Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

TOBI 300 mg/5 mL Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule of 5mL contains tobramycin 300mg as a single dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.

Clear, slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TOBI is indicated in cystic fibrosis (CF) patients aged 6 years and older for long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa*.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

TOBI is supplied for use via inhalation and is not for parenteral use.

Posology

The recommended dose for adults and children is one ampoule twice daily for 28 days. The dose interval should be as close as possible to 12 hours and not less than 6 hours. After 28 days of therapy, patients should stop TOBI therapy for the next 28 days. A cycle of 28 days of active therapy and 28 days of rest from treatment should be maintained.

Dosage is not adjusted for weight. All patients should receive one ampoule of TOBI (300 mg of tobramycin) twice daily.

Controlled clinical studies, conducted for a period of 6 months using the following TOBI dosage regimen, have shown that improvement in lung function was maintained above baseline during the 28 day rest periods.

TOBI Dosing Regimen in Controlled Clinical Studies

Cycle 1		Cycle 2		Cycle 3	
28 Days	28 Days	28 Days	28 Days	28 Days	28 Days
TOBI 300 mg twice daily plus standard care	standard care	TOBI 300 mg twice daily plus standard care	standard care	TOBI 300 mg twice daily plus standard care	standard care

Safety and efficacy for long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa* have been assessed in controlled and open label studies for up to 96 weeks (12 cycles), but have not been studied in patients under the age of 6 years, patients with forced expiratory volume in 1 second (FEV_1) <25% or >75% predicted, or patients colonised with *Burkholderia cepacia*.

Therapy should be initiated by a physician experienced in the management of cystic fibrosis. Treatment with TOBI should be continued on a cyclical basis for as long as the physician considers the patient is gaining clinical benefit from the inclusion of

TOBI in their treatment regimen. If clinical deterioration of pulmonary status is evident, additional anti-pseudomonal therapy should be considered. Clinical studies have shown that a microbiological report indicating *in vitro* drug resistance does not necessarily preclude a clinical benefit for the patient.

Special populations

Elderly (≥ 65 years)
There are insufficient data in this population to support a recommendation for or against dose adjustment.

Patients with renal impairment
There are no data in this population to support a recommendation for or against dose adjustment with TOBI. Please also refer to nephrotoxicity information in section 4.4 and excretion information in section 5.2.

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 of TOBI in patients after organ transplantation.

Paediatric population

The safety and efficacy of TOBI in children aged less than 6 years have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

The contents of one ampoule should be emptied into the nebuliser and administered by inhalation over approximately a 15-minute period using a hand-held PARI LC PLUS reusable nebuliser with a suitable compressor. Suitable compressors are those which, when attached to a PARI LC Plus nebuliser, deliver a flow rate of 4-6 L/min and/or a back pressure of 110-217 kPa. The manufacturers' instructions for the care and use of the nebuliser and compressor should be followed.

TOBI is inhaled whilst the patient is sitting or standing upright and breathing normally through the mouthpiece of the nebuliser. Nose clips may help the patient breathe through the mouth. The patient should continue their standard regimen of chest physiotherapy. The use of appropriate bronchodilators should continue as thought clinically necessary. Where patients are receiving several different respiratory therapies it is recommended that they are taken in the following order: bronchodilator, chest physiotherapy, other inhaled medicinal products, and finally TOBI.

Maximum tolerated daily dose

The maximum tolerated daily dose of TOBI has not been established.

4.3 Contraindications

Administration of TOBI is contraindicated in any patient with known hypersensitivity to any aminoglycoside or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General Warnings

For information on pregnancy and lactation see section 4.6.

TOBI should be used with caution in patients with known or suspected renal, auditory, vestibular or neuromuscular dysfunction, or with severe, active haemoptysis.

Monitoring of serum tob ramycin concentrations

Serum tobramycin concentrations should be monitored in patients with known or suspected auditor y or renal dysfunction. If ot o-or nephrotoxicity occurs in a patie nt receiving TOBI, tobramycin therapy should be discontinued until serum concentration falls below 2 microgram/mL.

