not observed during TOBI PODHALER clinical studies. Patients with serum creatinine 2 mg/dL or more and blood urea nitrogen (BUN) 40 mg/dL or more have not been included in clinical studies.

Baseline renal function should be assessed. Laboratory tests of urine and renal function should be conducted at the discretion of the treating physician, noting that the clinical trials provided safety data over 3 cycles.

If there is evidence of nephrotoxicity in a patient receiving TOBI PODHALER, all tobramycin therapy should be discontinued until trough serum concentrations fall below 2 µg/mL.

Respiratory

Bronchospasm

Bronchospasm can occur with inhalation of medicinal products and has been reported with TOBI PODHALER during clinical trials. The rates of bronchospasm (as measured by ≥20% decrease in FEV_1 within 30 minutes post-dose) during the clinical trials were comparable (5%) between TOBI PODHALER and TOBI. Bronchospasm should be treated as medically appropriate.

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

Cough

Cough can occur with the use of any inhaled medication and was reported with use of TOBI PODHALER in clinical trials.

In clinical trials the inhalation powder TOBI PODHALER was associated with a higher rate of cough reporting compared to the nebulizer solution TOBI (See ADVERSE REACTIONS). Cough was not related to bronchospasm.

If there is evidence of continued therapy-induced cough with TOBI PODHALER, the physician should consider the use of alternative therapeutic options.

Hemoptysis

Patients with clinically significant hemoptysis (> 60 ml) were excluded from the clinical studies, and so, no data exist on the use of TOBI PODHALER in these patients. The use of TOBI PODHALER in such patients should be undertaken only if the benefits of treatment are considered to outweigh the risks of inducing further hemorrhage.

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.

Susceptibility/Resistance

Decrease in susceptibility to tobramycin

The relationship between *in vitro* susceptibility test results and clinical outcome with TOBI PODHALER is not clear. In clinical studies, some patients on TOBI PODHALER therapy showed an increase in tobramycin Minimum Inhibitory Concentrations for *P. aeruginosa* isolates tested (See MICROBIOLOGY).

A potential risk that patients being treated with TOBI PODHALER may develop *P. aeruginosa* isolates resistant to intravenous tobramycin over time cannot be ruled out. Development of resistance during inhaled tobramycin therapy could limit treatment options during acute exacerbations.

Development of Drug-Resistant Bacteria
Prescribing TOBI PODHALER 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 use of TOBI PODHALER may promote the selection of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

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

Special Populations

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.

TOBI PODHALER should not be used during pregnancy unless the potential benefits to the mother clearly outweigh the risks to the fetus. Patients who use TOBI PODHALER during pregnancy, or become pregnant while taking TOBI PODHALER, should be apprised of the potential hazard to the fetus.

Nursing Women: Tobramycin is excreted in human breast milk after systemic administration. The amount of tobramycin excreted in human breast milk after administration by inhalation is not known. Because of the potential for ototoxicity and nephrotoxicity in infants, a decision should be made whether to discontinue nursing or discontinue treatment with TOBI PODHALER, taking into account the importance of the drug to the mother.

Geriatrics (≥*65* years of age): Clinical studies with TOBI PODHALER did not include sufficient number of elderly patients to establish safety and efficacy of TOBI PODHALER in this age group. Renal function in elderly patients should be taken into account when TOBI PODHALER is prescribed (See WARNINGS AND PRECAUTIONS, Nephrotoxicity).

Pediatrics (< 6 years of age): Safety and efficacy for TOBI PODHALER have not been studied in patients under the age of 6 years (See CLINICAL TRIALS).

Patients after organ transplantation: The use of TOBI PODHALER has not been studied in patients after organ transplantation.

Monitoring and Laboratory Tests

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

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 PODHALER, tobramycin therapy should be discontinued until trough serum concentration falls below 2 µg/mL.

Serum tobramycin concentrations are approximately 1 to 2 µg/mL one hour after TOBI PODHALER 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.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In clinical studies, TOBI PODHALER (Tobramycin Inhalation Powder) was generally well tolerated. Based on the Phase III pivotal studies C2301 and C2302, the most common adverse drug reaction (based on adverse events assessed by the Investigator to be possibly or probably related to study medication) was cough, occurring in 21.5% of patients treated with TOBI PODHALER, versus 10.2% of patients treated with placebo, and 4.3% of patients treated with TOBI (Tobramycin Solution for Inhalation) (Table 1).

In most patients, the adverse reactions were mild and moderate in the TOBI PODHALER treatment group with very few patients (3.5%) experiencing adverse reactions of severe intensity. Adverse reactions were reported to be serious in: 2.5% (10 patients) with TOBI PODHALER, 2.0% (1 patient) with placebo and 0.5% with TOBI (1 patient). The most frequent serious adverse drug reaction reported in the TOBI PODHALER group was lung disorder (1.0%). Study or study drug discontinuations due to adverse drug reactions were observed in 9.9% in the TOBI PODHALER group, 2.0% in the placebo and 4.3% in the TOBI group. The most frequent adverse reactions leading to discontinuation reported in the TOBI PODHALER group were cough (3.3%) and dyspnea (2.5%).

The frequency of adverse reactions to TOBI PODHALER progressively decreased over treatment cycles. The most frequent reactions in the TOBI PODHALER arm during the first cycle were: cough, dysphonia, productive cough and oropharyngeal pain; their frequency decreased over the study duration.

Patients 6 years and older were included in clinical studies with TOBI PODHALER. In TOBI PODHALER clinical studies no dosage adjustments were made for pediatric patients. Most frequent adverse drug reactions in patients below 20 years of age were cough, dysgeusia, dysphonia, and oropharyngeal pain. Dysgeusia was more commonly reported in younger patients (6 to 19 years of age) than in patients 20 years and older. One pediatric patient had a serious event reported to be probably related to study drug (*Pseudomonas* infection).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

TOBI PODHALER (Tobramycin Inhalation Powder) has been evaluated for safety in 395 cystic fibrosis patients exposed to at least one dose of TOBI PODHALER, including 273 who were exposed across three cycles (6 months) of on/off treatment. Each cycle consisted of 28 days on-treatment (with 112 mg administered twice daily) and 28 days off-treatment. From the total 395 patients, 68 were between 6 and 12 years of age, 108 were between 13 and 19 years of age and 219 were 20 years of age and older.

The safety population consisted of 308 patients treated with TOBI PODHALER and 209 patients treated with TOBI (Tobramycin Solution for Inhalation) in the C2302 study, an open-label study comparing TOBI PODHALER with TOBI over 3 treatment cycles; and, 87 patients treated with TOBI PODHALER and 49 treated with placebo in the C2301 study, which was double-blind for one treatment cycle, followed by all patients receiving TOBI PODHALER for 2 additional cycles.

Adverse drug reactions from the integrated Phase III pivotal studies C2301 and C2302 are listed in Table 1 according to MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first, and by treatment.

Table 1 - Adverse drug reactions experienced in one or more percent (≥1%) of TOBI PODHALER treated patients in the Phase 3 studies (C2301 and C2302)

System Organ Class/MedDRA Preferred Term	Placebo (N=49) % of patients C2301[(1)]	TOBI PODHALER (N=395) % of patients C2301+ C2302[(2)]	TOBI (N=209) % of patients C2302[(3)]
Any system organ class			
Total	**20.4**	**45.1**	**20.1**
Respiratory, thoracic and mediastinal disorders			
Cough	10.2	21.5	4.3
Dysphonia	0.0	11.1	3.3
Dyspnea	0.0	4.3	1.4
Oropharyngeal pain	0.0	4.1	1.0
Productive cough	2.0	3.5	1.0
Hemoptysis	0.0	2.5	3.3
Throat irritation	2.0	2.5	1.0
Lung disorder	4.1	2.3	1.4
Wheezing	4.1	2.0	1.0
Bronchospasm	0.0	1.0	0.5
Nervous system disorders			
Dysgeusia	0.0	5.1	0.5
Dizziness	2.0	1.0	0.0
Headache	2.0	1.0	1.4
Gastrointestinal disorders			
Dry mouth	0.0	1.5	0.5
Nausea	0.0	1.0	1.9
Vomiting	2.0	1.0	0.5
General disorders and administration site conditions			
Chest discomfort	0.0	2.5	1.0
Pyrexia	0.0	1.0	0.5
Investigations			
Forced expiratory volume decreased	0.0	1.5	0.0

Pulmonary function test decreased	0.0	1.5	1.0
Infections and infestations			
Upper respiratory tract infection	0.0	1.3	0.0

(1) Patients received placebo for one cycle in Study C2301
(2) Patients received TOBI PODHALER for two or three cycles in Study C2301; and for three cycles in Study C2302.
(3) Patients received TOBI for three cycles in Study C2302

Less Common Clinical Trial Adverse Drug Reactions (≥0.5 % and <1%)

In addition to the events listed in Table 1, the following uncommon adverse reactions, assessed as at least possibly related to treatment by the Investigator, were reported in ≥0.5 % and <1% of patients treated with TOBI PODHALER in the Phase 3 studies:

Respiratory, thoracic and mediastinal disorders: Epistaxis, Nasal congestion, Obstructive airways disorder, Painful respiration, Pulmonary congestion, Rales,

Nervous system disorders: Aphonia,

Gastrointestinal disorders: Diarrhoea, Hypoaesthesia oral,

General disorders and administration site conditions: Exercise tolerance decreased,

Investigations: Blood glucose increased, Breath sounds abnormal, Vital capacity decreased,

Infections and infestations: Lower respiratory tract infection, Oral candidiasis,

Ear and labyrinth disorders: Tinnitus, Deafness,

Skin and subcutaneous tissue disorders: Rash, Urticaria,

Musculoskeletal and connective tissue disorders: Musculoskeletal chest pain,

In addition, single occurrences of the following serious adverse drug reactions have been reported: increased bronchial secretion, pneumonitis, pseudomonas infection.

