NOVARTIS

TOBI® podhaler™

28 mg inhalation powder hard capsules

(tobramycin)

TOBI® Podhaler®

28 mg powder for inhalation, hard capsules

Composition

Active substance

Tobramycin

Excipients

Powder: 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), calcium chloride, sulfuric acid (for pH adjustment)
Capsule shell: capsule excipients, hypromellose, potassium chloride, carrageenan, carnauba wax, blue ink

Pharmaceutical form and quantity of active substance per unit

Dosage form

The (white to matt-white) powder for inhalation is filled into clear, colourless hypromellose capsules with "NVR AVCI" in blue radial imprint on one part of the capsule and the Novartis logo in blue radial imprint on the other part of the capsule.

Quantity of active substance

28 mg tobramycin per capsule

Indications/Potential uses

Tobi Podhaler is indicated for the management of pulmonary *Pseudomonas aeruginosa* infection in cystic fibrosis (CF) patients aged 6 years or older.
Treatment with Tobi Podhaler should be limited to 3 consecutive treatment cycles (i.e. 6 months) as no long-term safety data are available beyond this period (see Dosage and Administration).

Dosage and Administration

General target population: adults and children aged 6 years and above with cystic fibrosis (CF) and pulmonary Pseudomonas aeruginosa *infection.*
The dose of TOBI Podhaler is the same for all patients, regardless of age or weight. The recommended dosage is four capsules (4 × 28 mg = 112 mg tobramycin) twice daily for 28 days. Each dose of four capsules should be inhaled as close as possible to 12 hours apart and not less than six hours apart.
TOBI Podhaler is taken in alternating cycles of 28 days on drug followed by 28 days off drug.

On TOBI Podhaler	Off TOBI Podhaler
TOBI Podhaler twice daily every day for 28 days	Do not inhale TOBI Podhaler for next 28 days

Repeat cycle

Treatment with TOBI Podhaler should be limited to 3 consecutive treatment cycles (i.e. 6 months) as no long-term safety data are available beyond this period.
Once the active treatment period of the 3rd consecutive treatment cycle has been completed, treatment with TOBI Podhaler should be suspended for at least 3 months.
In case of missed dose with at least 6 hours until the next dose, the patient should inhale the dose as soon as possible. Otherwise the patient should wait until the next dose, but not inhale more capsules to make up for the missed dose.
Safety and efficacy have not been demonstrated in patients under 6 years of age, patients with forced expiratory volume in 1 second (FEV_1) < 25% or > 75% predicted or patients colonized with *Burkholderia cepacia*.

Use in special patient populations

Children under 6 years of age

TOBI Podhaler is not indicated for use in this age group. Clinical studies of TOBI Podhaler involved children aged 6 years and above. TOBI Podhaler has not been studied in younger children.

Elderly patients (≥ 65 years)

There are insufficient data in this population to support a recommendation for or against dose adjustment. Renal function should be taken into account in elderly patients using TOBI Podhaler (see *Nephrotoxicity* under Warnings and Precautions).

Patients with renal impairment

Tobramycin is primarily excreted unchanged in the urine, and renal function is expected to affect exposure to tobramycin. Patients with serum creatinine ≥ 2 mg/dL and blood urea nitrogen (BUN) ≥ 40 mg/dL have not been included in clinical studies, and there are no data in this population to support a recommendation for or against dose adjustment with TOBI Podhaler (see *Nephrotoxicity* under Warnings and Precautions).

Patients with hepatic impairment

No studies have been performed in patients with hepatic impairment. As tobramycin is scarcely metabolized, hepatic impairment is not expected to affect exposure to tobramycin.

Patients after organ transplantation

There are insufficient data on the use of TOBI Podhaler in patients following organ transplantation.

Method of administration

TOBI Podhaler is administered only by oral inhalation using the T-326 inhaler. It must not be administered by any other route or using any other inhaler (see *Handling* under Other information). Do not swallow TOBI Podhaler capsules!
In patients inhaling several drugs and receiving chest physiotherapy, it is recommended that TOBI Podhaler be inhaled last.

Contraindications

TOBI Podhaler is contraindicated in patients with known hypersensitivity to aminoglycosides or any of the excipients.

Warnings and Precautions

Tolerability

On comparing tolerability in clinical studies, a higher number of adverse effects such as cough or oropharyngeal pain were reported with TOBI Podhaler than with TOBI.
The tolerability of TOBI Podhaler should be regularly assessed by the patient every three months. In the event of persistent treatment-related intolerance, treatment should be continued with TOBI inhalation solution as an alternative.