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.

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.

Bronchospasm

Bronchospasm can occur with inhalation of medicinal products and has been reported with nebulised tobramycin. The first dose of TOBI should be given under supervision, using a pre-nebulisation bronchodilator if this is part of the current regimen for the patient. FEV_1 should be measured before and after nebulisation. If there is evidence of therapy-induced bronchospasm in a patient not receiving a bronchodilator the test should be repeated, on a separate occasion, using a bronchodilator. Evidence of bronchospasm in the presence of bronchodilator therapy may indicate an allergic response. If an allergic response is suspected TOBI should be discontinued. Bronchospasm should be treated as medically appropriate.

Neuromuscular disorders

TOBI should be used with great caution in patients with known or suspected neuromuscular disorders such as parkinsonism or other conditions characterised by myasthenia, including myasthenia gravis, as aminoglycosides may aggravate muscle weakness due to a potential curare-like effect on neuromuscular function.

Nephrotoxicity

Although nephrotoxicity has been associated with parenteral aminoglycoside therapy, there was no evidence of nephrotoxicity during clinical trials with TOBI, however acute kidney injury (AKI) has been reported post-marketing with the use of inhaled tobramycin (see section 4.8).

The product should be used with caution in patients with known or suspected renal dysfunction and serum concentrations of tobramycin should be monitored. Patients with severe renal impairment, i.e., serum creatinine >2 mg/dL (176.8 micromol/L), were not included in the clinical studies.

Current clinical practice suggests baseline renal function should be assessed. Urea and creatinine levels should be reassessed after every 6 complete cycles of TOBI therapy (180 days of nebulised aminoglycoside therapy).
See also “Mo n itoring of serum tobram y cin concentrations” above.

Ototoxicity

Ototoxicity, manifested as both auditory and vestibular toxicity, has been reported with parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness. Ototoxicity, as measured by complaints of hearing loss or by audiometric evaluations, did not occur with TOBI therapy during controlled clinical studies. In open label studies and post-marketing experience, some patients with a history of prolonged previous or concomitant use of intravenous aminoglycosides have experienced hearing loss. Patients with hearing loss frequently reported tinnitus. Physicians should consider the potential for aminoglycosides to cause vestibular and cochlear toxicity and carry out appropriate assessments of auditory function during TOBI therapy. In patients with a predisposing risk due to previous prolonged, systemic aminoglycoside therapy it may be necessary to consider audiological assessment before initiating TOBI therapy. The onset of tinnitus warrants caution as it is a sentinel symptom of ototoxicity.

Caution should be exercised when prescribing TOBI to patients with known or suspected auditory or vestibular dysfunction. Physicians should consider an audiological assessment for patients who show any evidence of auditory dysfunction, or who are at increased risk for auditory dysfunction.

Risk of ototoxicity due to mitochondrial DNA variants

Cases of ototoxicity with aminoglycosides have been observed in patients with certain variants in the mitochondrially encoded 12S rRNA gene (*MT-RNR1*), particularly the m.1555A>G variant. Ototoxicity occurred in some patients even when their aminoglycoside serum levels were within the recommended range. In case of known maternal history of ototoxicity due to aminoglycoside use or a known mitochondrial DNA variant in the patient, it may be necessary to consider alternative treatments other than aminoglycosides unless the increased risk of permanent hearing loss is outweighed by the severity of infection and lack of safe and effective alternative therapies.

If a patient reports tinnitus or hearing loss during aminoglycoside therapy the physician should consider referring them for audiological assessment.

See also "Monitoring of serum tobramycin concentrations" above.

Haemoptysis

Inhalation of nebulised solutions may induce a cough reflex. The use of TOBI in patients with active, severe haemoptysis should be undertaken only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.

