

# TOBRAMYCIN WOCKHARDT Solution for inhalation

## *Tobramycin*

### **NAME OF THE MEDICINE**

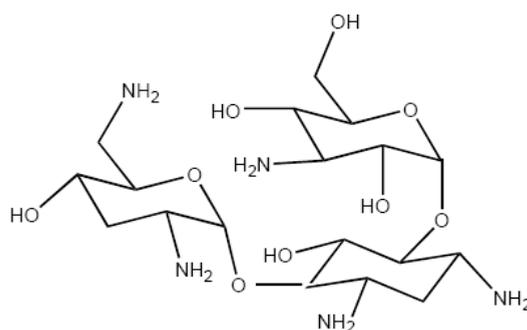
Chemical name: *O*-3-amino-3-deoxy- $\alpha$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-*O*-[2,6-diamino-2,3,6-trideoxy- $\alpha$ -D-ribo-hexopyranosyl-(1  $\rightarrow$  6)]-2-deoxy-L-streptamine.

Chemical formula: C<sub>18</sub>H<sub>37</sub>N<sub>5</sub>O<sub>9</sub>

Molecular weight: 467.52

CAS number: 32986-56-4

Chemical structure:



### **DESCRIPTION**

Tobramycin is an aminoglycoside antibiotic obtained from cultures of *Streptomyces tenebrarius*.

Tobramycin is a white or almost white hygroscopic powder. It is freely soluble in water, very slightly soluble in alcohol and practically insoluble in chloroform and in ether. The dissociation constant pKa's are pKa1 5.8; pKa2 6.8; pKa3 7.1 pKa4 7.9; pKa5 9.3. The partition coefficient is Log P-4.224  $\pm$  0.848.

TOBRAMYCIN WOCKHARDT solution for inhalation is formulation of tobramycin specifically developed for administration by inhalation.

TOBRAMYCIN WOCKHARDT solution is a sterile, clear, slightly yellow, non-pyrogenic, aqueous solution with the pH and salinity adjusted specifically for administration by a compressed air driven reusable nebuliser.

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

## **PHARMACOLOGY**

### **Pharmacodynamic properties**

Pharmacotherapeutic group: Aminoglycoside antibacterials; ATC Code: J01GB01

### **Microbiology**

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

### **Susceptibility Testing**

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

The *in vitro* antimicrobial susceptibility test methods used for parenteral tobramycin therapy can be used to monitor the susceptibility of *P. aeruginosa* isolated from CF patients. If decreased susceptibility is noted, the results should be reported to the clinician.

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

### **Pharmacokinetics**

#### **Absorption**

Tobramycin is a cationic polar molecule that does not readily cross epithelial membranes. Following inhalation of tobramycin, it is concentrated primarily in the airways. The systemic exposure to tobramycin after inhalation is expected to result from pulmonary absorption of the dose fraction delivered to the lungs as tobramycin is not absorbed to any appreciable extent when administered via the oral route.

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

#### **Sputum Concentrations**

Ten minutes after inhalation of the first 300 mg dose, the average concentration of tobramycin was 1237 µg/g (ranging from 35 to 7414 µg/g) in sputum. Tobramycin does not accumulate in sputum; after 20 weeks of therapy with the Tobramycin solution regimen, the average concentration of tobramycin at ten minutes after inhalation was 1154 µm/g (ranging from 39 to 8085 µm/g) in sputum. High variability of tobramycin concentration in sputum was observed. Two hours after inhalation, sputum concentrations declined to approximately 14% of tobramycin levels at ten minutes after inhalation.

#### **Serum Concentrations:**

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

**Distribution**

A population pharmacokinetic analysis for Tobramycin using the capsules for inhalation dosage form in CF patients estimated the apparent volume of distribution of tobramycin in the central compartment to be 84.1 L for a typical CF patient. While the volume was shown to vary with body mass index (BMI) and lung function (as FEV<sub>1</sub>% predicted), model-based simulations showed that peak (C<sub>max</sub>) and trough (C<sub>trough</sub>) concentrations were not impacted markedly with changes in BMI or lung function. Binding of tobramycin to serum proteins is negligible.

**Metabolism**

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

**Excretion**

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

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

**Effect of food**

Assessments of food-effect were not performed as Tobramycin solution is administered by inhalation.

**Characteristics in special populations****Renal impairment**

Tobramycin is primarily excreted unchanged in the urine and renal function is expected to affect the exposure to tobramycin. Patients with serum creatinine 153 mmol/L or more and blood urea nitrogen (BUN) 14 mmol/L or more have not been included in clinical studies and there are no data in this population to support a recommendation for or against dose adjustment with Tobramycin solution. Refer to PRECAUTIONS –Nephrotoxicity and DOSAGE AND ADMINISTRATION.

**Hepatic impairment**

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

**Patients after organ transplantation**

Adequate data do not exist for the use of Tobramycin solution in these patients.

**Elderly patients**

Renal function in elderly patients should be taken into account as systemically absorbed tobramycin is primarily excreted unchanged in the urine. Refer to PRECAUTIONS – Nephrotoxicity and DOSAGE AND ADMINISTRATION.

**Paediatric population below 6 years**

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

**Race**

Ethnic sensitivity studies have not been conducted. Since tobramycin is not metabolized, it is

not expected that ethnic origin would influence exposure.

## **CLINICAL TRIALS**

*Tobramycin capsules for inhalation are unavailable in this brand, however this dosage form is available in other brands. Clinical trial information obtained using the Tobramycin capsules for inhalation formulation are also included for prescriber information.*