Microbial resistance

In clinical studies of TOBI Podhaler, some patients showed an increase in minimum inhibitory concentrations (MICs) for tested *P. aeruginosa* isolates. These MIC increases were largely reversible during off-treatment periods.
There is nevertheless a theoretical risk that, compared to TOBI nebulizer inhalation, patients on TOBI Podhaler will be more likely to develop *P. aeruginosa* strains that may prove resistant to intravenous tobramycin. This should be regularly checked at least every 3 months. If MIC increases significantly (beyond the fluctuations observed in the patient), treatment with an alternative inhaled antibiotic should be considered in the light of the clinical response hitherto achieved in the patient with TOBI Podhaler.
No comparative long-term safety data are available for TOBI Podhaler use exceeding 6 months.
TOBI Podhaler should be used with caution in patients with known or suspected renal, auditory, vestibular or neuromuscular dysfunction or severe active haemoptysis.

Ototoxicity

Ototoxicity in the form of damage to both hearing and vestibular function has been reported with parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness. Tinnitus may be 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 studies (see Adverse effects). Caution should be exercised when prescribing TOBI Podhaler to patients with known or suspected auditory or vestibular dysfunction.
Audiological assessment should be considered before initiating TOBI Podhaler therapy in patients with evidence of auditory dysfunction or any predisposing risk factor.
Any patient complaining of tinnitus or hearing loss during TOBI Podhaler therapy should be referred by the physician for audiological assessment.
For monitoring of serum tobramycin levels, see *Laboratory tests* below.

Nephrotoxicity

Nephrotoxicity has been reported with parenteral aminoglycosides. Nephrotoxicity was not observed during TOBI Podhaler clinical studies. Caution should be exercised when prescribing TOBI Podhaler to patients with known or suspected renal dysfunction (see *Laboratory tests* below).
Renal function should be assessed before starting treatment with TOBI Podhaler. Repeat measurement of urea and creatinine levels is indicated after every 6 complete treatment cycles with TOBI Podhaler/TOBI inhalation solution.

Laboratory tests – serum levels

Serum tobramycin levels should be monitored in patients with known or suspected auditory or renal dysfunction. If ototoxicity or nephrotoxicity occurs on treatment with TOBI Podhaler, tobramycin therapy should be discontinued until the serum level falls below 2 µg/mL.
Serum tobramycin levels are approximately 1 to 2 µg/mL one hour after TOBI Podhaler administration. Serum levels greater than 12 µg/mL are associated with tobramycin toxicity and treatment should be discontinued above this concentration.
Blood for serum tobramycin measurement should be taken by venepuncture and not by finger prick. Contamination of the skin of the fingers with tobramycin may lead to a falsely elevated value for the serum level of the drug. Even hand washing before blood withdrawal cannot completely avoid this contamination.

Bronchospasm

Bronchospasm can occur with inhalation of medicinal products and has been reported with TOBI Podhaler during clinical studies. Bronchospasm should be treated as medically appropriate.
The first dose of TOBI Podhaler should be given under supervision. FEV_1 should be measured before and after the first inhalation of TOBI Podhaler.
If there is evidence of therapy-induced bronchospasm, the physician should carefully evaluate whether the benefit of continued use of TOBI Podhaler outweighs the risk to the patient. If an allergic reaction is suspected, TOBI Podhaler should be discontinued.

Cough

Inhaled medicinal products can provoke cough, which has been reported with TOBI Podhaler in clinical studies. Cough was not related to bronchospasm. Children under 13 years of age may be more likely to cough when treated with TOBI Podhaler.
If there is evidence of continued therapy-induced cough with TOBI Podhaler, the physician should consider alternative treatments.

Antibiotic comedication

Serum tobramycin levels should be monitored in patients receiving a concomitant parenteral aminoglycoside (or other drugs that may affect renal excretion). Such patients should be monitored as clinically appropriate, taking into account the risk of cumulative toxicity (see *Laboratory tests* above).

Neuromuscular disorders

Caution should be exercised when prescribing TOBI Podhaler 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.

Haemoptysis

Patients with clinically significant haemoptysis were excluded from the clinical studies, so no data are available on the use of TOBI Podhaler in these patients. Such patients should receive TOBI Podhaler only if the physician considers the benefit of treatment to outweigh the risk of inducing further haemorrhage.

Decreased response to tobramycin

In clinical studies, some patients treated with TOBI Podhaler showed an increase in aminoglycoside minimum inhibitory concentrations for the *P. aeruginosa* strains isolated.
There is a theoretical risk that patients being treated with TOBI Podhaler may develop tobramycin-resistant strains of *P. aeruginosa*.
The *in vitro* antimicrobial susceptibility test methods used for parenteral tobramycin therapy are also suitable for monitoring the susceptibility of *P. aeruginosa* isolated from cystic fibrosis patients (see Properties and Actions).