Microbial Resistance

In clinical studies, some patients on TOBI therapy showed an increase in aminoglycoside Minimum Inhibitory Concentrations for *P. aeruginosa* isolates tested. There is a theoretical risk that patients being treated with nebulised tobramycin may develop *P. aeruginosa* isolates resistant to intravenous tobramycin (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with TOBI.

In clinical studies, patients taking TOBI concomitantly with dornase alfa, β-agonists, inhaled corticosteroids, and other oral or parenteral anti-pseudomonal antibiotics, demonstrated adverse experience profiles which were similar to those of the control group.

Concurrent and/or sequential use of TOBI with other medicinal products with neurotoxic, nephrotoxic or ototoxic potential should be avoided. Some diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. TOBI should not be administered concomitantly with ethacrynic acid, furosemide, urea or intravenous mannitol.

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

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

Platinum compounds (risk of increased nephrotoxicity and ototoxicity);

Anticholinesterases, botulinum toxin (neuromuscular effects).

4.6 Fertility, pregnancy and lactation

TOBI should not be used during pregnancy or lactation unless the benefits to the mother outweigh the risks to the foetus or baby.

Pregnancy

There are no adequate data from the use of tobramycin administered by inhalation in pregnant women. Animal studies do not indicate a teratogenic effect of tobramycin (see 5.3 Preclinical data). However, aminoglycosides can cause foetal harm (e.g., congenital deafness) when high systemic concentrations are achieved in a pregnant woman. If TOBI is used during pregnancy, or if the patient becomes pregnant while taking TOBI, she should be informed of the potential hazard to the foetus.

Breast-feeding

Systemic tobramycin is excreted in breast milk. It is not known if administration of TOBI will result in serum concentrations high enough for tobramycin to be detected in breast milk. Because of the potential for ototoxicity and nephrotoxicity with tobramycin in infants, a decision should be made whether to terminate nursing or discontinue TOBI therapy

Fertility

No effect on male or female fertility was observed in animal studies after subcutaneous administration (see section 5.3).

4.7 Effects on ability to drive and use machines

On the basis of reported adverse drug reactions, TOBI is presumed to be unlikely to produce an effect on the ability to drive and use machinery.

4.8 Undesirable effects

Summary of the safety profile

Two parallel, 24-week, randomised, double-blind, placebo-controlled clinical studies were conducted with TOBI in 520 cystic fibrosis patients ranging in age from 6 to 63 years.

The most commonly (≥ 10%) reported adverse events in the placebo-controlled studies with TOBI were cough, pharyngitis, productive cough, asthenia, rhinitis, dyspnoea, pyrexia, lung disorder, headache, chest pain, sputum discoloured, haemoptysis, anorexia, pulmonary function test decreased, asthma, vomiting, abdominal pain, dysphonia, nausea, and weight loss.

Most events were reported at similar or higher frequencies in patients receiving placebo. Dysphonia and tinnitus were the only undesirable effects reported in significantly more patients treated with TOBI; (12.8% TOBI vs. 6.5% placebo) and (3.1% TOBI vs. 0% placebo) respectively. These episodes of tinnitus were transient and resolved without discontinuation of TOBI therapy, and were not associated with permanent loss of hearing on audiogram testing. The risk of tinnitus did not increase with repeated cycles of exposure to TOBI (see section 4.4 Ototoxicity).

Tabulated summary of adverse reactions

In the 24-week placebo-controlled studies and their open-label extensions on active treatment, a total of 313, 264 and 120 patients completed treatment with TOBI for 48, 72 and 96 weeks respectively.

Table 1 provides the incidence of treatment-emergent adverse drug reactions, according to the following criteria: reported with an incidence of ≥ 2% for patients receiving TOBI, occurring at a higher rate in the TOBI arm, and assessed as drug-related in ≥ 1% of patients.

Adverse drug reactions from clinical trials are listed according to system organ classes in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100, to <1/10); uncommon (≥1/1,000, to <1/100); rare (≥1/10,000, to <1/1,000) very rare (<1/10,000).