### **Placebo-controlled studies**

#### **Tobramycin solution**

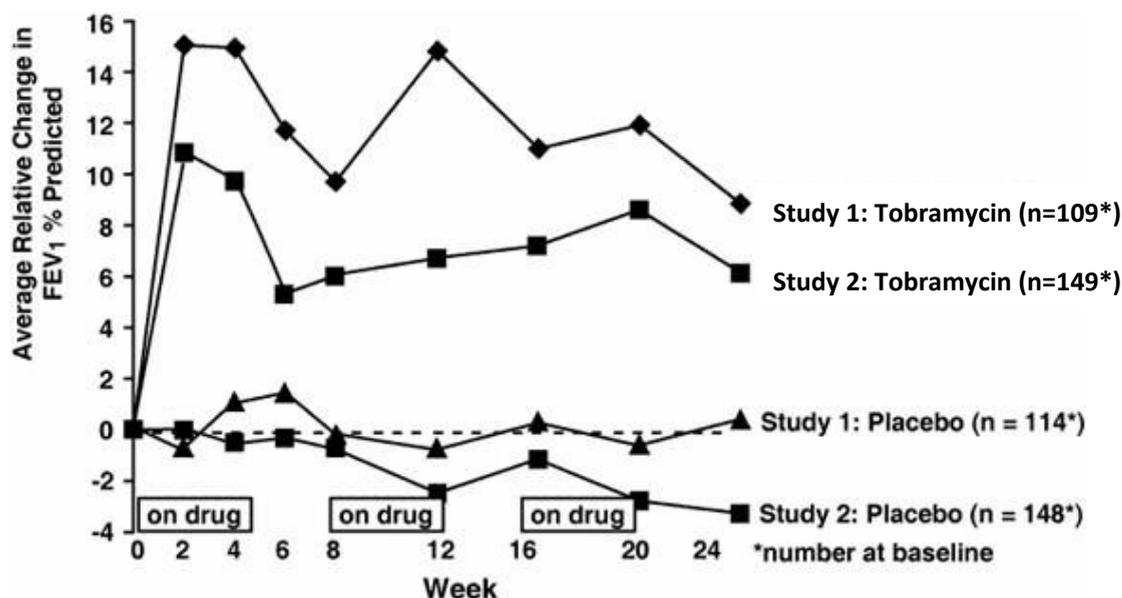
Two identically designed, double-blind, randomised, placebo-controlled, parallel group, 24-week clinical studies were conducted in 520 cystic fibrosis patients aged  $\geq 6$  years who had baseline FEV<sub>1</sub> % predicted between 25 % and 75 % and were positive for *P. aeruginosa*. Patients with a baseline creatinine of  $> 0.18$  mmol/L or who had *Burkholderia cepacia* isolated from sputum were excluded. A cyclical treatment regimen consisting of 28 days on therapy followed by 28 days off therapy was used in these studies. This cycle was repeated twice for a total of three cycles. Patients received either Tobramycin solution (300 mg) or placebo (saline with 1.25 mg quinine) twice daily, delivered by aerosol using a hand-held PARI LC PLUS Reusable Nebuliser with a DeVilbiss Pulmo-Aide Compressor.

All patients received study drug in addition to standard treatment recommended for cystic fibrosis patients, which included oral and parenteral anti-pseudomonal therapy,  $\beta_2$ -agonists, sodium cromoglycate, inhaled steroids, and airway clearance techniques. In addition, approximately 77 % of patients were concurrently treated with dornase alfa.

The randomised clinical studies were followed by a 48-week open label extension where all patients who chose to continue received up to 6 cycles of treatment with Tobramycin solution following the same regimen of 28 days on and 28 days off. Thus, patients who continued into the open label extension received a total exposure of either up to 9 cycles or up to 6 cycles, depending on their original assignment in the controlled studies.

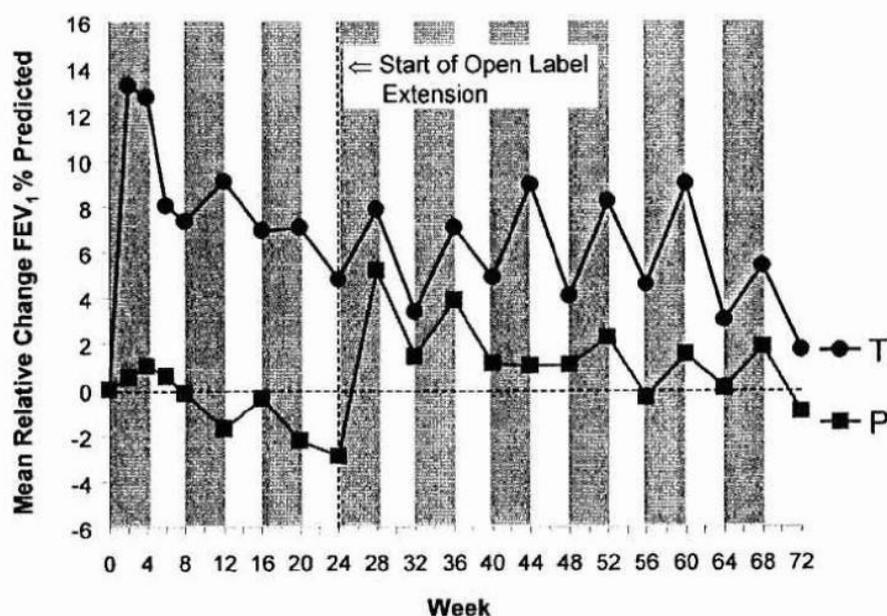
In each of the two placebo-controlled studies, Tobramycin solution-treated patients experienced significant improvement in pulmonary function. Improvement was demonstrated in the Tobramycin solution group in Study 1 by an average increase in FEV<sub>1</sub> % predicted of about 11 % relative to baseline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

**Figure 1:** Relative change from baseline in FEV<sub>1</sub> % predicted for Tobramycin solution 300 mg or placebo (saline with 1.25 mg quinine) twice daily



Three hundred ninety-six (396) patients from the controlled studies participated in the open label extension. Of these, a total of 192 patients received up to 9 cycles of Tobramycin solution, 3 cycles during the controlled studies and 6 cycles during the open label extension. At the end of cycle 9, in these patients FEV<sub>1</sub> % predicted was 1.7 % above baseline (measured at the start of the controlled trials). A total of 204 patients received placebo for 3 cycles followed by 6 cycles of Tobramycin solution. Whilst on placebo, these patients experienced a mean 2.9 % decrease in FEV<sub>1</sub> % predicted from baseline. After 6 cycles of Tobramycin solution, FEV<sub>1</sub> % predicted had improved to 1 % below baseline (see Figure 2).