Abnormal Audiometry, Hematologic and Clinical Chemistry Findings

Audiology testing was performed in selected centers in a subset of approximately 25% of the patients in studies C2301 and C2302, including 91 patients treated with TOBI PODHALER. In total, six TOBI PODHALER patients experienced significant decreases in hearing (defined as 10-15 dB in at least two consecutive frequencies, or 20 dB or more at a single frequency): four patients in Study C2302, including three with transient and one with persistent hearing loss; and two patients in Study C2301, one of them with transient hearing loss and one of unknown outcome (no subsequent audiometry testing).

Abnormal hematologic and clinical chemistry findings that were observed were assessed

as due to the underlying disease.

Post-Market Adverse Drug Reactions

The following adverse drug reactions have been derived from post marketing experience with TOBI PODHALER via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

General disorders and administration site conditions

Malaise

Respiratory, thoracic and mediastinal disorders

Sputum discolored

The adverse reactions reported in post marketing surveillance for TOBI (Tobramycin Solution for Inhalation), a different formulation of inhaled tobramycin, are presented below. These spontaneously reported adverse reactions are reported voluntarily and it is not always possible to reliably establish frequency or a causal relationship to drug exposure.

Ear and labyrinth disorders

Hearing loss

Immune

Hypersensitivity (allergic reactions)

Nervous system disorders

Aphonia

Respiratory, thoracic, and mediastinal disorders

Oropharyngeal pain

Skin and subcutaneous tissue disorders

Pruritus, urticaria, rash

In post marketing experience, some patients receiving TOBI with previous or concomitant parenteral aminoglycosides have reported severe hearing loss.

DRUG INTERACTIONS

Drug-Drug Interactions

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

Based on the interaction profile for tobramycin following intravenous and aerosolized administration, concurrent and/or sequential use of TOBI PODHALER 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 PODHALER 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).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Interactions with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

TOBI PODHALER (Tobramycin Inhalation Powder) should only be administered by the oral inhalation route and only using the PODHALER device. It must not be administered by any other route or using any other inhaler. TOBI PODHALER capsules must not be swallowed. Do not administer other drugs with the PODHALER.

The dose of TOBI PODHALER 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 under the age of 6 years, patients with FEV_1 (Forced Expiratory Volume in 1 second) <25% or >75% predicted, or patients colonized with *Burkholderia cepacia*.

Recommended Dose and Dosage Adjustment

The recommended dosage is the content of four capsules (4 × 28 mg = 112 mg tobramycin) administered twice daily for 28 days. TOBI PODHALER is taken in alternating cycles of 28 days on drug followed by 28 days off drug. Each dose of four capsules should be inhaled as closely as possible to 12 hours apart and not less than six hours apart.

Dosing in special populations

Pediatrics (< 6 years of age): TOBI PODHALER 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): There are insufficient safety, efficacy and pharmacokinetic data in this population to recommend for or against dose adjustment. Renal function in elderly patients should be taken into account while using TOBI PODHALER.

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

Patients with renal impairment: Patients with serum creatinine 2 mg/dl or more and blood urea nitrogen (BUN) 40 mg/dl or more were not included in clinical studies and there are no data in this population to support a recommendation for or against dose adjustment with TOBI PODHALER. Tobramycin is primarily excreted unchanged in the urine and renal function is expected to affect exposure to tobramycin. Caution should be exercised when prescribing TOBI PODHALER to patients with known or suspected renal dysfunction.

No studies have been conducted in patients requiring hemodialysis.

Patients after organ transplant: There are not data for the use of TOBI PODHALER in patients after organ transplant. No recommendation for or against dose adjustment can be made for patients after organ transplant.

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 capsules to make up for the missed dose.

Administration

TOBI PODHALER is administered only by the oral inhalation route and only using the PODHALER device. It must not be administered by any other route or using any other inhaler. TOBI PODHALER capsules must not be swallowed.

To ensure proper administration of the drug, the physician or other health professional should show the patient how to operate the PODHALER inhalation device (See SPECIAL HANDLING INSTRUCTIONS).

Where patients are using a short-acting bronchodilator, it should be inhaled 15-90 minutes prior to TOBI PODHALER treatment. The order of chest physiotherapy and other inhaled therapies should follow the physician's recommendation. TOBI PODHALER should always be taken last.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

The maximum tolerated daily dose of TOBI PODHALER (Tobramycin Inhalation Powder) has not been established. Tobramycin serum concentrations may be helpful in monitoring overdosage.

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

In the event of accidental oral ingestion of TOBI PODHALER capsules, toxicity is unlikely as tobramycin is poorly absorbed from an intact gastrointestinal tract.

If necessary, hemodialysis may be helpful in removing tobramycin from the body.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TOBI PODHALER (Tobramycin Inhalation Powder) is a dry-powder formulation of tobramycin designed specifically for administration by inhalation.

Tobramycin is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. Tobramycin has *in vitro* activity against a wide range of Gram-negative organisms including *Pseudomonas aeruginosa* (*P. aeruginosa*). It acts primarily by disrupting protein synthesis through interaction with 30S ribosomal subunit, leading to altered cell membrane permeability, progressive disruption of the cell envelope, and eventual cell death. It is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Aminoglycosides demonstrate concentration-dependent killing of the bacteria (the ratio of maximum drug concentration to the minimum inhibitory concentration (MIC)).

Pharmacokinetics

A summary of TOBI PODHALER serum and sputum pharmacokinetic parameters after a single 112 mg dose in cystic fibrosis patients is presented in Table 2.

Table 2 - Summary of TOBI PODHALER pharmacokinetic parameters after inhalation of a single 112 mg dose in cystic fibrosis patients (4 x 28 mg capsules)

	Serum	Sputum
Tmax (h)	1 (0.5-2)	0.5 (0.5-1.0)
Cmax	1.02 ± 0.53 µg/mL	1048 ± 1080 µg/g
AUC0-12h	4.6 ± 2.0 µg.h/mL	1307 ± 978 µg.h/g
AUCinf	5.1 ± 2.0 µg.h/mL	1740 ± 809 µg.h/g
T1/2 (h)	3.1 ± 0.4	2.2 ± 1.7

All parameters except Tmax presented as Mean ± SD; Tmax in Median (Range)
Cmax, maximum concentration; Tmax, time to reach Cmax; AUC, area under the concentration-time curve; T1/2, apparent terminal half life

Absorption:

The systemic exposure to tobramycin after inhalation of TOBI PODHALER is expected to result from pulmonary absorption of the dose fraction delivered to the lungs as tobramycin is not absorbed to any appreciable extent when administered via the oral route.

Serum and sputum concentrations: At the end of a 4-week dosing cycle of TOBI PODHALER (112 mg twice daily), maximum serum concentration of tobramycin 1 hour after dosing was 1.99 ± 0.59 µg/mL. Concentrations of tobramycin in the sputum vary widely, and the variability in pharmacokinetic parameters was higher in sputum as compared to serum (Table 2). High inter-subject variability affects the use of sputum levels as a marker for overall lung deposition.

Distribution:

Population pharmacokinetic analysis for TOBI PODHALER in cystic fibrosis patients estimated the apparent volume of distribution of tobramycin in the central compartment to be 85.1 L for a typical CF patient.

Binding of tobramycin to serum proteins is negligible.

Metabolism:

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

Elimination:

Tobramycin is eliminated from the systemic circulation primarily by glomerular filtration of the unchanged compound. Unabsorbed tobramycin, following TOBI PODHALER administration, may be eliminated in expectorated sputum or via the gastrointestinal tract.

A population pharmacokinetic analysis for TOBI PODHALER in cystic fibrosis patients aged 6 to 58 years estimated the apparent serum clearance of tobramycin to be 14.5 L/h.