Interactions

No clinical interaction studies have been performed with TOBI Podhaler. 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 mannitol.
Based on the interaction profile of tobramycin after intravenous and aerosolized administration, concurrent and/or sequential use of TOBI Podhaler with other drugs with neurotoxic, nephrotoxic or ototoxic potential should be avoided.
Other medicinal products that have been reported to increase the potential toxicity of parenterally administered aminoglycosides include:
amphotericin B, cefalotin, ciclosporin, tacrolimus, polymyxins (risk of increased nephrotoxicity);
platinum compounds (risk of increased nephrotoxicity and ototoxicity);
anticholinesterases, botulinum toxin (neuromuscular effects).
During the treatment phase of the EAGER study, similar proportions of patients in the TOBI Podhaler and TOBI groups continued to take dornase alfa, bronchodilators, inhaled corticosteroids and macrolides.

Pregnancy and Lactation

Pregnancy

There are no adequate data on the use of tobramycin via inhalation in pregnant women.
Aminoglycosides can cause fetal harm (e.g. congenital deafness) when high systemic concentrations are achieved in pregnant women.
TOBI Podhaler must not be used during pregnancy unless clearly necessary.
Patients who use TOBI Podhaler during pregnancy or become pregnant while using TOBI Podhaler should be informed of the potential hazard to the fetus.

Lactation

It is not known how much tobramycin is excreted in breast milk after inhalation. Because of the potential for ototoxicity and nephrotoxicity in infants, TOBI Podhaler must not be used while breastfeeding unless clearly necessary.

Fertility

Data from animal studies with subcutaneous administration of tobramycin did not reveal any problems or potential problems of fertility in either males or females (see Preclinical data).

Effects on ability to drive and use machines

Based on the reported adverse drug reactions, TOBI Podhaler is considered unlikely to affect the patient's ability to drive or use machinery.

Adverse effects

Summary of drug safety

The safety of TOBI Podhaler was assessed in 395 cystic fibrosis patients who had received at least one dose of TOBI Podhaler, including 273 patients treated for three cycles (6 months). Each cycle consisted of 28 days on treatment (112 mg twice daily) and 28 days off treatment.
The primary safety population was randomized in a planned 3:2 ratio and consisted of 308 patients treated with TOBI Podhaler and 209 patients treated with TOBI® (300 mg/5 mL tobramycin nebulizer solution) in the EAGER study, an open-label study comparing TOBI Podhaler with TOBI over 3 treatment cycles. In both the TOBI Podhaler and TOBI groups, the mean duration of drug exposure in each cycle was 28-29 days. The supportive safety population comprised an additional 87 patients treated with TOBI Podhaler and 49 treated with placebo in the EVOLVE study [5,20], which was double-blind in the first treatment cycle, followed by all patients receiving TOBI Podhaler for 2 additional cycles.
In the EAGER study the most frequent adverse drug reactions (ADRs) were observed in the "respiratory, thoracic and mediastinal" system organ class. The most common ADRs (by preferred term) in both the TOBI Podhaler and TOBI treatment groups were cough and lung disorder.
During the placebo-controlled cycle of the EVOLVE study, the overall incidence of ADRs in the TOBI Podhaler treatment group was lower than in the placebo group, with the exceptions of pharyngolaryngeal pain, dysphonia and dysgeusia.
In the EVOLVE study, no patients complained of hearing disorders and there was no evidence of ototoxicity. In the EAGER study, approximately 2% of patients reported hearing disorders such as tinnitus. In a subset of patients in the EAGER study who received serial audiometric testing, 25.6% of those on TOBI Podhaler and 15.6% on TOBI showed decreases from baseline on at least one visit (80% of the subset had normal hearing assessments at baseline). However, the majority of such changes were transient and had resolved by the end of the study. Four patients in the TOBI Podhaler treatment group experienced significant decreases in hearing, which were transient in three patients and persistent in one case. Significant hearing loss (defined as a decrease from baseline of 10-15 dB in at least 2 consecutive frequencies on at least 2 consecutive visits, or ≥ 20 dB at a single frequency) occurred in fewer than 3% of patients in either group. Based on the criterion of unilateral hearing loss of 10 dB at 3 consecutive frequencies or 15 dB at 2 consecutive frequencies or 20 dB at any frequency, 3 TOBI Podhaler patients and 2 TOBI patients (matching the randomization ratio) had ototoxicity.
Cough is a common symptom in cystic fibrosis, reported in 42% of patients in the EAGER study at baseline. Cough was the most frequently reported adverse event in both clinical studies. It is noteworthy that the frequency of bronchospasm was similar in the TOBI Podhaler, TOBI and placebo groups. In the EVOLVE study, cough occurred more frequently in placebo-treated patients (26.5%) than with TOBI Podhaler (13%), while in the EAGER study cough was reported by a greater percentage of patients on treatment with TOBI Podhaler (48%) than with TOBI (31%). [5] Twelve patients (4%) receiving treatment with TOBI Podhaler discontinued the study medication because of coughing episodes; five of these patients had cough as an isolated adverse event, compared with two (1%) in the TOBI treatment group. Cough with TOBI Podhaler was more common during the on-treatment phase in each of the three treatment cycles.