**Figure 2:** Relative change from baseline in FEV<sub>1</sub> % predicted (Open label extension Tobramycin solution 300 mg twice daily)



T = 9 Cycles of Tobramycin solution;

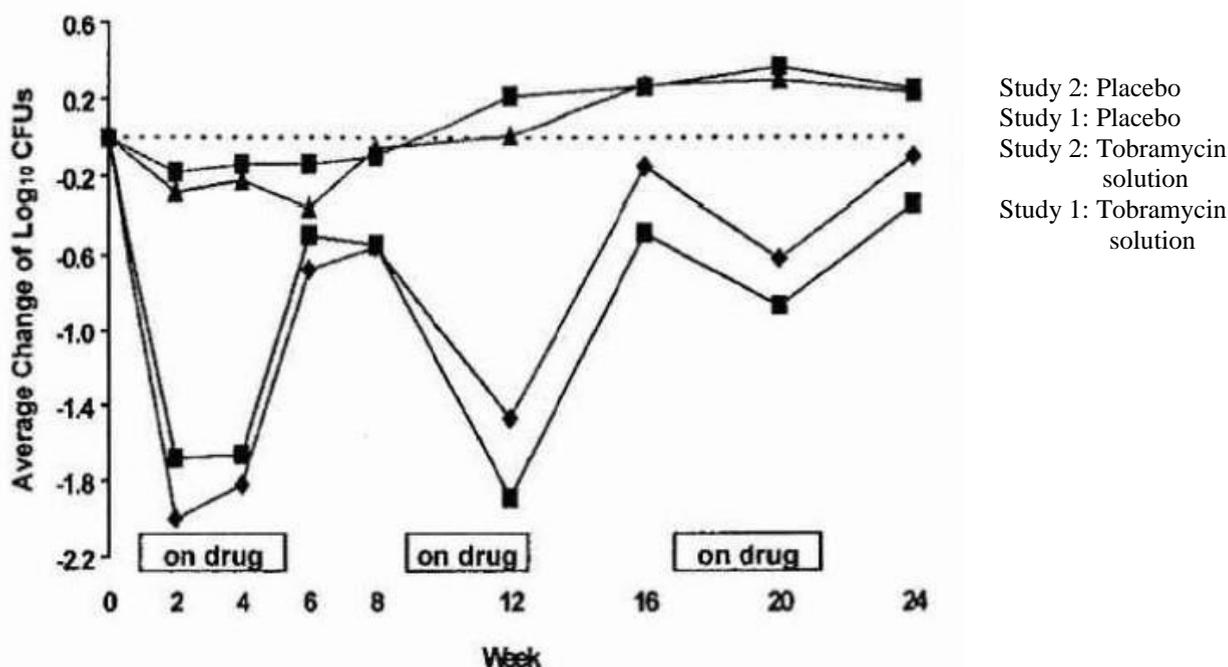
P = 3 Cycles of placebo followed by 6 cycles of Tobramycin solution

Shaded areas represent On-Drug periods

*P. aeruginosa* density in sputum was measured during the 24-week placebo-controlled studies. Treatment with Tobramycin solution resulted in a significant reduction in the number of *P. aeruginosa* colony forming units (CFUs) in sputum during the on-drug periods. Sputum bacterial density returned to baseline during the off drug periods. Reductions in sputum bacterial density were smaller in each successive cycle see Figure 3. *P. aeruginosa* density in sputum was not measured during the open label extension.

During the 24 weeks of the placebo-controlled studies, patients treated with Tobramycin solution were hospitalised for an average of 5.1 days compared to 8.1 days for placebo patients. Patients treated with Tobramycin solution required an average of 9.7 days of parenteral anti-pseudomonal antibiotic treatment compared to 14.1 days for placebo patients. During the 24 weeks of treatment, 40 % of Tobramycin solution patients and 53 % of placebo patients were treated with parenteral anti-pseudomonal antibiotics. Over the subsequent 48 weeks of the open label extension, patients were hospitalised for a mean of 11.1 days. Patients were treated with parenteral anti-pseudomonal antibiotics for a mean of 22.4 days and 60.6 % of patients were treated with parenteral anti-pseudomonal antibiotics.

**Figure 3: Absolute Change in Log<sub>10</sub> CFUs for Tobramycin solution 300 mg or placebo (saline with 1.25 mg quinine) twice daily**



The relationship between *in vitro* susceptibility test results and clinical outcome with Tobramycin solution therapy is not clear. However, four Tobramycin solution patients who began the clinical trial with *P. aeruginosa* isolates having MIC values  $\geq 128$   $\mu\text{g}/\text{mL}$  did not experience an improvement in FEV<sub>1</sub> or a decrease in sputum bacterial density during the first 24 weeks of therapy.

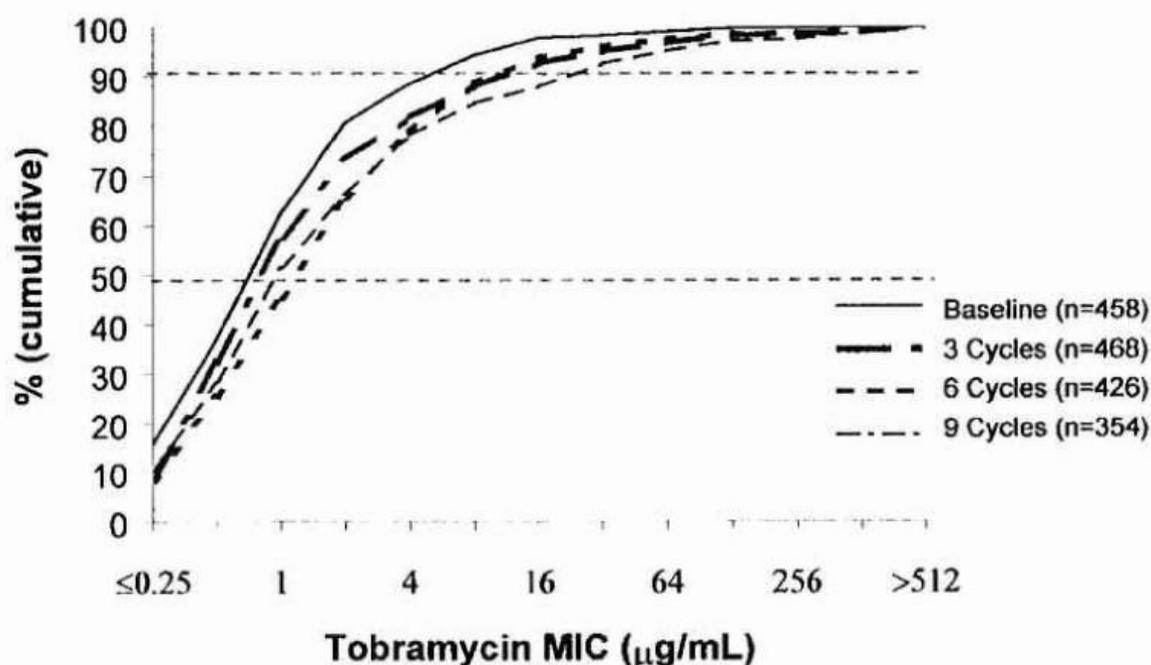
For patients given 9 cycles of active treatment, the proportion of patients with isolates of *P. aeruginosa* with an MIC  $\geq 16$   $\mu\text{g}/\text{mL}$  increased from 13.7 % at baseline to 29.8 % at the end of cycle 9. The proportion of patients with isolates of *P. aeruginosa* with MIC  $\geq 128$   $\mu\text{g}/\text{mL}$  increased from 2.1 % at baseline to 9.2 % at the end of cycle 9.