In rat inhalation studies tobramycin did not accumulate in serum, but accumulated in lung tissues. Estimates of the lung tissue elimination half-life ranged between 57 hours and 19 days after 6 months of daily inhalation in rats. In dogs, after 28 days of daily inhalation, the lung elimination half-life was about 4 weeks (See DETAILED PHARMACOLOGY – Animal Pharmacology - Pharmacokinetics).

Special Populations and Conditions

Pediatrics (< 6 years of age): TOBI PODHALER has not been studied in this age group.

Geriatrics (≥ 65 years of age): There are insufficient safety, efficacy and pharmacokinetic data in this population. Renal function in elderly patients should be taken into account while using TOBI PODHALER.

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

Renal Insufficiency: Patients with serum creatinine 2 mg/dL or more and blood urea nitrogen (BUN) 40 mg/dL or more have not been included in clinical studies. Renal function is expected to affect exposure to tobramycin.

STORAGE AND STABILITY

Store between15 - 30 ºC; store in the original package to protect from moisture. Store the inhaler in its tightly closed case when not in use. TOBI PODHALER (Tobramycin Inhalation Powder) is not sensitive to light, refrigeration or freezing.

SPECIAL HANDLING INSTRUCTIONS

TOBI PODHALER (Tobramycin Inhalation Powder) capsules must be kept out of the sight and reach of children other than when administered therapeutically under appropriate adult supervision.

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

The PODHALER is the only inhaler to be used with TOBI PODHALER capsules; this inhaler must not be used for any drug product other than TOBI PODHALER.

Instructions for use and handling

Each weekly box contains seven blister strips (corresponding to the seven days of the week) and each blister strip contains eight capsules (corresponding to a daily dose: 4 capsules to be taken in the morning and 4 capsules to be taken in the evening).

TOBI PODHALER capsules must always be stored in the blister strip, and only removed immediately before use. Allow the device and capsules to reach room temperature before use. Each PODHALER inhaler and its case are used for seven days and then discarded and replaced.

Basic instructions for use are given below:

<u>TOBI PODHALER Preparation</u>

1. Wash and fully dry your hands.
2. Just before use, remove the PODHALER inhaler from its case by holding the base and twisting off the top of the case in a counter-clockwise direction. Set the top of the case aside. Briefly inspect the inhaler to make sure it is not damaged or dirty, and then stand it in the base of the case.
3. Holding the body of the inhaler, unscrew and remove the mouthpiece from the inhaler body. Set the mouthpiece aside on a clean, dry surface.
4. Separate the 4 morning capsules and the 4 evening capsule on the blister strip. Peel back the foil from the blister strip to reveal one TOBI PODHALER capsule and remove it from the card.
5. Immediately insert the capsule into the inhaler chamber. Replace the mouthpiece and screw it on firmly until it stops. Do not overtighten.

6. To puncture capsule, hold the inhaler with the mouthpiece down, press the blue button firmly with your thumb as far as it will go, then release the button. The medication is now ready for inhalation. **It is important for the patient to understand that the hypromellose (HPMC) capsule might fragment and small pieces might reach the mouth or throat during inhalation. It is not harmful if these pieces are swallowed or inhaled. The tendency for this to happen is minimized by not piercing the capsule more than once.**

TOBI PODHALER Inhalation

7. Fully exhale away from the inhaler. Position the inhaler with the mouthpiece facing towards you.
8. Place mouth over the mouthpiece creating a tight seal with your lips. Inhale the powder deeply with a single continuous inhalation.
9. Remove inhaler from mouth, and hold breath for a count of approximately 5 seconds, then exhale normally away from the inhaler.
10. After a few normal breaths, perform a second inhalation from the same capsule, repeating steps 7–9 above.

Check and continue

11. Unscrew the mouthpiece and remove the 'empty' or 'used' capsule from the chamber.
12. Inspect the used capsule. It should appear punctured and empty. If it is empty, discard the capsule.
    - If the capsule is punctured but still contains some powder, place it back into the chamber with the punctured side of the capsule inserted first, replace the mouthpiece and take another two inhalations from the capsule (repeat step 5, then steps 7–12, do not repuncture the capsule). Reinspect capsule.
    - If the capsule appears to be unpunctured, place it back into the chamber, replace the mouthpiece, press the button firmly as far as it goes and take another two inhalations from the capsule (repeat steps 5–11). After this if the capsule is still full and appears to be unpunctured, replace the inhaler with the reserve inhaler and try again (repeat steps 3 and 5–12).
13. Repeat, starting at step 4, for the remaining three capsules of the dose.
14. Replace the mouthpiece and screw it on firmly until it stops. When the full dose (4 capsules) has been inhaled, wipe mouthpiece with a clean dry cloth. The inhaler should never be washed with water.
15. Place inhaler back in storage case and close tightly.

(See DOSAGE AND ADMINISTRATION)

DOSAGE FORMS, COMPOSITION AND PACKAGING

TOBI PODHALER (Tobramycin Inhalation Powder) is available as a 28 mg inhalation powder capsule.

28 mg **TOBI PODHALER package** contains: aluminum blister-packaged 28 mg TOBI PODHALER clear, colorless hypromellose capsules with "MYL TPH" in blue radial

imprint on one part of the capsule and the Mylan logo in blue radial imprint on the other part of the capsule and one PODHALER inhalation device in its plastic container.

TOBI PODHALER is supplied in monthly kits containing 4 weekly cartons and a reserve PODHALER device in its plastic container. Each weekly carton contains 56 x 28 milligram capsules: 7 blisters strips x 8 capsules per strip), and a PODHALER inhalation device in its plastic container.

For patient starts, TOBI PODHALER is also available as an 8 capsules and 2 inhaler sample pack.

TOBI PODHALER also contains the following non-medicinal ingredients: 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), blue ink, calcium chloride, carnauba wax, carrageenan, hypromellose, potassium chloride, sulfuric acid (for pH adjustment).

The delivered dose (the dose that leaves the mouthpiece of the PODHALER inhalation device) is 25.5 milligram tobramycin.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

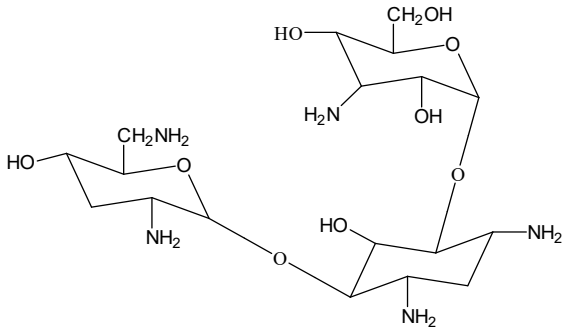
Drug Substance

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 or almost white powder; visually free from any foreign contamination, freely soluble in water, very slightly soluble in ethanol and practically insoluble in chloroform and ether. The pH of a 1 in 10 solution is 9-11. Tobramycin decomposes at approximately 287°C.

Drug Product:

TOBI PODHALER (Tobramycin Inhalation Powder) is a dry-powder formulation of tobramycin manufactured using the novel PULMOSPHERE® technology containing highly dispersible particles. TOBI PODHALER is available as a 28 mg inhalation powder capsule. The delivered dose (the dose that leaves the mouthpiece of the PODHALER inhalation device) is 25.5 milligram tobramycin.

Inhalation Device:

The PODHALER device is a light, discrete and portable inhalation device that requires no internal or external power source. The PODHALER is a plastic inhalation device used for inhaling the content of TOBI PODHALER capsules.

CLINICAL TRIALS

Study demographics and trial design

Clinical efficacy of TOBI PODHALER (Tobramycin Inhalation Powder) was assessed in two Phase III studies that randomized and dosed 612 patients aged > 6 years with cystic fibrosis (CF) and *P. aeruginosa* infection. The trial population received standard of care for CF. The most frequently used concomitant medications included enzyme preparations, mucolytics (especially dornase alfa), and selective β_2-adrenoreceptor agonists.

The trial design and patient demographics for studies C2301 and C2302 are summarized in Table 3 below.