Table 1 Adverse reactions in clinical trials

Adverse reactions	Frequency category
Infections and infestations	
Laryngitis	Common
Ear and labyrinth disorders	
Tinnitus	Common
Respiratory, thoracic, and mediastinal disorders	

Lung disorder	Very common
Rhinitis	Very common
Dysphonia	Very common
Sputum discoloured	Very common
Musculoskeletal and connective tissue disorders	
Myalgia	Common
General disorders and administration site conditions	
Malaise	Common
Investigations	
Pulmonary function test decreased	Very common

As the duration of exposure to TOBI increased over the two open-label extension studies, the incidence of productive cough and pulmonary function test decreased appeared to increase; however, the incidence of dysphonia appeared to decline. Overall, the incidence of adverse events related to the following MedDRA System Organ Class (SOC) decreased with increasing exposure to TOBI: Respiratory, thoracic, and mediastinal disorders, Gastrointestinal disorders, and General disorders and administration site conditions.

Adverse reactions derived from spontaneous reports

Spontaneously reported adverse reactions, presented below, are reported voluntarily and it is not always possible to reliably establish frequency or a causal relationship to drug exposure.

Nervous system disorders
Aphonia, dysgeusia
Ear and labyrinth disorders
Hearing loss
Respiratory, thoracic, and mediastinal disorders
Bronchospasm, oropharyngeal pain
Skin and subcutaneous tissue disorders
Hypersensitivity, pruritus, urticaria, rash
Renal and urinary disorders
Acute kidney injury (AKI)

In open label studies and post-marketing experience, some patients with a history of prolonged previous or concomitant use of intravenous aminoglycosides have experienced hearing loss (see 4.4). Parenteral aminoglycosides have been associated with hypersensitivity, ototoxicity and nephrotoxicity (see 4.3, 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie

4.9 Overdose

Administration by inhalation results in low systemic bioavailability of tobramycin. Symptoms of aerosol overdose may include severe hoarseness.

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

In the event of inadvertent administration of TOBI by the intravenous route, signs and symptoms of parenteral tobramycin overdose may occur that include dizziness, tinnitus, vertigo, loss of hearing acuity, respiratory distress and/or neuromuscular blockade and renal impairment.

Acute toxicity should be treated with immediate withdrawal of TOBI, and baseline tests of renal function should be undertaken. Tobramycin serum concentrations may be helpful in monitoring overdose. In the case of any overdosage, the possibility of drug interactions with alterations in the elimination of TOBI or other medicinal products should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:Aminoglycoside Antibacterials, 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 disruption of the cell envelope and eventual cell death. It is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Breakpoints
Established susceptibility breakpoints for parenteral administration of tobramycin are inappropriate in the aerosolised administration of the medicinal product.
Cystic fibrosis (CF) sputum exhibits an inhibitory action on the local biological activity of nebulised aminoglycosides. This necessitates sputum concentrations of aerosolised tobramycin to be some ten and twenty–five fold above the Minimum Inhibitory Concentration (MIC) for, respectively, *P. aeruginosa* growth suppression and bactericidal activity. In controlled clinical trials, 97% of patients receiving TOBI achieved sputum concentrations 10 fold the highest *P. aeruginosa* MIC cultured from the patient, and 95% of patients receiving TOBI achieved 25 fold the highest MIC. Clinical benefit is still achieved in a majority of patients who culture strains with MIC values above the parenteral breakpoint.

Susceptibility
In the absence of conventional susceptibility breakpoints for the nebulised route of administration, caution must be exercised in defining organisms as susceptible or insusceptible to nebulised tobramycin. However, the TOBI clinical studies showed that a microbiological report indicating in vitro drug resistance did not necessarily preclude a clinical benefit for the patient.