During the open-label extension, susceptibility testing of other aminoglycosides (amikacin and gentamicin) indicated a shift toward increasing MIC values similar in magnitude to that seen for tobramycin. The MIC values for ciprofloxacin, aztreonam, ceftazidime and ticarcillin remained unchanged.

As noted in Figure 4, treatment for 18 months (9 cycles) with Tobramycin solution in clinical studies demonstrated a trend to decreasing *in vitro* susceptibility of *P. aeruginosa* isolates. The clinical significance of changes in Minimum inhibitory concentrations (MICs) for *P.*

*aeruginosa* has not been clearly established in the treatment of CF patients.

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



#### **TOBRAMYCIN capsules for inhalation dosage form (Study C2301)**

TOBRAMYCIN capsules for inhalation dosage form was studied in a randomized, placebo-controlled, multicentre, three-cycle, two treatment group trial in CF patients, aged between 6 and 21 years (mean age 13.3 years), with FEV<sub>1</sub> values from 25 % to 80 % (inclusive) predicted, who were infected with *P. aeruginosa*. Patients had no exposure to inhaled anti-pseudomonal antibiotics within 4 months prior to screening. The first cycle of this trial was conducted as a double-blind, randomized, placebo-controlled, parallel group trial. During the second and third cycles, all subjects were treated with TOBRAMYCIN capsules for inhalation dosage form. Four capsules (112 mg tobramycin) were administered twice daily (each morning and evening), for three cycles of 28 days on- treatment and 28 days off-treatment (a total treatment period of 24 weeks).

TOBRAMYCIN capsules for inhalation dosage form significantly improved lung function compared with placebo, as shown by the results for the primary endpoint: relative increase in percent predicted FEV<sub>1</sub> after 28 days of treatment (Table 1, , and Figure 5). An analysis of covariance was employed for the efficacy analysis, with factors for treatment groups and regions and two continuous covariates (baseline FEV<sub>1</sub>% predicted and age). The sequential boundaries and stopping rules for the interim analysis were based on the Lan-DeMets procedure with an alpha-spending function that resembles the O'Brien-Fleming boundaries, to ensure control of the overall Type I error at the 0.5 level. A blinded review of the acceptability of spirometry data was conducted prior to study termination (recommended by an external Data Monitoring Committee) at the time of the interim analysis; all efficacy results below are derived from the sensitivity interim analysis after exclusion of technically unreliable spirometry data.

The improvements in lung function achieved during the first treatment cycle were maintained during the subsequent cycles of treatment with capsules. When patients in the placebo treatment group were switched from placebo to capsules at the start of the second treatment cycle, the relative change from baseline in percent predicted FEV<sub>1</sub> was the same as that seen during the first treatment cycle in the TOBRAMYCIN capsules for inhalation dosage form treatment group and the improvements were also maintained over time during the third treatment cycle.

The distribution of tobramycin MICs of *P. aeruginosa* isolates was characterized by biotype: mucoid, dry, small colony variants, and overall. Sputum assessments in this study showed that at baseline, 91 % of TOBRAMYCIN Capsules for inhalation dosage form patients had *P. aeruginosa* isolates with an MIC at least 20 times lower than the mean sputum concentration observed within 30 minutes of dosing. At the end of the third 28 day dosing cycle, 86 % of TOBRAMYCIN Capsules for inhalation dosage form patients had *P. aeruginosa* with an MIC at least 30 times lower and 89 % of TOBRAMYCIN Capsules for inhalation dosage form patients had *P. aeruginosa* with a MIC at least 15 times lower than mean sputum concentration observed within 30 minutes of dosing. The sub-group of patients with MIC values > 8 µg/mL at baseline had an improvement in FEV<sub>1</sub> % predicted measurements after 3 cycles of treatment when treated with TOBRAMYCIN Capsules for inhalation dosage form.

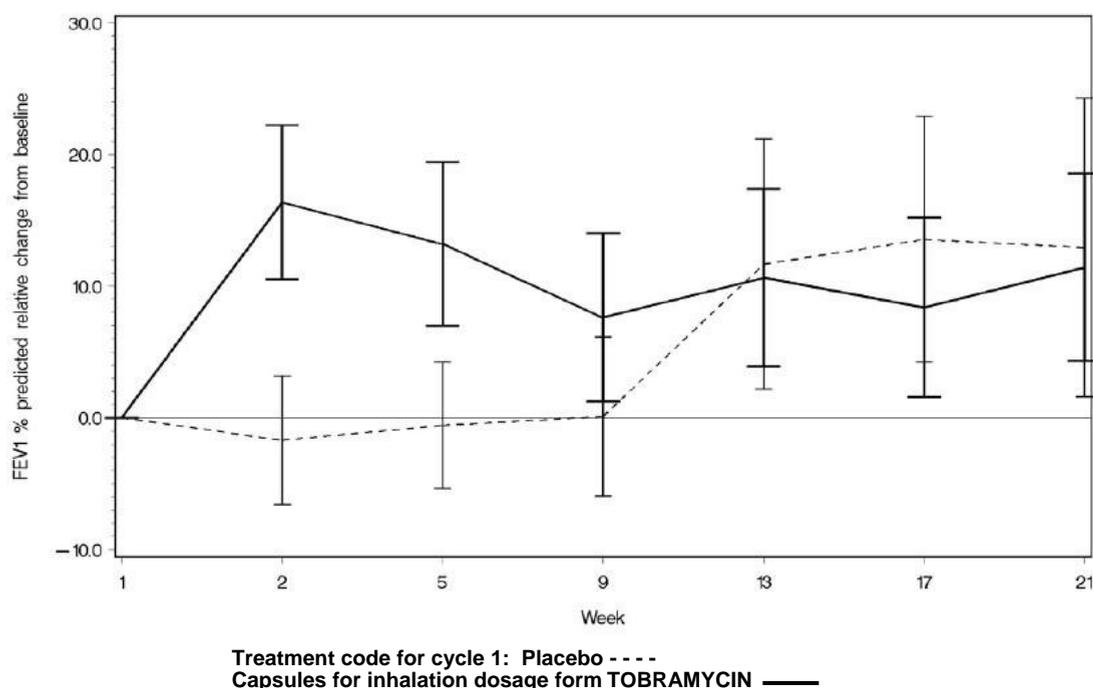
**Table 1: Relative change in percent predicted FEV<sub>1</sub> from baseline to end of dosing in Cycle 1 (Study C2301)**