Table 3 - Summary of trial design and patient demographics for Phase III clinical trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender n (%)
C2301[1]	6-month multicenter, randomized (1:1), double-blind, placebo-controlled parallel-arm study	**Cycle 1:** Arm 1: TOBI PODHALER (4 x 28 mg capsules) administered twice a day for 28 days followed by 28 days off-treatment compared with Arm 2: Placebo[5] administered twice a day for 28 days followed by 28 days off-treatment **Cycles 2 and 3:** Arms 1 and 2: TOBI PODHALER (4 x 28mg capsules) administered twice a day for 28 days followed by 28 days off-treatment, for 2 cycles	Total: n = 95 TOBI PODHALER: n = 46 Placebo: n=49 Patients with cystic fibrosis; inhaled anti-pseudomonal treatment naive [2]; FEV_1 [6] at screening > 25% and < 80 %; Caucasian (84%)	TOBI PODHALER : 13 years (6-21) Placebo: 13 years (6-21)	Male: 42 (44%) Female: 53 (56%)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender n (%)
C2302[3]	6-month multicenter, randomized (3:2), open-label, active-controlled, parallel-arm study	**Cycle 1, 2 and 3:** Arm 1: TOBI PODHALER (4 x 28 mg capsules) administered twice a day for 28 days followed by 28 days off-treatment, for 3 cycles compared with Arm 2: TOBI [1 ampoule (300 mg in 5 mL)] administered twice a day for 28 days followed by 28 days off-treatment, for 3 cycles	Total: n = 517 TOBI PODHALER: n = 308 TOBI : n=209 Patients with cystic fibrosis [4]; FEV_1 [6] at screening > 25% and < 75 %; Caucasian (90%)	TOBI PODHALER : 26 years (6-66) TOBI : 25 years (7-59)	Male: 286 (55%) Female: 231 (45%)

(1) Participating countries: Argentina, Brazil, Bulgaria, Chile, Lithuania, Mexico, Serbia, and United States
(2) In Study C2301, patients were required to have been off inhaled anti-pseudomonal antibiotics for at least 4 months prior to screening.
(3) Participating countries: Australia, Canada, Chile, Columbia, France, Germany, Greece, Hungary, Israel, Italy, Mexico, Netherlands, Spain, Switzerland, UK, and United States
(4) In Study C2302, patients were required to have been off anti-pseudomonal antibiotics for at least 28 days prior to study drug administration.
(5) Containing 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and calcium chloride ($CaCl_2$)
(6) FEV_1 % of predicted normal values for age, sex and height based upon Knudson criteria

Study results

The results of the two pivotal studies are provided below, by study.

Study C2301

TOBI PODHALER significantly improved lung function compared with placebo, as shown by the relative increase in percent predicted FEV_1 after 28 days of treatment (Table 4).

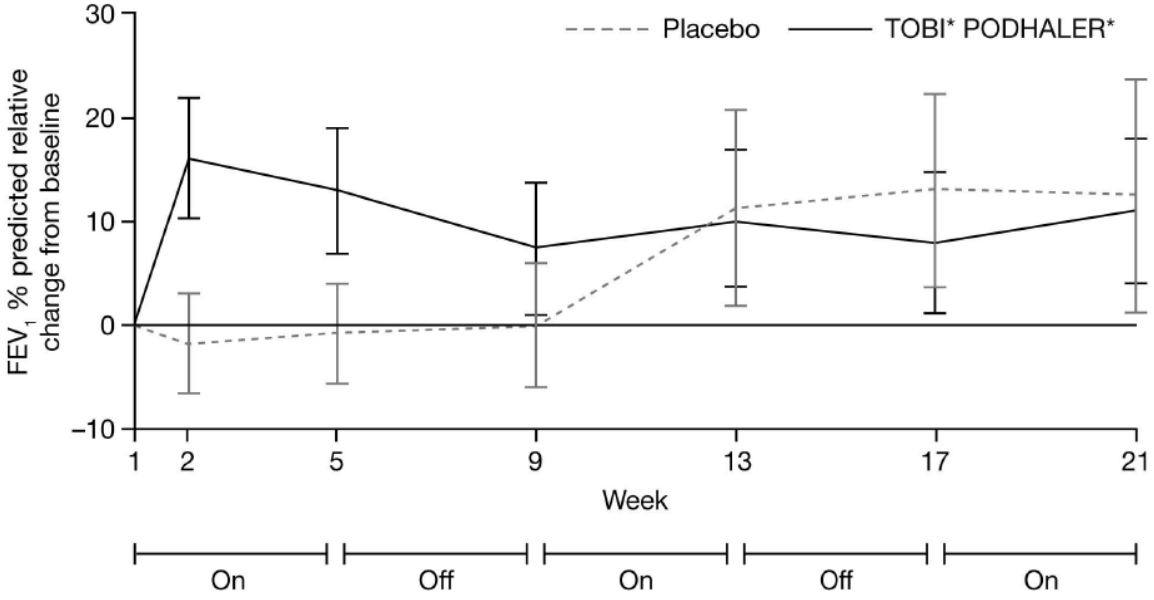
Table 4 – Study C2301: Relative change in percent predicted FEV_1 from baseline to end of dosing in Cycle 1[1]

	TOBI PODHALER N=29	Placebo N=32	Difference (SE)	95% CI of difference	P-value
n	27	31			
Mean [2]	13.21	-0.57	13.79 (3.95)	(5.87, 21.70)	0.0010
LS Mean [3]	13.97	0.68	13.29 (3.98)	(5.31, 21.28)	0.0016

(1) The primary efficacy endpoint was the relative change in FEV_1 percent predicted from baseline to the end of cycle 1 dosing of TOBI PODHALER as compared to placebo.
(2) Mean, p-value, mean difference, and its 95% confidence interval are calculated from ANOVA with treatment in the model.
(3) Least square mean, p-value, least square mean difference, and its 95% confidence interval are calculated from ANCOVA with treatment, baseline value, age and region in the model. SE = standard error, N is number of eligible subjects in the final efficacy analysis for the primary endpoint, n is number of subjects with complete FEV_1 values at baseline and Day 28. The analysis is based on observed data only, no imputation is performed for missing data.

Figure 1 demonstrates the relative change in percent predicted FEV_1 from baseline in Cycles 1-3 for Study C2301. The improvement in lung function for patients who switched from placebo to TOBI PODHALER at the start of the second treatment cycle were comparable to the improvement seen during the first treatment cycle in the TOBI PODHALER treatment group. The improvements in the percent predicted FEV_1 were maintained over time during the third treatment cycle.

Figure 1 – Study C2301: Relative change in percent predicted FEV_1 from baseline in Cycles 1-3 by treatment group



Note: the vertical bar is 95% confidence interval.
Off-treatment phases: from week 5 to 9, week 13 to 17 and week 21 to 25.
X-axis is not linear between 1 to 5 weeks.

Treatment with TOBI PODHALER for 28 days resulted in a reduction in *P. aeruginosa* sputum density (log_{10} CFUs) compared with placebo from baseline to end of dosing in cycle 1 (mean reduction of - 2.79 log_{10} CFUs in the TOBI PODHALER treatment group and - 0.21 log_{10} CFUs in the placebo group). Density was defined as the sum of bio-types (mucoid, dry and small colony variant).

Study C2302

Treatment with both TOBI PODHALER and TOBI resulted in relative increases in percent predicted FEV_1 from baseline to Day 28 of the third treatment cycle (Table 5 and Figure 2). The magnitude of improvement in lung function was smaller in this study compared to Study C2301; the differing designs and populations of these studies are described in Table 3.

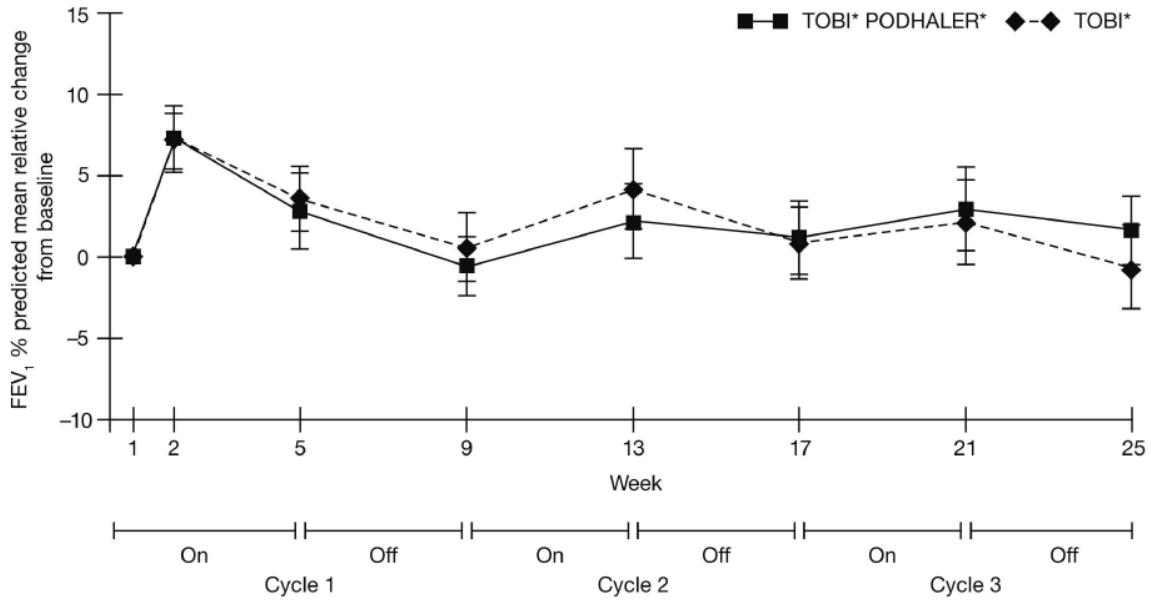
Table 5 - Study C2302: Relative change in percent predicted FEV_1 from baseline to end of dosing in Cycle 3[(1)]