Tabulated summary of adverse drug reactions in clinical studies

The adverse drug reactions in the EAGER studies (Table 1) are listed according to MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first, and by database. Within each frequency grouping the adverse effects are ranked by decreasing seriousness. In addition, the frequency category is stated for each adverse effect using the following convention (CIOMS III): very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10 000 to < 1/1000); very rare (< 1/10 000), including isolated reports.

Table 1 Adverse drug reactions in ≥ 2% of TOBI Podhaler patients in the EAGER study (TOBI Podhaler vs TOBI, open label), all randomized safety population

System organ class/ MedDRA preferred term	TOBI Podhaler (n = 308) % of patients	TOBI (n = 209) % of patients	Frequency category
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	15.6	12.4	Very common
Haemoptysis	13.0	12.4	Very common
Lung disorder	33.8	30.1	Very common
Dysphonia	13.6	3.8	Very common
Productive cough	18.2	19.6	Very common
Cough	48.4	31.1	Very common
Oropharyngeal pain	14.0	10.5	Very common
Wheezing	6.8	6.2	Common
Rales	7.1	6.2	Common
Chest discomfort	6.5	2.9	Common
Nasal congestion	8.1	7.2	Common
Throat irritation	4.5	1.9	Common
Gastrointestinal disorders			
Vomiting	6.2	5.7	Common
Diarrhoea	4.2	1.9	Common
Nausea	7.5	9.6	Common
Dysgeusia	3.9	0.5	Common
Infections and infestations			
Upper respiratory tract infection	6.8	8.6	Common
Investigations			
Forced expiratory volume decreased	3.9	1.0	Common
Pulmonary function test decreased	6.8	8.1	Common
Blood glucose increased	2.9	0.5	Common
Vascular disorders			
Epistaxis	2.6	1.9	Common
Nervous system disorders			
Headache	11.4	12.0	Very common
General disorders and administration site conditions			
Pyrexia	15.6	12.4	Very common
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain	4.5	4.8	Common
Skin and subcutaneous tissue disorders			
Rash	2.3	2.4	Common

Events in all treatment cycles on and off treatment
Additional adverse drug reactions observed in the EAGER study at lower frequencies include: bronchospasm (TOBI Podhaler 1.6%, TOBI 0.5%; common), deafness including deafness unilateral (reported as mild to moderate hearing loss or increased hearing loss) (TOBI Podhaler 1.0%, TOBI 0.5%, common) and tinnitus (TOBI Podhaler 1.9%, TOBI 2.4%; common).
In the placebo-controlled cycle 1 of the EVOLVE study with 46 TOBI Podhaler- and 49 placebo-treated patients, ADRs included: pharyngolaryngeal pain (10.9% TOBI Podhaler vs 0% placebo, very common) and dysphonia (4.3% TOBI Podhaler vs 0% placebo, common) in the system organ class (SOC) *Respiratory, thoracic and mediastinal disorders* and dysgeusia (6.5% TOBI Podhaler vs 2.0% placebo, common) in the SOC *Gastrointestinal disorders*.
No long-term safety data are available for a period exceeding 6 months.

Overdose

The maximum tolerated daily dose of TOBI Podhaler is not known. Determination of tobramycin serum levels may be useful for monitoring overdose.
Acute toxicity requires immediate withdrawal of TOBI Podhaler and baseline tests of renal function.
In the event of accidental ingestion of TOBI Podhaler capsules, toxicity is unlikely as tobramycin is poorly absorbed from an intact gastrointestinal tract.
Haemodialysis may be helpful for eliminating tobramycin from the body.

Properties and Actions

ATC code: J01GB01

Mechanism of action

Tobramycin is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. It acts primarily by disrupting protein synthesis, leading to altered cell membrane permeability, progressive destruction of the cell envelope and eventual cell death. It is bactericidal at concentrations equal to or slightly greater than the inhibitory concentration.

Pharmacodynamic properties – microbiology

In the EAGER study the distribution of tobramycin minimum inhibitory concentrations (MICs) of *P. aeruginosa* isolates was characterized by biotype: mucoid, dry, small colony variants and overall. Sputum assessments in this study showed that at baseline, 91% of TOBI Podhaler patients had *P. aeruginosa* isolates with MICs at least 20 times lower than the mean sputum concentration observed within 30 minutes of inhalation. At the end of the third 28-day treatment cycle, 86% and 89% of TOBI Podhaler patients had *P. aeruginosa* isolates with MICs at least 30 and 15 times lower, respectively, than the mean sputum concentration observed within 30 minutes of dosing.
Treatment for 25 weeks with TOBI Podhaler in two clinical studies did not affect the susceptibility of the majority of *P. aeruginosa* isolates tested. Most samples had a tobramycin MIC between 0.5 µg/mL and 8 µg/mL. There was no relevant shift in the MIC distribution for the sum of all *P. aeruginosa* biotypes with TOBI Podhaler treatment in the EAGER study.
The MIC distribution for mucoid isolates remained almost identical at baseline and after 25 weeks treatment, and for dry biotypes there was a small shift, which remained below the conventional systemic exposure resistance cut-off of 8 µg/mL. The maximum MIC of all biotypes in both the TOBI Podhaler and TOBI treatment groups remained relatively consistent over the course of the study for each biotype.
The clinical significance of changes in MICs for *P. aeruginosa* in the treatment of cystic fibrosis patients is still unclear. Clinical studies have shown that *in vitro* microbiological resistance to the antibiotic does not necessarily preclude clinical benefit to the patient. In the EAGER study the subgroup of patients with MIC values > 8 µg/mL at baseline had an improvement in *FEV_1% predicted* measurements after 3 cycles of treatment with TOBI Podhaler.