	<b>TOBRAMYCIN Capsules for inhalation</b>	<b>Placebo N=32</b>	<b>Difference (SE)</b>	<b>95% CI of difference</b>	<b>P-value</b>
n	27	31			
Mean <sup>(1)</sup>	13.21	-0.57	13.79 (3.95)	(5.87,21.70)	0.0010
LS Mean <sup>(2)</sup>	13.97	0.68	13.29 (3.98)	(5.31,21.28)	0.0016

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

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

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



**Figure 5: Study C2301 FEV<sub>1</sub> percent predicted relative change in cycles 1-3 from baseline (on-treatment and off-treatment), by treatment group**

Note: Vertical bars show the 95% confidence interval.

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

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

### **Active-controlled studies**

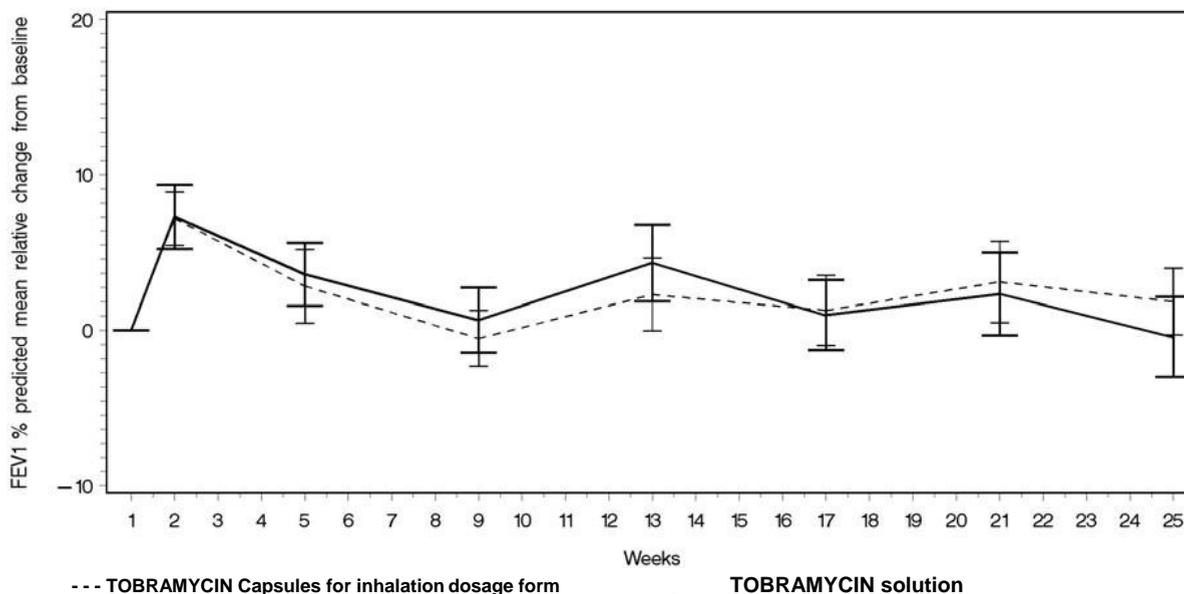
#### **TOBRAMYCIN Capsules for inhalation dosage form and TOBRAMYCIN solution (Study C2302)**

TOBRAMYCIN Capsules for inhalation dosage form and TOBRAMYCIN solution were studied in a randomized, open-label, multicentre, three-cycle, parallel-arm trial in 553 CF patients, aged between 6 and 66 years (mean age 25.6 years), with FEV<sub>1</sub> values from 25 % to 75 % (inclusive) predicted, who were infected with *P. aeruginosa*. Patients with no exposure to inhaled anti-pseudomonal antibiotics within 28 days prior to study drug administration were randomized in a 3:2 ratio to receive either TOBRAMYCIN Capsules for inhalation dosage form 112 mg (four 28 mg capsules) or TOBRAMYCIN solution 300 mg (one 300 mg/5 mL ampoule). The study medications were administered twice daily, at the same time each morning and evening, approximately 12 hours (but not less than 6 hours) apart, for three cycles of 28 days on-treatment and 28 days off-treatment (a total treatment period of 24 weeks). Blinding was not possible due to differences in study drug administration. Baseline demographics, disease characteristics and use of concomitant medications were similar between the two treatment groups.

The primary objective of the study was to assess the safety of TOBRAMYCIN Capsules for inhalation dosage form compared to TOBRAMYCIN solution. The main secondary objective was to assess the efficacy of TOBRAMYCIN Capsules for inhalation dosage form compared to TOBRAMYCIN solution, the key efficacy variable was the relative change in FEV<sub>1</sub> percent predicted at the end of Cycle 3 compared to baseline. A formal analysis of non-inferiority of TOBRAMYCIN Capsules for inhalation dosage form relative to TOBRAMYCIN solution was conducted based on a one-sided 85% confidence interval calculated from an analysis of covariance (ANCOVA) of relative change in FEV<sub>1</sub> % predicted from baseline to pre-dose Day 28 of Cycle 3. The non-inferiority margin of  $\Delta = 6\%$  was pre-defined. Treatment with both TOBRAMYCIN Capsules for inhalation dosage form and TOBRAMYCIN solution resulted in relative increases from baseline to Day 28 of the third treatment cycle in percent predicted FEV<sub>1</sub> of 5.8 %

and 4.7 % respectively (Figure 6).