	TOBI PODHALER N=308	TOBI N=209	Difference (SE)	85% one-sided CI of difference	95% one-sided CI of difference
n	227	171			
Mean [(2)]	3.1	2.3	0.8 (1.92)	(-1.22, 2.77)	(-2.39, 3.94)
LS Mean [(3)]	5.8	4.7	1.1 (1.75)	(-0.67, 2.96)	(-1.74, 4.03)

(1) The primary objective of this study was to demonstrate safety of TOBI PODHALER. The main secondary efficacy endpoint was the relative change in FEV_1 percent predicted from baseline to the end of Cycle 3 dosing of TOBI PODHALER as compared to TOBI.
(2) Mean, mean difference, and its one-sided 85% and 95% confidence interval are calculated from ANOVA with treatment in the model.
(3) Least square mean, least square mean difference (TOBI PODHALER – TOBI), and its one-sided 85% and 95% confidence interval are calculated from ANCOVA with treatment, baseline % predicted FEV_1, age, chronic macrolide use, and region in the model. SE = standard error, N is number of eligible subjects in final analysis population, n is number of subjects with complete FEV_1 values at baseline and Day 28 of Cycle 3. The analysis is based on observed data only, no imputation is performed for missing data. Claim of non-inferiority efficacy is based on the one-side 85% confidence interval in the ITT population (lower limit is greater than -6%).

Figure 2 demonstrates the relative change in percent predicted FEV_1 from baseline in Cycles 1-3 for Study C2302.

Figure 2 – Study C2302: Relative change in percent predicted FEV_1 from baseline in Cycles 1-3



A difference in FEV_1 response by age was noted. The relative change in percent predicted FEV_1 from baseline to end of dosing for Study C2302 by age group is presented in Table 6.

Table 6 – Study C2302: Relative change in percent predicted FEV_1 from baseline to end of dosing by age group

	TOBI PODHALER N=308	TOBI N=209
	Mean (SD)	**Mean (SD)**
6-< 13 years	10.4 (25.9)	9.4 (18.9)
> 13-< 20 years	6.8 (18.5)	3.9 (19.4)
>20 years	0.3 (18.6)	0.9 (16.6)

Treatment with TOBI PODHALER and TOBI resulted in suppression of sputum *P. aeruginosa* density (log_{10} CFUs) from baseline to end of dosing in cycle 3 (mean reduction of -1.61 log_{10} CFUs in the TOBI PODHALER treatment group and -0.77 log_{10} CFUs in the TOBI treatment group). Suppression of sputum *P. aeruginosa* density was similar across age groups in both treatment arms. Density was defined as the sum of bio-types (mucoid, dry and small colony variant).

Both clinical studies demonstrated that TOBI PODHALER decreased sputum *P. aeruginosa* density during on-treatment periods. There was a trend for a recovery of *P. aeruginosa* density after 28 days off-treatment which was reversed after a further 28 days on-treatment. The susceptibility and resistance of *P. aeruginosa* strains isolated in the Phase III clinical trials is further presented in the MICROBIOLOGY section.

Other health outcomes in 3 cycles for Study C2302 are presented in Table 7.

Table 7 – Study C2302: Other health outcomes in 3 cycles, by treatment arms

	TOBI PODHALER N=308	TOBI N=209
	Mean	**Mean**
Frequency of new anti-pseudomonal antibiotics use	64.9 %	54.5%
Duration of anti-pseudomonal antibiotics use	30.9 days	33.4 days
Respiratory-related hospitalizations	24.4 %	22.0 %
Duration of Respiratory-related hospitalization	15.6 days	15.3 days
Administration time (1)(2)	5.6 min	19.7 min
Patients reported treatment satisfaction (1)(2)(3)(4):		
• Effectiveness	74.8	65.4
• Side effects	92.1	92.6
• Convenience	82.7	58.4
• Global satisfaction	76.2	71.0

(1) Calculated as LS mean - Least square means are calculated from repeated measures model with treatment, baseline FEV_1 % predicted, age, chronic macrolide use, region, visit, visit-by treatment interaction in the model.
(2) Average across all 3 treatment periods.

(3) Assessed by a modified Treatment Satisfaction Questionnaire for Medication (TSQM)
(4) Higher score indicates higher satisfaction for that domain

DETAILED PHARMACOLOGY

ANIMAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of tobramycin in serum and lung tissue after inhalation administration of TOBI PODHALER (Tobramycin Inhalation Powder) or TOBI (tobramycin solution for inhalation) was assessed as part of the toxicology studies in rats and dogs (See TOXICOLOGY).

Tobramycin did not accumulate in serum with once daily administration in either species.

In the 6-month rat study the highest tobramycin group mean and individual predose (trough) concentrations observed were 0.38 ± 0.15 µg/mL and 0.54 µg/mL, respectively (female, 40.1 mg/kg/day inhaled dose, at day 78). The Cmax and AUC values of tobramycin in lung tissue were on average 43 and 279 times, respectively, greater than in serum. Accumulation in rat lung tissues (approximately 7-fold in Cmax, 20-fold in AUC) was observed upon daily inhalation for 6 months. The apparent tobramycin lung tissue elimination half-life estimates were shorter for all groups on day 1 (2.3 to 6.0 hours) compared with day 22 (31.5 to 99.3 hours), and day 176 (56.9 to 124 hours); if the lung concentration at day 211 (recovery phase) is taken into account; the lung elimination half-life was estimated to be approximately 19 days. Based on the half-life estimates from days 176 and 211, steady-state in the lungs would have been achieved by one to four months after start of dosing.

In a 28-day dog inhalation toxicity study with TOBI PODHALER, lung tobramycin concentrations on day 57 (i.e. four weeks after the end of administration) were approximately half of those observed at day 29, suggesting a lung elimination half-life of about 4 weeks.

In a 95-week rat carcinogenicity study using TOBI (tobramycin solution for inhalation), lung tissue accumulation appeared to plateau at approximately 26 weeks of daily dosing.

HUMAN PHARMACOLOGY

Pharmacokinetics

A summary of pharmacokinetic parameters in serum after inhalation of TOBI PODHALER (28 mg, 56 mg, 84 mg, 112 mg) and TOBI (300 mg) is presented in Table 8. A single dose of 112 mg TOBI PODHALER (4 capsules of 28 mg each) showed comparable systemic exposure to the approved 300 mg dose of TOBI.

Table 8 - Pharmacokinetic parameters of tobramycin in serum after inhalation of a single dose of TOBI PODHALER (28 – 112 mg) or TOBI (300 mg) in cystic fibrosis patients

	TOBI PODHALER					TOBI
Dose	28 mg (2 x 14 mg capsules)	56 mg (4 x 14 mg capsules)	56 mg (2 x 28 mg capsules)	84 mg (3 x 28 mg capsules)	112 mg (4 x 28 mg capsules)	300 mg
N (PK population)	11	13	13	15	12	20
Tmax (h)	1 (0.5-2)	1 (0.5-1)	1 (0.5-2)	1 (1-2)	1 (0.5-2)	1 (0.5-2)
Cmax (µg/mL)	0.33 ± 0.09	0.56 ± 0.23	0.50 ± 0.21	0.70 ± 0.33	1.02 ± 0.53	1.04 ± 0.58
AUC0-12h (µg.h/mL)	1.3 ± 0.6	2.8 ± 0.9	2.5 ± 1.2	3.5 ± 1.3	4.6 ± 2.0	4.8 ± 2.5
AUCinf (µg.h/mL)	1.7 ± 0.6	3.1 ± 0.8	2.9 ± 1.2	4.1 ± 1.5	5.1 ± 2.0	5.3 ± 2.6
T1/2 (h)	2.8 ± 1.1	3.5 ± 0.8	3.3 ± 0.8	3.4 ± 1.0	3.1 ± 0.4	3.0 ± 0.8

All PK parameters except Tmax presented as Mean ± SD; Tmax in Median (Range)
Tmax was observed relative to the start of inhalation

Serum tobramycin concentrations after single and multiple twice daily inhalation of 112 mg of TOBI PODHALER were low relative to the maximum systemic levels recommended for avoidance of the toxicity that is associated with intravenous tobramycin therapy (greater than 12 µg/mL). Trough (pre-dose) concentrations also were below the recommended maximum trough level (2 µg/mL). Minimal accumulation of tobramycin in serum, consistent with the short half-life, was observed based on trough concentration levels after multiple twice daily administration in the Phase III studies; the highest tobramycin trough concentration observed at the end of a 4-week dosing cycle in the Phase III studies was 0.38±0.44 µg/mL (mean±SD).