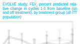
Susceptibility testing

The *in vitro* antimicrobial susceptibility test methods used for parenteral tobramycin therapy can be used to monitor the susceptibility of *P. aeruginosa* strains isolated from cystic fibrosis patients. Susceptibility breakpoints determined for parenteral tobramycin administration do not apply to inhaled tobramycin (see *Clinical studies* under Properties and Actions).

Clinical studies

The phase III clinical development programme consisted of two studies involving 612 randomized patients treated with the study medication with a clinical diagnosis of CF, confirmed by quantitative pilocarpine iontophoresis sweat chloride test or well-characterized disease causing mutations in each CFTR gene or abnormal nasal transepithelial potential difference characteristic of CF.
All patients were aged ≥ 6 years and had an FEV_1 at screening of ≥ 25% and ≤ 80% of predicted normal values for their age, sex and height, based on Knudson criteria. In addition, all patients were infected with *P. aeruginosa*, as demonstrated by a positive sputum or throat culture (or bronchoalveolar lavage) within 6 months prior to screening and by a sputum culture taken at the screening visit. The 395 patients treated with TOBI Podhaler were almost evenly divided between males and females, and between those aged under and over 20 years. Patients had a mean baseline FEV_1 of 54% of predicted normal value.
The following health outcome effects were demonstrated:
In a randomized, double-blind, placebo-controlled, multicentre study (EVOLVE), 112 mg TOBI Podhaler was administered twice daily (at the same time each morning and evening) for three cycles of 28 days on treatment and 28 days off treatment (total treatment period 24 weeks). All patients were aged less than 22 years (mean age 13.3 years) and had not received inhaled anti-pseudomonal antibiotics within 4 months prior to screening; 55.8% were female and 84.2% were Caucasian. Patients randomized to placebo treatment received this in the first treatment cycle and TOBI Podhaler in the subsequent two cycles.
TOBI Podhaler significantly improved lung function compared to placebo, as shown by the relative increase in percent predicted FEV_1 after 28 days of treatment (Figure 1). The improvement in lung function achieved during the first treatment cycle was maintained during the subsequent cycles of treatment with TOBI Podhaler. When patients in the placebo group were switched to TOBI Podhaler at the start of the second treatment cycle, the relative change from baseline in percent predicted FEV_1 was the same as that seen during the first treatment cycle in the TOBI Podhaler treatment group, and the improvement was also maintained over time during the third treatment cycle.

Figure 1 EVOLVE study: FEV_1 percent predicted relative change in cycles 1-3 from baseline (on and off treatment), by treatment group (all ITT population)

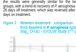


Vertical bars indicate the 95% confidence interval.
Off-treatment phases: weeks 5 to 9, weeks 13 to 17 and weeks 21 to 25
The x-axis is not linear between weeks 1 and 5.
In a second, open-label, multicentre study (EAGER), patients received either TOBI Podhaler 112 mg or TOBI 300 mg twice daily (at the same time each morning and evening) for three cycles of 28 days on treatment and 28 days off treatment (total treatment period 24 weeks). Patients were predominantly aged ≥ 20 years (including 4 patients aged over 60 years) with no inhaled anti-pseudomonal antibiotic use within 28 days prior to study drug administration; 90% were Caucasian and 55% were male.
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 of 5.8% and 4.7%, respectively (Figure 2). The improvement in percent predicted FEV_1 was numerically greater in the TOBI Podhaler treatment group and was statistically non-inferior to TOBI. Although the improvement in lung function was smaller in this study, this is explained by the previous treatment of this patient population with inhaled tobramycin.