**Figure 6: Relative change from baseline in percent predicted FEV<sub>1</sub> in Cycles 1-3 (Study C2302)**



In Study C2302, at the end of the third active treatment period, there was a greater decrease in the mean change from baseline in log<sub>10</sub> CFUs in both the TOBRAMYCIN Capsules for inhalation dosage form treatment group (-1.61 log<sub>10</sub> CFUs) and TOBRAMYCIN solution treatment group (-0.77 log<sub>10</sub> CFUs) especially during the third treatment cycle (a mean change of -1.61 log<sub>10</sub> CFUs in the Capsules for inhalation dosage form capsule treatment group compared with -0.77 log<sub>10</sub> CFUs in the TOBRAMYCIN solution treatment group). As in the previous study, there was a partial recovery of *P. aeruginosa* density at the end of the 28 day off-treatment phase in both treatment groups, but this was reversed during the on-treatment phase of each treatment cycle.

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

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

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

## **INDICATIONS**

TOBRAMYCIN WOCKHARDT solution is indicated for the management of cystic fibrosis patients with *P. aeruginosa* infections. Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with FEV<sub>1</sub>

≤ 25 % or ≥ 80 % predicted at screening, or patients colonized with *Burkholderia cepacia* (see CLINICAL TRIALS).

## **CONTRAINDICATIONS**

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

## **PRECAUTIONS**

Tobramycin solution is for oral inhalation only.

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

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

Caution should be exercised when prescribing Tobramycin solution to patients with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction. Patients receiving concomitant parenteral aminoglycoside therapy should be monitored as clinically appropriate.

Aminoglycosides can cause foetal harm when administered to a pregnant woman. Aminoglycosides cross the placenta, and streptomycin has been associated with several reports of total, irreversible, bilateral congenital deafness in paediatric patients exposed *in utero*. Patients who use Tobramycin solution during pregnancy, or become pregnant while taking one of these products should be apprised of the potential hazard to the foetus.

### **Ototoxicity**

In clinical studies, 4 patients (1 %) reported mild to moderate hearing loss in clinical studies of up to 9 treatment cycles of Tobramycin solution. Hearing loss was transient for 3 patients and ongoing at the end of study for one patient. Three of these patients had received IV aminoglycosides concomitantly to receiving Tobramycin solution.

In post-marketing experience, some patients receiving Tobramycin solution and extensive previous or concomitant parenteral aminoglycosides have reported hearing loss. Some of these reports occurred in patients with previous or concomitant treatment with systemic aminoglycosides. Patients with hearing loss frequently reported tinnitus. Tinnitus is a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution (see ADVERSE REACTIONS). Ototoxicity, manifested as both auditory and vestibular toxicity, has been reported with parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness.

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

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

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

## **Nephrotoxicity**

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

If nephrotoxicity occurs in a patient receiving Tobramycin solution, tobramycin therapy should be discontinued until tobramycin serum concentrations fall below 2 µg/mL. Also see PRECAUTIONS - Laboratory Tests.

Laboratory tests of renal function should be monitored as clinically appropriate. Urea and creatinine levels should be reassessed after every 6 complete cycles of therapy.

## **Laboratory tests**

### Audiograms:

Tinnitus may be a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution. Physicians should consider an audiogram for patients who show any evidence of auditory dysfunction, or who are at increased risk for auditory dysfunction.

### Serum concentrations:

In patients with normal renal function treated with Tobramycin solution serum tobramycin concentrations are approximately 1 µg/mL one hour after dose administration and do not require routine monitoring.

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

Serum concentrations of tobramycin should be monitored in patients with known or suspected auditory or renal dysfunction. Patients treated with concomitant parenteral tobramycin should be monitored at the discretion of the treating physician.

The serum concentration of tobramycin should only be monitored through venipuncture and not finger prick blood sampling. Contamination of the skin of the fingers with tobramycin may lead to falsely increased measurements of serum levels of the drug. This contamination cannot be completely avoided by hand washing before testing.

### Renal function:

The clinical studies with Tobramycin solution did not reveal any imbalance in the percentage of patients in the Tobramycin and placebo groups who experienced at least a 50 % rise in serum creatinine from baseline (see ADVERSE REACTIONS). Laboratory tests of urine and renal function should be conducted at the discretion of the treating physician.

## **Neuromuscular dysfunction**

Tobramycin solution should be used cautiously in patients with muscular disorders, such as myasthenia gravis or Parkinson's disease, since aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.

## **Bronchospasm**

Bronchospasm can occur with inhalation of medicinal products and has been reported with Tobramycin solution. Bronchospasm should be treated as medically appropriate. If an allergic response is suspected, Tobramycin solution should be discontinued.

In clinical studies of Tobramycin, changes in FEV<sub>1</sub> measured after the inhaled doses were similar in the Tobramycin and placebo groups.

## **Cough**

Cough was the most commonly reported adverse event considered treatment related for Tobramycin solution. If there is evidence of continued therapy-induced cough, the physician should consider the use of alternative therapeutic options.

## **Haemoptysis**

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

## **Concomitant antibiotic therapy**

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

## **Animal Toxicology**

Bronchoepithelial hyperplasia and chronic interstitial inflammation around terminal bronchioles occurred in studies in rats after daily inhalational exposures to Tobramycin for 6 months.

## **Carcinogenicity**

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

## **Genotoxicity**

Tobramycin has been evaluated for genotoxicity in a battery of assays for gene mutations and chromosomal damage. Tobramycin was negative in the bacterial reverse mutation and the mouse lymphoma forward mutation assays. Tobramycin did not induce chromosomal aberrations in Chinese hamster ovary cells and was negative in the mouse micronucleus test.

## **Effects on Fertility**

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

Subcutaneous administration of up to 600 mg/m<sup>2</sup>/day of tobramycin did not affect mating behaviour or cause impairment of fertility in male or female rats, although fertility of the offspring was not examined.

## **Use in Pregnancy**

Category D. There are no adequate data from the use of tobramycin administered by inhalation

in pregnant women.

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

Aminoglycosides can cause foetal harm (e.g., congenital deafness) when administered to a pregnant woman and high systemic concentrations are achieved. Ototoxicity was not evaluated in offspring during nonclinical reproduction toxicity studies with tobramycin.