Population pharmacokinetic modeling of covariates (age 6 – 58 years, creatinine clearance ≥63.9 mL/min, gender, lung function as FEV_1% predicted, and BMI) did not lead to a dose adjustment recommendation.

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. It acts primarily by disrupting protein synthesis through interaction with 30S ribosomal subunit, leading to altered cell membrane permeability, progressive disruption of the cell envelope, and eventual cell death.

Susceptibility

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

The standard *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 PODHALER. The relationship between *in vitro* susceptibility test results and clinical outcome with TOBI PODHALER therapy is not clear.

In study C2302, the majority of *P. aeruginosa* isolates had a tobramycin MIC between 0.5 µg/mL and 8 µg/mL at baseline and over the course of the study. In general, a small numerical increase in the percentage of patients with tobramycin MIC values above 8 µg/mL was observed in both the TOBI PODHALER and TOBI treatment groups at the end of the treatment period of each cycle. However, the overall distribution of tobramycin MIC values over the course of the study remained relatively consistent with those at baseline.

In addition, the vast majority of the isolates remained "susceptible". In Study C2302, at least 89% of TOBI PODHALER patients had *P. aeruginosa* isolates with MIC values at least 10 times lower than mean sputum concentrations observed within 0.5 hour of inhalation, both at baseline and at the end of the third active treatment cycle. The clinical significance of changes in MICs for *P. aeruginosa* has not been clearly established in the treatment of cystic fibrosis patients.

Sputum density of pathogens other than *P. aeruginosa*

A range of pathogens other than *P. aeruginosa* was identified in the sputum of the CF patients in this study, as would be expected, as CF patients have frequently multiple respiratory infections. The majority of pathogens were present in only a small percentage of patients and no clinically significant changes were identified.

Emergence of cross-resistant strains to the following antibiotics were tested: aztreonam ceftazidime, ciprofloxacin, imipenem and meropenem. No significant pattern of emerging cross-resistant strains was evidenced.

TOXICOLOGY

Repeat Dose Inhalation Studies

Repeat dose daily inhalation toxicology studies were performed with TOBI PODHALER (Tobramycin Inhalation Powder) in rats (dose range: 6.4 to 72.9 mg/kg/day estimated total tobramycin inhaled dose; study duration: 4 and 26 weeks) and dogs (dose range: 8.2-38.7 mg/kg/day estimated total tobramycin inhaled dose; study duration: 1 and 4 weeks). Also, a 95 week daily inhalation carcinogenicity study was performed with TOBI (Tobramycin Solution for Inhalation) in rats at doses of: 2.9, 7.6 and 25.7 mg/kg/day

estimated total tobramycin inhaled dose. The primary target organs were the respiratory tract (larynx, lung, bronchial lymph nodes, nose, trachea) and the kidney. Table 9 provides a more in depth summary of the observed treatment-related findings from the rat inhalation toxicity studies (See DETAILED PHARMACOLOGY: Animal Pharmacology).

Table 9 - Repeated Dose Daily Inhalation Toxicity Studies with TOBI PODHALER and TOBI

Species strain	Duration weeks	Formulation, Route of administration, Exposure Duration (minutes/day)	No. of animals/ group (M = male, F = female)	Estimated total tobramycin inhaled dose (mg/kg/day)[1]	Study Number GLP status	Treatment Related Findings
Rat Sprague-Dawley	Treatment: 4 Recovery: 4	tobramycin: Tobramycin Inhalation Powder vehicle: Pulmosphere placebo powder Inhalation: Air: 240 Vehicle: 240 Low: 30 Mid: 60 High: 240	Treatment: 10M, 10F Recovery: 5M, 5F Pharmacokinetic: 36M, 36F	air, vehicle, 9.9, 19.7, 72.9	MN103741 GLP[2]	Daily administration resulted in tobramycin accumulation in the lungs, but not the serum. The target organs identified were respiratory tract (larynx, lung, nose/turbinate, trachea, bronchial lymph node) and kidney. Treatment related findings in the respiratory tract occurred at tobramycin doses ≥ 9.9 mg/kg/day (Low dose: mean exposure levels on Day 28: serum C_{max} 8.5 to 16.3 µg/mL; serum AUC 27 µg.h/mL; Day 28 lung C_{max} 334 µg/g; Day 1 lung AUC 1120 µg.h/g). Treatment related findings in the kidney occurred at tobramycin doses ≥19.7 mg/kg/day (Mid dose: mean exposure levels on Day 28: serum C_{max} 18.6 µg/mL; serum AUC 39.5 µg.h/mL; Day 29 lung C_{max} 535 µg/g; Day 1 lung AUC 1732 µg.h/g). There was a dose-responsive increase in lung weights at end of treatment that was statistically significant in the high dose groups of both sexes and in the mid dose males compared to the air and vehicle groups. **Histopathology** *End of treatment phase* Gross lesions observed included foci in the lungs of one low dose group male and one high dose group male, microscopically determined to be macrophages and were attributed to tobramycin exposure. Treatment-related

Species strain	Duration weeks	Formulation, Route of administration, Exposure Duration (minutes/day)	No. of animals/ group (M = male, F = female)	Estimated total tobramycin inhaled dose (mg/kg/day)[1]	Study Number GLP status	Treatment Related Findings
						microscopic lesions were present in the larynx (inflammation, hyperplasia, ulcer/erosion), lungs (macrophage accumulation, hyperplasia, inflammation), nose/turbinates (olfactory epithelial degeneration, inflammation and hyperplasia), trachea (inflammation), bronchial lymph nodes (hyperplasia) and kidneys (nephropathy) *End of recovery phase* In the mid and low dose groups with the exception of the olfactory changes, all microscopic findings had recovered to background levels of incidence and severity. In the high dose group changes in the lung and nose/turbinates were still present (Day 57 tobramycin lung concentration 242 µg/g).
	Treatment: 26 Recovery: 4	tobramycin: Tobramycin Inhalation Powder vehicle: Pulmosphere placebo powder Inhalation: Air: 180 Vehicle: 180 Low: 30 Mid: 60 High: 180	Toxicology: 10M 10F Recovery: 5M, 5F Pharmacokinetic: 51M, 51F	air, vehicle, 6.4, 11, 38	N103748 GLP[2]	Daily administration resulted in tobramycin accumulation in the lungs, but not the serum. Minimal treatment related effects were observed in decreased total protein and decreased serum globulin in treated groups as compared to air control or vehicle groups. Increased lung weights were present in females at Day 183 necropsy. The target organs identified were respiratory tract (larynx, lung, and nose) and kidney. Treatment related findings in the respiratory tract occurred at tobramycin doses of ≥ 6.4 mg/kg/day (Low dose: mean exposure levels on Day 176; serum C_{max} male, female: 5.9, 12.1 µg/mL; serum AUC male, female: 9.2 ,60 µg.h/mL; lung C_{max} 479 µg/g, lung AUC 10285 µg.h/g). Treatment related findings in the kidney occurred at tobramycin doses ≥ 11 mg/kg/day (mean

Species strain	Duration weeks	Formulation, Route of administration, Exposure Duration (minutes/day)	No. of animals/ group (M = male, F = female)	Estimated total tobramycin inhaled dose (mg/kg/day)[1]	Study Number GLP status	Treatment Related Findings
						exposure levels on Day 176: serum C_{max} male, female: 4.7, 13.6 µg/mL; serum AUC male, female: 18, 37 µg.h/mL; lung C_{max} 637 µg/g; lung AUC 13131 µg.h/g). **Histopathology** *End of treatment phase* Treatment related lesions were present in kidneys (nephropathy), lungs (macrophage accumulation, hyperplasia), nose (inflammation, degeneration, hyperplasia, metaplasia) and larynx (hyperplasia) *End of recovery phase* Lesions in the kidney, lungs, nose and larynx were still present, but with reduced severity and/or incidence.
	Treatment 95	tobramycin: Tobramycin Inhalation Powder vehicle: Pulmosphere placebo powder Inhalation: Air: 90 Vehicle: 90 Low: 10 Mid: 30 High: 90	Carcinogenicity: 50M, 50 F Pharmacokinetic: 50 M, 50F	Air, vehicle, 2.9, 7.6, 25.7	N002938A GLP[2]	Daily administration resulted in tobramycin accumulation in the lungs, but not the serum. The target organs identified were respiratory tract (larynx, lung, nasal mucosa), with treatment related findings at tobramycin doses ≥ 2.9 mg/kg/day (Low dose: range of mean exposure levels: serum C_{max} (weeks 1 to 95) male, female: 1.4 to 5.8, 0.5 to 8.9 µg/mL; lung concentration (24 hr post-dose; weeks 4 to 95) male, female: 67 to 358, 81 to 274 µg/g) Lung weights were significantly increased in both males and females in dose responsive fashion. **Histopathology** Treatment related lesions were increased alveolar

Species strain	Duration weeks	Formulation, Route of administration, Exposure Duration (minutes/day)	No. of animals/ group (M = male, F = female)	Estimated total tobramycin inhaled dose (mg/kg/day)[(1)]	Study Number GLP status	Treatment Related Findings
						macrophage infiltrates, hyperplasia of bronchiolar/alveolar epithelium / nasal respiratory epithelium / mucosal glands of the nasal olfactory epithelium / squamous epithelium in the larynx.