Figure 2 EAGER study: Relative change from baseline in percent predicted FEV_1 in cycles 1-3 (ITT population)

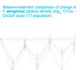
With regard to suppression of *Pseudomonas aeruginosa* (*P. aeruginosa*) infection, both studies showed reduced *P. aeruginosa* sputum density on TOBI Podhaler (see following two figures). Treatment with TOBI Podhaler for 28 days resulted in a statistically significant reduction in *P. aeruginosa* sputum density (log_{10} CFUs) compared to placebo (least-squares mean difference = 2.70, 95% CI: -3.60, -1.79, p < 0.001), with the greatest difference observed at day 28 of treatment. After the patients were switched from placebo to TOBI Podhaler, the results were generally similar for the two treatment groups, with a trend to recovery of *P. aeruginosa* density after 28 days off treatment, which was reversed after a further 28 days on treatment.

Figure 3 Between-treatment comparison of change from baseline in ***P. aeruginosa*** sputum density (log_{10} CFUs) – EVOLVE study (ITT population)



The vertical bars represent the 95% confidence interval. Overall density is used, defined as the sum of biotypes (mucoid, dry and small colony variant).
In the EAGER study there was a greater decrease in mean change from baseline log_{10} CFUs in the TOBI Podhaler treatment group than with TOBI, especially during the third treatment cycle (mean change of -1.61 log_{10} CFUs in the TOBI Podhaler treatment group vs -0.77 log_{10} CFUs in the TOBI group (Figure 4). As in the previous study, there was a partial recovery of *P. aeruginosa* density at the end of the 28-day off-treatment phase in both treatment groups, but this was reversed during the on-treatment phase of each treatment cycle.

Figure 4 Between-treatment comparison of change in P **aeruginosa** sputum density (log_{10} CFUs) – EAGER study (ITT population)



In both clinical studies, negative shifts from baseline to the end of the treatment period were observed in the maximum tobramycin MIC for each *P. aeruginosa* biotype. In general, a higher percentage of patients treated with TOBI Podhaler had increases in tobramycin MIC compared with decreases. Nevertheless, compared with placebo, approximately half the proportion of patients receiving TOBI Podhaler had a ≥ 2-fold decrease in tobramycin MIC at week 25 (40.5% and 20.0% patients in the placebo and TOBI Podhaler treatment groups, respectively).
The percentage of patients using anti-pseudomonal antibiotics in cycle 1 was greater in the placebo treatment group (20.4%) than in the TOBI Podhaler treatment group (13.0%); these antibiotics were also used for longer in the placebo

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group (18.2 days) than in the TOBI Podhaler group (13.3 days). In cycle 1 none of the patients in the TOBI Podhaler treatment group required respiratory-related hospitalization, compared to 6 patients (12.2%) in the placebo group, with an average hospital stay of 12.3 days. In the EAGER study, over half the patients in both the TOBI Podhaler and TOBI treatment groups required new anti-pseudomonal antibiotics over the three treatment cycles (64.9% and 54.5%, respectively), and the durations of use were similar in the two groups (30.9 and 33.4 days). Similar proportions of patients in the TOBI Podhaler and TOBI treatment groups required hospitalization for respiratory symptoms (24.4% and 22.0%, respectively), and the durations of hospitalization were also similar (15.6 and 15.3 days).

Concomitant medication

In both clinical studies, over 90% of patients received concomitant therapies for CF-related indications. As predicted by baseline disease characteristics and in line with the CF patient population recruited in this study, the most frequently used concomitant medications included enzyme preparations, mucolytics – especially dornase alfa – and selective β_2-adrenergic agonists. In addition, the majority of patients had received anti-pseudomonal antibiotics and macrolides in the past. The most frequently used agents (any route of administration) were tobramycin (EAGER study only), azithromycin, ciprofloxacin and ceftazidime.

Pharmacokinetics

Absorption

Systemic exposure to tobramycin after inhalation of TOBI Podhaler is assumed to result from pulmonary absorption of the dose fraction delivered to the lungs, as tobramycin is not absorbed to an appreciable extent after oral ingestion.

Serum levels: A phase I study evaluated systemic exposure to tobramycin after inhalation of a single 112 mg dose (4 × 28 mg capsules) of TOBI Podhaler and a single 300 mg dose of TOBI. The comparison showed similar results. Median time to peak serum level (T_{max}) was one hour with both TOBI Podhaler and TOBI. C_{max} was 1.02 ± 0.53 µg/mL (mean ± standard deviation [SD]) in patients given a single 112 mg dose of TOBI Podhaler and 1.04 ± 0.58 µg/mL in those given 300 mg TOBI [3,28]. The extent of systemic exposure ($AUC_{0-\infty}$) was also similar for the 112 mg TOBI Podhaler dose and 300 mg TOBI dose (5.3 ± 2.6 vs 5.1 ± 2 µg·h/mL).

In another study, patients were treated with the recommended dosage regimen over 3 treatment cycles. At the end of the first 4-week treatment cycle, the serum tobramycin level 0-2 hours after inhalation was 1.39 ± 0.8 µg/mL (mean ± SD) with TOBI Podhaler (112 mg twice daily) and 1.18 ± 0.72 µg/mL with TOBI (300 mg twice daily); the tobramycin serum trough level before the next inhalation at the end of the cycle was 0.47 ± 0.73 µg/mL with TOBI Podhaler and 0.21 ± 0.15 µg/mL with TOBI.