Treatment with Tobramycin during pregnancy should be undertaken only if the benefits to the mother outweigh the risks to the foetus or baby. If Tobramycin is used during pregnancy, or if the patient becomes pregnant while taking Tobramycin, the patient should be apprised of the potential hazard to the foetus.

Aminoglycosides can cross the placenta. There is evidence of selective uptake of aminoglycosides by foetal kidney resulting in damage (probably reversible) to immature nephrons. Eighth cranial nerve damage has also been reported following *in utero* exposure to some of the aminoglycosides. Because of their chemical similarity, all aminoglycosides must be considered potentially nephrotoxic and ototoxic to the foetus. It should also be noted that therapeutic blood concentrations in the mother do not equate with safety to the foetus.

### **Use in Lactation**

It is not known if Tobramycin will reach sufficient concentrations after administration by inhalation to be excreted in human breast milk. Because of the potential for ototoxicity and nephrotoxicity in infants, a decision should be made whether to terminate nursing or discontinue treatment with Tobramycin, taking into account the importance of the drug to the mother.

### **Paediatric Use**

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

### **Patients with renal impairment**

Tobramycin is primarily excreted unchanged in the urine and renal function is expected to affect the exposure to tobramycin. See PRECAUTIONS - Nephrotoxicity.

### **Patients with hepatic impairment**

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

## **INTERACTIONS WITH OTHER MEDICINES**

No clinical drug interaction studies have been performed with Tobramycin solution.

Some diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. Tobramycin solution should not be administered concomitantly with ethacrynic acid, frusemide, urea, or intravenous mannitol.

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

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

Other medicinal products that have been reported to increase the potential toxicity of

parenterally administered aminoglycosides include: amphotericin B, cefalotin, cyclosporin, tacrolimus, polymyxins (risk of increased nephrotoxicity); platinum compounds (risk of increased nephrotoxicity and ototoxicity); anticholinesterases, and botulinum toxin (neuromuscular effects).

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

### **Absence of interactions**

In clinical studies of Tobramycin solution, patients taking Tobramycin solution concomitantly with domase alfa,  $\beta_2$ -agonists, inhaled corticosteroids, other anti-pseudomonal antibiotics, or parenteral aminoglycosides demonstrated adverse experience profiles similar to the study population as a whole.

## **ADVERSE EFFECTS**

### **Adverse Events in Clinical Trials**

#### **Tobramycin solution**

Tobramycin solution was generally well tolerated during two placebo-controlled clinical studies in 258 cystic fibrosis patients ranging in age from 6 to 48 years. Patients received Tobramycin solution in alternating periods of 28 days on and 28 days off drug in addition to their standard cystic fibrosis therapy for a total of 24 weeks.

Voice alteration and tinnitus were the only adverse experiences reported by significantly more Tobramycin solution-treated patients. Thirty-three patients (13 %) treated with Tobramycin solution complained of voice alteration compared to 17 (7 %) placebo patients. Voice alteration was more common in the on-drug periods.

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

Nine (3%) patients in the Tobramycin solution group and nine (3%) patients in the placebo group had increases in serum creatinine of at least 50% over baseline. In all nine patients in the Tobramycin group, creatinine decreased at the next visit.

Table 2 lists the percent of patients with treatment-emergent adverse experiences that occurred in 25 % of patients during the 48 weeks of the open label extension. The table also presents the corresponding data from the 24-week placebo-controlled studies, where one group of patients received placebo and the other group received Tobramycin solution during the first three cycles of therapy.

**Table2: Percent of patients treated with Tobramycin solution or placebo with treatment-emergent adverse events occurring in  $\geq 5$  % of patients in any group**

<b>Adverse Event</b>	<b>During the Open Label Extension <sup>a</sup></b>		<b>During the Placebo-Controlled Studies</b>	
	<b>9 Cycles (n = 192)</b>	<b>6 Cycles (n = 204)</b>	<b>3 Cycles (n = 258)</b>	<b>Placebo (n = 262)</b>

<b>Respiratory System</b>				
Cough Increased	50	48	46	47
Pharyngitis	48	44	38	39
Sputum Increased	44	38	38	40
Dyspnea	42	34	34	39
Rhinitis	38	33	35	34
Lung Disorder	34	36	31	31
Hemoptysis	31	27	19	24
Asthma	28	24	16	20
Lung Function Decreased	29	23	16	15
Sputum Discoloration	25	19	21	20
Upper Respiratory Tract Infection	14	10	5	8
Sinusitis	7	14	8	9
Voice Alteration	12	6	13	7
Epistaxis	8	8	7	7
Lower Respiratory Tract Infection	7	9	6	8
Respiratory Disorder	6	9	2	6
Hyperventilation	9	5	5	10
Hypoxia	6	6	5	4
Nasal Polyp	4	5	4	2
Laryngitis	5	3	4	3
<b>Body as a Whole</b>				
Fever	40	46	33	44
Asthenia	44	38	36	39
Chest pain	37	35	26	30
Headache	29	34	27	32
Abdominal Pain	21	27	13	24
Pain	18	24	8	13
Back Pain	10	6	7	8
Chills	7	6	3	2
Accidental Injury	5	6	4	3
Malaise	3	7	6	5
Flu Syndrome	4	5	1	2

**Table 2 (continued): Percent of Patients treated with Tobramycin solution or placebo with Treatment-Emergent Adverse Events Occurring in  $\geq 5\%$  of Patients in Any Group**

Otitis Media	5	2	3	3
<b>Haemic and Lymphatic System</b>				
Lymphadenopathy	8	7	4	2
<b>Nervous System</b>				17
Dizziness	6	6	6	8
Somnolence	6	6	2	4
<b>Musculoskeletal</b>				
Myalgia	6	5	5	3

<sup>a</sup> Patients with newly-occurring or worsening adverse events since Week 24. The 6-Cycle group received Placebo during the controlled study (first 3 cycles). The 9-Cycle group received Tobramycin solution during both the controlled study and the open label extension.

### **TOBRAMYCIN Capsules for inhalation dosage form**

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

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

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

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

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

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

Adverse drug reactions reported in Study C2302 regardless of relationship to study medication are

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

Bronchospasm was reported for 1.6 % of the TOBRAMYCIN Capsules for inhalation dosage form group and 0.5 % of the TOBRAMYCIN solution group.