(1) Mean daily inhaled tobramycin dose of male and female animals. Inhaled dose (mg/kg/day) = mean aerosol tobramycin concentration (mg/L) x Accumulated inhaled volume (L/day)/body weight (kg). A pulmonary deposition factor of 10% was used for the rat.
(2) Evaluation criteria: Clinical observations, body weight, food consumption (not in 95 week study) , respiratory function, ophthalmic examinations, toxicokinetic evaluation lung/serum, clinical pathology (hematology and serum chemistry), anatomic pathology (necropsy, gross pathology, organ weight, histopathology)

Reproductive Toxicology

No reproduction toxicology studies have been conducted with tobramycin administered by inhalation. However, subcutaneous administration of tobramycin at doses of up to 100 mg/dose (rat) or 20 mg/kg/day (rabbit) during organogenesis was not teratogenic. Doses of tobramycin 40 mg/kg/day were severely maternally toxic to female rabbits (i.e. nephrotoxicity leading to spontaneous abortions and death) and precluded the evaluation of teratogenicity. 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.

Tobramycin intramuscular doses of a 100 mg/kg/day administered to pregnant guinea pigs in early gestation from the beginning of the second week to the end of the fifth week, resulted in hearing loss and histological damage to the six mothers. The litters born to these mothers, however, showed no hearing loss or damage to the inner ear. In contrast, when tobramycicn was administered intramuscularly at 50 to 100 mg/kg daily to females during the terminal four weeks of gestation one of the eighteen newborns had pinna reflex loss at 20,000 Hz and four of the thirty-eight had unilateral, incomplete loss of outer hair cells at the basal end of cochlea.

Mutagenicity

Tobramycin was 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, did not induce chromosomal aberrations in Chinese hamster ovary cells, and was negative in the mouse micronucleus test.

Carcinogenicity

Carcinogenicity studies were not conducted with TOBI PODHALER. A 95 week daily inhalation study in rats to assess carcinogenic potential of TOBI (Tobramycin Solution for Inhalation) has been completed (see Table 9). The analysis of survival and tumor incidence found no treatment related effects on mortality, survival or increases in tumor incidence among the study groups for either males or females at up to 25.7 mg/kg/day estimated total tobramycin inhaled dose (See DETAILED PHARMACOLOGY: Animal Pharmacology).

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrTOBI® PODHALER®
Tobramycin Inhalation Powder Capsules

Read this carefully before you start taking **TOBI PODHALER** 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 PODHALER**.

What is TOBI PODHALER used for?

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

How does TOBI PODHALER work?

TOBI PODHALER contains a medicine called tobramycin. Tobramycin belongs to the aminoglycoside class of antibiotics. TOBI PODHALER 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 PODHALER?
Medicinal ingredients: Tobramycin
Non-medicinal ingredients: 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), blue ink, calcium chloride, carnauba wax, carrageenan, hypromellose, potassium chloride, sulfuric acid (for pH adjustment)

TOBI PODHALER comes in the following dosage forms:
28 mg inhalation powder capsules

Do not use TOBI PODHALER if you are allergic:
- to tobramycin, or to any other aminoglycoside antibiotic such as amikacin,

gentamycin, kanamycin, paromomycin, streptomycin,
- to any of the other ingredients in TOBI PODHALER (see What are the ingredients in TOBI PODHALER?).

If this applies to you, **tell your healthcare professional without taking TOBI PODHALER**. 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 PODHALER. Talk about any health conditions or problems you may have, including if:
- You have hearing problems (including noises in the ears).
- You have vestibular problems (problems with your inner ear and brain) that can cause vertigo (loss of balance) and dizziness.
- You have kidney problems.
- You have unusual difficulty in breathing with wheezing or coughing and chest tightness.
- You have blood in your sputum (the substance you cough up).
- You have Parkinson's disease.
- You have a condition called myasthenia gravis which is a chronic disease that causes muscle weakness.
- You are breastfeeding or planning to breastfeed.
- You are receiving an antibiotic called an aminoglycoside by injection since this can cause hearing loss, kidney problems or dizziness.
- You are taking any other medicines.

Other warnings you should know about:

Pregnancy:
Before taking TOBI PODHALER, 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 PODHALER can harm an unborn baby and cause deafness. Your healthcare professional will talk to you about whether you can take TOBI PODHALER if you are pregnant.

Breastfeeding:
When given by injection, the medicine in TOBI PODHALER can be found in the breast milk. The quantity found in the breast milk after inhaling TOBI PODHALER is not known. TOBI PODHALER may cause problems to your baby's hearing or kidneys. Because of the importance of the medicine to your well-being, you should stop breastfeeding or stop taking TOBI PODHALER.

TOBI PODHALER is in a class of antibiotics that may cause hearing loss, dizziness, or kidney problems. While you are using TOBI PODHALER 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 PODHALER is affecting your hearing.

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 PODHALER:

You should not take the following medicines while you are taking TOBI PODHALER:
- Furosemide or ethacrynic acid, a diuretic ("water pills")
- Urea or intravenous mannitol

You should not take the following medicines while you are taking TOBI PODHALER, or soon after finishing TOBI PODHALER 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 you are receiving infusions of tobramycin or other aminoglycoside antibiotic. Talk with your healthcare professional before taking these medications:
- Amphotericin B, cefalotin, cyclosporine, tacrolimus, polymyxins: these medicines may harm your kidneys.
- Platinum compounds (such as carboplatin 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 PODHALER:

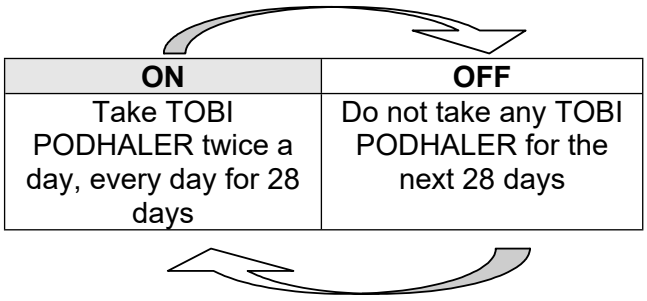
- TOBI PODHALER is a powder specifically formulated for inhalation using the PODHALER inhaler (see the step-by-step Instructions in the"**How To Administer TOBI PODHALER"** section below**)**,
- Take TOBI PODHALER exactly as your healthcare professional tells you to. Ask your healthcare professional if you are not sure.
    - Do not swallow the capsules.
    - TOBI PODHALER capsules should be taken by inhalation using only the PODHALER that is provided in the pack.
    - Each PODHALER is used for seven days and then discarded and replaced.
    - No other capsules should be used with the PODHALER.
- Take TOBI PODHALER at the same time each day. This will help you remember when to take TOBI.
- Space the morning and evening doses as close as possible to 12 hours and not less than 6 hours apart.
- Please check the order of medications with your doctor. If you are taking several medications and have other therapies for cystic fibrosis, TOBI PODHALER should always be taken last. Take your medicines in the following order :
    - 1st bronchodilator

- 2nd chest physiotherapy
- 3rd other inhaled medications
- 4th TOBI PODHALER

- Continue taking TOBI PODHALER as your healthcare professional tells you.
- If you have questions about how long to take TOBI PODHALER, talk to your doctor or your pharmacist.

Usual dose:

- Usual dose of TOBI PODHALER in adults and children 6 years of age and older:
  - Inhale the content of 4 capsules (with 112 milligrams (mg) of tobramycin) in the morning and 4 capsules in the evening for 28 days using the PODHALER.
- After taking TOBI PODHALER 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 PODHALER 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	OFF
Take TOBI PODHALER twice a day, every day for 28 days	Do not take any TOBI PODHALER for the next 28 days

Repeat cycle

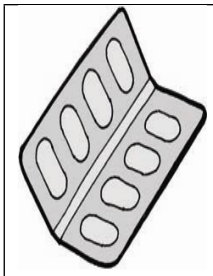
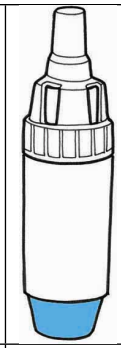
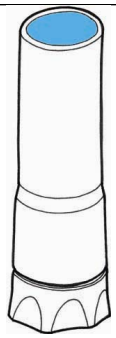
Overdose:

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

Missed Dose:

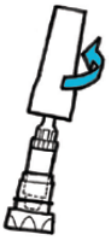
- If you forget to take TOBI PODHALER and there are at least 6 hours to your next dose, take your dose as soon as you can. Otherwise, wait for your next dose.
- Do not take a double dose to make up for a missed dose.