Sputum concentration: The study by Geller already mentioned above also measured the concentration in sputum (Geller et al., 2007). After inhalation of a single 112 mg dose (4 × 28 mg capsules) of TOBI Podhaler, sputum C_{max} of tobramycin was 1048 ± 1080 µg/g (mean ± SD). In comparison, after inhalation of a single 300 mg dose of TOBI (active control), sputum C_{max} was 737.3 ± 1028.4 µg/g [3,28]. The variability of the pharmacokinetic parameters was higher in sputum than in serum.

Distribution

A population pharmacokinetic analysis for TOBI Podhaler in cystic fibrosis patients estimated the apparent volume of distribution of tobramycin in the central compartment to be 84.1 L for a typical CF patient. While the volume was shown to vary with body mass index (BMI) and lung function (as FEV_1% predicted), model-based simulations showed that changes in BMI or lung function did not have a marked impact on peak (C_{max}) and trough (C_{trough}) concentrations.

Binding of tobramycin to serum proteins is negligible.

Metabolism

Tobramycin is scarcely metabolized and is primarily excreted unchanged in the urine.

Elimination

Tobramycin is eliminated from the systemic circulation primarily by glomerular filtration of the unchanged molecule.

The apparent terminal half-life of tobramycin in serum after inhalation of a 112 mg single dose of TOBI Podhaler was approximately 3 hours in cystic fibrosis patients and consistent with the half-life of tobramycin after TOBI inhalation.

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

Preclinical data

Based on preclinical data from studies of safety pharmacology, repeated-dose toxicity, genotoxicity and reproductive toxicity, the main hazard to humans is nephrotoxicity and ototoxicity. In general, toxicity is seen at higher systemic tobramycin levels than are achievable by inhalation at the recommended clinical dose.

Preclinical carcinogenicity studies with inhaled tobramycin produced no clear evidence of specific risks to humans.

No reproductive toxicity studies have been conducted with inhaled tobramycin. However, subcutaneous administration of tobramycin at doses up to 100 mg/kg/day in rats or 20 mg/kg/day in rabbits during organogenesis was not teratogenic. Doses of tobramycin ≥ 40 mg/kg/day were severely maternally toxic to rabbits (nephrotoxicity leading to spontaneous abortions and death) and precluded evaluation of teratogenicity. Based on available data from animal studies, a risk of toxicity (e.g. ototoxicity) at prenatal exposure levels cannot be excluded.

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

Other information

Shelf-life

Do not use after the expiry date (= EXP) printed on the container.

Special precautions for storage

Do not store above 30°C. Store in the original pack to protect from moisture. Store the inhaler in its tightly closed case when not in use.

Store TOBI Podhaler out of the reach and site of children except for therapeutic use under appropriate adult supervision.

Handling

Only the T-326 inhaler may be used with TOBI Podhaler capsules. It is not suitable for any drug other than TOBI Podhaler.

Each weekly pack contains seven capsule cards (corresponding to the seven days of the week) and each capsule card contains eight capsules (corresponding to a daily dose of 4 capsules in the morning and 4 capsules in the evening).

TOBI Podhaler capsules must always be stored in the capsule card, and only removed immediately before use. Each T-326 inhaler and its case are used for seven days and then disposed of and replaced.

Basic instructions for use are given below:

1. Wash and fully dry your hands.
2. Just before use, remove the T-326 inhaler from its case by holding the base of the case and twisting off the top in an anti-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 the mouthpiece and place it on a clean, dry surface.
4. Separate the two halves of the capsule card with the morning and evening capsules. Peel back the foil from the capsule card 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 the capsule, hold the inhaler with the mouthpiece downwards, press the button with your thumb as far as it will go, then release the button. The medication is now ready for inhalation.
7. Fully exhale away from the inhaler.
8. Hold the inhaler with the mouthpiece facing towards you. Place your mouth over the mouthpiece creating a tight seal. Inhale the powder deeply with a single continuous inhalation.
9. Remove the inhaler from your mouth and hold your breath for about 5 seconds, then exhale normally away from the inhaler.
10. After a few normal breaths, inhale again from the same capsule, repeating steps 7, 8 and 9 above.
11. Unscrew the mouthpiece and remove the capsule from the chamber.
12. Inspect the used capsule. It should appear punctured and empty.
    - 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 11). Reinspect the capsule.
    - If the capsule appears to be unpunctured, place it back into the chamber, replace the mouthpiece, press the button as far as it will go and take another two inhalations from the capsule (repeat steps 5 to 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 2, 3 and 5 to 11).
13. Dispose of the empty capsule.
14. Repeat, starting at step 4, for the remaining three capsules of the dose.
15. Replace the mouthpiece and screw it on firmly until it stops. After inhaling the full dose (4 capsules), wipe the mouthpiece with a clean dry cloth.
16. Place the inhaler back in its storage case and close tightly. Never wash the inhaler with water.