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

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

**Table 3 Adverse drug reactions experienced<sup>1</sup> in two or more percent of TOBRAMYCIN Capsules for inhalation dosage form patients in Study C2302 (TOBRAMYCIN Capsules for inhalation dosage form vs. TOBRAMYCIN solution, open label), all randomized safety population**

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

	Vomiting	6.2	5.7
	Diarrhoea	4.2	1.9
	Nausea	7.5	9.6
	Dysgeusia	3.9	0.5
<b>Infections and infestations</b>			
<i>Common</i>			
	Upper Respiratory Tract Infection	6.8	8.6
<b>Investigations</b>			
<i>Common</i>			
	Pulmonary Function Test Decreased	6.8	8.1
	Forced Expiratory Volume Decreased	3.9	1.0
	Blood Glucose Increased	2.9	0.5
<b>Vascular disorders</b>			
<i>Common</i>			
	Epistaxis	2.6	1.9
<b>Nervous system disorders</b>			
<i>Very common</i>			
	Headache	11.4	12.0
<b>General Disorders and Administration Site Conditions</b>			
<i>Very common</i>			
	Pyrexia	15.6	12.4
<b>Musculoskeletal and Connective Tissue Disorders</b>			
<i>Common</i>			
	Musculoskeletal Chest Pain	4.5	4.8
<b>Skin and Subcutaneous Tissue Disorders</b>			
<i>Common</i>			

<sup>1</sup> Frequency category using CIOMS III

<sup>2</sup> Most commonly reported as pulmonary exacerbation

System Organ Class/MedDRA Preferred Term	TOBRAMYCIN Capsules for inhalation (N=308) % of patients	TOBRAMYCIN solution (N=209) % of patients
Rash	2.3	2.4

Events inclusive of all treatment cycles on and off treatment

### **Post-marketing Surveillance**

Some patients receiving Tobramycin solution and extensive previous or concomitant parenteral aminoglycosides have reported hearing loss during post-marketing surveillance (see PRECAUTIONS).

#### ***Adverse drug reactions derived from spontaneous reports for Tobramycin solution***

The following adverse drug reactions have been derived from post marketing experience with Tobramycin solution via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

#### **Ear and labyrinth disorders:**

Hearing loss

#### **Skin and subcutaneous tissue disorders:**

Hypersensitivity, pruritus, urticaria, rash

#### **Nervous system disorders:**

Aphonia, dysgeusia

#### **Respiratory, thoracic, and mediastinal disorders:**

Bronchospasm, oropharyngeal pain, sputum increased, chest pain

#### **General disorders and administration site conditions**

Decreased appetite

## **DOSAGE AND ADMINISTRATION**

### **Dosage**

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

Otherwise, the patient should wait for the next dose and not inhale more medication to make up for the missed dose.

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

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

### ***Adults and paediatric patients 6 years of age and older***

The recommended dosage for both adults and paediatric patients 6 years of age and older is one single-use ampoule (300 mg) administered twice daily for 28 days.

### ***Dosing in special populations***

#### Paediatric population below 6 years

Tobramycin solution have not been studied and are not indicated for use in paediatric patients less than 6 years of age. Clinical studies with Tobramycin solution have included children aged 6 years and above (see PHARMACOLOGY).

#### Elderly patients ( $\geq 65$ years)

There are insufficient data in this population to support a recommendation for or against dose adjustment. Renal function in elderly patients should be taken into account while using Tobramycin Solution (see PRECAUTIONS).

#### Patients with renal impairment

Patients with serum creatinine  $\geq 153$  mmol/L or more and blood urea nitrogen (BUN)  $\geq 14$  mmol/L or more have not been included in clinical studies and there are no data in this population to support a recommendation for or against dose adjustment with Tobramycin solution. Also see PRECAUTIONS - Nephrotoxicity.

#### Patients with hepatic impairment

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

#### Patients after organ transplantation

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

### **Administration**

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

Tobramycin solution is supplied as a single-use, ready to use ampoule and is administered by inhalation, over an approximately 15 minute period, using a hand-held nebuliser and compressor. See PRECAUTIONS.

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

Tobramycin solution should not be diluted or mixed with dornase alfa or other medications in the nebuliser. See PRECAUTIONS - Drug Interactions with other medicines.

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

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

## **OVERDOSAGE**

### **Signs and symptoms**

In the event of inadvertent administration of tobramycin by the IV route, signs and symptoms of parenteral toxicity from overdosage may occur that include dizziness, tinnitus, vertigo, loss of high-tone hearing acuity, respiratory distress or failure, renal impairment, and neuromuscular blockade. Administration by inhalation results in low systemic bioavailability of tobramycin.

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

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

### **Treatment**

In all cases of suspected overdosage, physicians should contact the Poison Information Centre on 131 126 for advice on management. In the case of any overdosage, the possibility of drug interactions with alterations in drug disposition should be considered.

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

Haemodialysis may be helpful in removing tobramycin from the body.

## **PRESENTATIONS AND STORAGE CONDITIONS**

### **Presentation:**

TOBRAMYCIN WOCKHARDT solution for inhalation is supplied in single-use, low-density polyethylene plastic 5 mL ampoules, containing 300 mg tobramycin. TOBRAMYCIN WOCKHARDT solution is packaged in laminated foil over-pouches, each containing 7 ampoules. AUST R 279354.

### **Storage:**

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

TOBRAMYCIN WOCKHARDT solution should not be used beyond the expiration date stamped on the ampoule when stored under refrigeration (2 °C-8°C) or beyond 6 months when stored at room temperature (up to 25°C). TOBRAMYCIN WOCKHARDT solution should not be used if it is cloudy or if there are particles in the solution.

TOBRAMYCIN WOCKHARDT solution ampoules should not be exposed to intense light. The solution in the ampoule is slightly yellow, but may darken with age if not stored in the refrigerator; however, the colour change does not indicate any change in the quality of the product as long as it is stored within the recommended storage conditions.

The contents of the whole ampoule should be used directly after opening; opened ampoules should never be stored for re-use.

## **POISON SCHEDULE**

Schedule 4

## **NAME AND ADDRESS OF THE SPONSOR**

Wockhardt Bio Pty Ltd  
Suite 103, 39 East Esplanade,  
MANLY NSW 2095

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)  
23 February 2018