Contents of the TOBI PODHALER Inhaler pack:
Each weekly box contains seven blister strips (corresponding to the seven days of the week) and each blister strip contains eight capsules (corresponding to a daily dose: content of 4 capsules to be inhaled in the morning and content of 4 capsules to be inhaled in the evening).

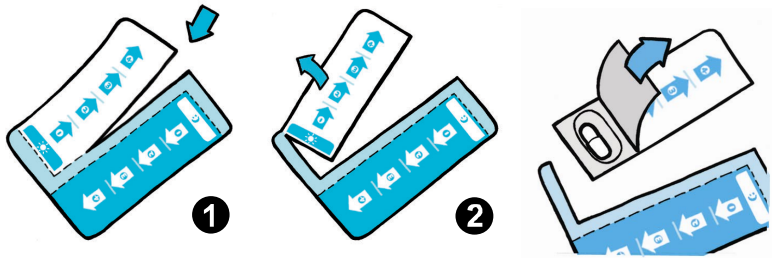
		
Blister strip	Inhaler	Storage case

How to administer TOBI PODHALER:

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.

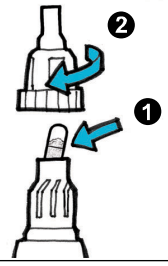
TOBI PODHALER Preparation	
1. Wash and fully dry your hands.	
Allow the device and capsules to reach room temperature before use.	
2. Just before use, remove the PODHALER from its case by holding the base and twisting off the top of the case in a counter-clockwise direction.	
Set the top of the case aside. Briefly inspect the inhaler to make sure it is not damaged or dirty, then stand it in the base of the case.	
3. Holding the body of the inhaler, unscrew and remove the mouthpiece from the inhaler body. Set the mouthpiece aside on a clean, dry surface.	
4. Separate the morning and evening doses from the blister strip as indicated in pictures (1) and (2). Peel back the foil from the blister strip to reveal one TOBI PODHALER	

capsule and remove it from the card.

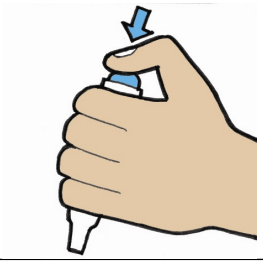


Always keep the TOBI PODHALER capsules in the blister strip. Only remove a capsule just before you are going to use it. Do not store the capsules in the inhaler.

5. Immediately insert the capsule into the inhaler chamber (1). **Never place a TOBI PODHALER capsule directly into the mouthpiece of the device.** Replace the mouthpiece and screw it on firmly until it stops (2). **Do not overtighten**.



6. To puncture capsule, hold the inhaler with the mouthpiece down, press the blue button firmly with your thumb as far as it will go, then release the button. **Do not press the piercing button more than once at a time.** The medication is now ready for inhalation.

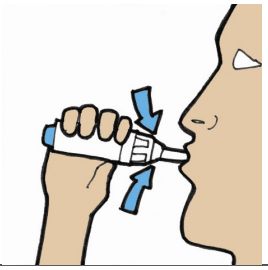


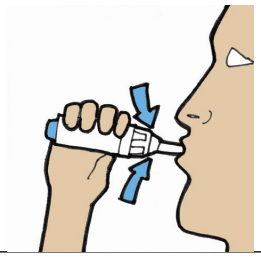
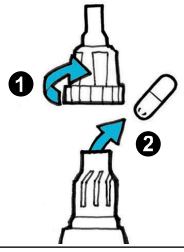
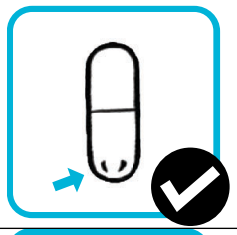
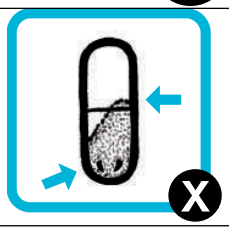
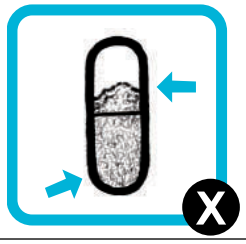
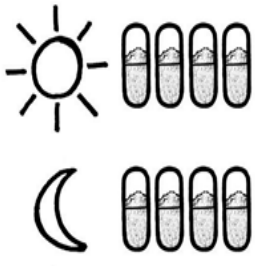
Occasionally, very small pieces of the capsule can get past the screen and get into your mouth.

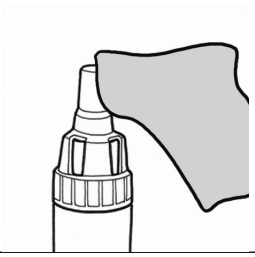
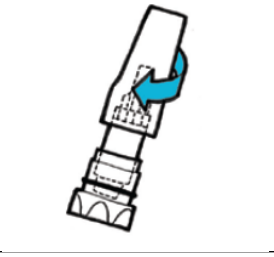
- *If this happens, you may be able to feel these pieces on your tongue.*
- *It is not harmful if these pieces are swallowed or inhaled.*
- *The chances of the capsule breaking into pieces will be increased if the capsule is accidentally pierced more than once during step 6 .*

TOBI PODHALER Inhalation

7. Fully exhale away from the inhaler. **Never blow into the mouthpiece of the device.** Position the inhaler with the mouthpiece facing towards you. Place mouth over the mouthpiece creating a tight seal. Inhale the powder deeply with a single continuous inhalation. Remove inhaler from mouth, and hold breath for a count of approximately 5 seconds, then exhale normally away from the inhaler.



8. After a few normal breaths, perform a second inhalation from the same capsule, repeating step 7 above.	
Check and Continue	
9. Unscrew mouthpiece (1) and remove the capsule from the chamber (2).	
10. Inspect the used capsule. It should appear punctured and empty. If it is empty, discard the capsule.	
If the capsule is punctured *but still contains some powder, place it back into the chamber with the punctured side of the capsule inserted first, replace the mouthpiece and take another two inhalations from the capsule (repeat step 5, then steps 7 to 10 – do not repuncture the capsule). Reinspect capsule.*	
If the capsule appears to be unpunctured*, place it back into the chamber, replace the mouthpiece, press the button firmly as far as it goes and take another two inhalations from the capsule (repeat steps 5 to 10). After this if the capsule is still full and appears to be unpunctured, replace the inhaler with the reserve inhaler and try again (repeat steps 3, and 5 to 10).*	
11. Repeat, starting at step 4 , for the remaining three capsules of the dose.	

12. Replace the mouthpiece and screw it on firmly until it stops. When the full dose (4 capsules) has been inhaled, wipe mouthpiece with a clean dry cloth. *The inhaler should never be washed with water.*	
13. Place inhaler back in storage case and close tightly.	
Always keep the TOBI PODHALER capsules and device in a dry place	

Older people
If you are aged 65 years and older, your healthcare professional may perform additional tests to decide if TOBI PODHALER is right for you.

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

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

Driving and using machines
TOBI PODHALER should not affect your ability to drive and use machines.

What are possible side effects from using TOBI PODHALER?

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

Some side effects are very common (these side effects may affect more than 1 in 10 patients):
- Cough.
- Difficulty speaking.

Some side effects are common (these side effects may affect between 1 and 10 in every 100 patients):
- Difficult or laboured breathing.
- Change in sense of taste.
- Mouth pain.
- Sore throat.

Some side effects are uncommon (these side effects may affect between 1 and 10 in every 1000 patients):

- Loss of voice (aphonia)

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

- Change in the colour of your sputum (substance you cough up).
- General feeling of being unwell.

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 PODHALER and contact your healthcare professional immediately.

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

- If you are not getting better. Strains of *Pseudomonas* can become resistant to treatment with the antibiotic over time. This can mean TOBI PODHALER 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**
Coughing up blood		**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	**X**		

blood			
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, talk to 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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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:

- Store TOBI PODHALER capsules between 15-30°C.
- Store TOBI PODHALER capsules in the original package to protect from moisture.
- Store the inhaler in its tightly closed case when not in use.
- Do not use TOBI PODHALER beyond the expiration date stamped on the box.
- Keep out of reach and sight of children.

If you want more information about TOBI PODHALER:

- 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 (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.mylan.ca, or by calling 1-844-596-9526.

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