See Dosage and Administration.

How supplied

The TOBI Podhaler device and its storage case are made of plastic.

TOBI Podhaler is supplied in monthly packs containing 4 weekly cartons and a reserve inhaler in its storage case. Each weekly carton contains 56 × 28 mg capsules (7 blister strips with 8 capsules per strip) and a TOBI Podhaler device in its storage case.

Pack sizes

Country specific pack sizes.

Manufacturer

See folding box

Information last revised

November 2011

® = registered trademark
Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

INSTRUCTIONS FOR USE AND HANDLING

Inside your monthly pack

Each monthly pack contains:
- 4 weekly packs (see contents below).
- 1 reserve (extra) inhaler (the Podhaler inhaler) and its storage case.

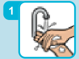
Inside your weekly pack

Each weekly pack contains:
- 1 inhaler (the Podhaler inhaler) and its storage case.
- 7 capsule cards (one card for each day of the week).
- Each capsule card contains 8 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).

How to inhale your medicine with the Podhaler inhaler
- **Only use the Podhaler inhaler contained in this pack.** Do not use TOBI Podhaler capsules with any other device, and do not use the Podhaler inhaler to take any other medicine.
- When you start a new weekly pack of capsules, use the new Podhaler inhaler that is supplied in the pack and discard the used inhaler and its case. Each Podhaler inhaler is only used for 7 days.
- **Do not swallow the capsules.** The powder in the capsules is for you to inhale.
- Always keep the capsules in the capsule card until you need to use them. Do not take the capsules out of the card in advance.

Store the Podhaler inhaler in its tightly closed case when not in use.

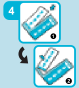
Basic instructions for use are given below.



1. Wash and fully dry your hands.

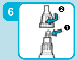
2. Just before use, remove the inhaler from its case by holding the base and twisting off the top of the case in a counter-clockwise direction.
   - Set the top of the case aside.
   - Look at the inhaler to make sure it is not damaged or dirty.
   - Stand the inhaler upright in the base of the case.

3. Hold the body of the inhaler and unscrew the mouthpiece in a counter-clockwise direction.
   - Set the mouthpiece aside on a clean, dry surface.



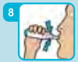
4. Tear along the perforations lengthwise then widthwise, as indicated in pictures (1) and (2).

5. Peel back the foil from the capsule card to reveal one capsule only.
   - Remove the capsule from the card.



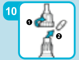
6. Immediately insert the capsule into the inhaler chamber (1).
   - Replace the mouthpiece.
   - Screw the mouthpiece on firmly until it stops. Do not overtighten (2).

7. To pierce the capsule, hold the inhaler with the mouthpiece pointing down.
   - Press the blue button firmly with your thumb as far as it will go, then release the button.
   - You are now ready to inhale the capsule in two separate breaths (Steps 8 and 9).



8. Inhale the capsule contents – first breath:
   - Before putting the mouthpiece in your mouth, breathe out fully, away from the inhaler.
   - Place your mouth over the mouthpiece – to make a tight seal.
   - Inhale the powder deeply with a single breath.
   - Remove the inhaler from your mouth, and hold your breath for about 5 seconds.
   - Then breathe out normally, away from the inhaler.

9. Inhale the capsule contents – second breath:
   - Take a few normal breaths away from the inhaler.
   - When you are ready, take your second breath by repeating Step 8, using the same capsule.



10. Unscrew mouthpiece (1) and remove the capsule from the chamber (2).

11. Look at the used capsule. It should appear pierced and empty. If it is empty, discard the capsule.

If the capsule is pierced but still contains some powder:

- Put the capsule back into the inhaler chamber (step 6). Put the pierced side of the capsule in first.
- Replace the mouthpiece and repeat steps 8, 9 and 10.

If the capsule does not look pierced:

- Put the capsule back into the inhaler chamber (step 6)
- Replace the mouthpiece and repeat Steps 7, 8 and 9.
- After this, if the capsule is still full and does not appear to be pierced, replace the inhaler with the reserve inhaler (found in the monthly pack) and repeat Steps 2, 3, 6, 7, 8, 9 and 10.

12. Take the other 3 capsules in the same way.
    - For each remaining capsule, repeat steps 5, 6, 7, 8, 9, 10 and 11.
    - Discard all the empty capsules.

13. 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.
    - Do not wash the inhaler with water.

14. Place inhaler back in storage case
    - Twist the top of the case in a clockwise direction until it is closed tighly.

Please also refer to section DOSAGE AND ADMINISTRATION. TOBI Podhaler must be kept out of the reach and sight of children other than when administered therapeutically under appropriate adult supervision.

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