Most patients with *P. aeruginosa* isolates with tobramycin MICs <128 microgram/mL at baseline showed improved lung function following treatment with TOBI. Patients with a *P. aeruginosa* isolate with a MIC ≥ 128 microgram/mL at baseline are less likely to show a clinical response. However, seven of 13 patients (54%) in the placebo-controlled trials who acquired isolates with MICs of ≥ 128 microgram/mL while using TOBI had improvement in pulmonary function.
Over the entire 96 week duration of the extension studies, the tobramycin MIC50 for *P. aeruginosa* increased from 1 to 2 microgram/mL and the MIC90 increased from 8 to 32 microgram/mL.

Based upon *in vitro* data and/or clinical trial experience, the organisms associated with pulmonary infections in CF may be expected to respond to TOBI therapy as follows:

Susceptible	*Pseudomonas aeruginosa* *Haemophilus influenzae* *Staphylococcus aureus*
Insusceptible	*Burkholderia cepacia* *Stenotrophomonas maltophilia* *Alcaligenes xylosoxidans*

Treatment with the TOBI regimen in clinical studies showed a small but clear increase in tobramycin, amikacin and gentamicin Minimum Inhibitory Concentrations for *P. aeruginosa* isolates tested. Each additional 6 months of treatment resulted in incremental increases similar in magnitude to that observed in the 6 months of controlled studies. The most prevalent aminoglycoside resistance mechanism seen in *P. aeruginosa* isolated from chronically infected CF patients is impermeability, defined by a general lack of susceptibility to all aminoglycosides. *P. aeruginosa* isolated from CF patients has also been shown to exhibit adaptive aminoglycoside resistance that is characterised by a reversion to susceptibility when the antibiotic is removed.

Other Information
There is no evidence that patients treated with up to 18 months of TOBI were at a greater risk for acquiring B. *cepacia, S. maltophilia* or *A. xylosoxidans*, than would be expected in patients not treated with TOBI. *Aspergillus* species were more frequently recovered from the sputum of patients who received TOBI; however, clinical sequelae such as Allergic Bronchopulmonary Aspergillosis (ABPA) were reported rarely and with similar frequency as in the control group.

There are insufficient clinical safety and efficacy data in children < 6 years of age.

In an open-label uncontrolled study, 88 patients with CF (37 patients between 6 months and 6 years, 41 patients between 6 and18 years of age and 10 patients above 18 years of age) with early (non-chronic) *P aeruginosa* infection were treated for 28 days with TOBI. After 28 days, patients were randomised 1:1 to either stop (n=45) or to receive a further 28 days treatment (n=43).
Primary outcome was the median time to recurrence of *P aeruginosa* (any strain) which was 26.1 and 25.8 months for the 28-day and 56-day groups, respectively. It was found that 93% and 92% of the patients were free of *P aeruginosa* infection 1 month after the end of treatment in the 28-day and 56-day groups, respectively. The use of TOBI with a dosing regimen longer than 28 days continuous treatment is not approved.

In a double-blind, randomized, placebo-controlled trial, 51 patients aged 3 months to less than 7 years with a confirmed diagnosis of CF and an early colonization with *P. aeruginosa* (defined as: either first positive culture overall or first positive culture after at least a 1-year history of negative cultures) were treated with TOBI 300 mg/5 mLor placebo, both inhaled via a nebuliser (PARI LC Plus®) twice daily for 28 days. Patients who were treated with anti-pseudomonal therapy in the previous year were excluded. A total of 26 patients were randomized to receive TOBI and 25 patients to placebo. The primary outcome was based on the proportion of patients free from *P. aeruginosa* colonization assessed by sputum/throat swab culture after completion of a 28-day treatment period which was 84.6% (22 out of 26 patients) for the TOBI group and 24% (6 out of 25 patients) for the placebo group ($p<0.001$).
The frequency, type and severity of the observed adverse events in children < 7 years of age were consistent with the known safety profile of TOBI.
The use of TOBI is not indicated in children < 6 years of age (see section 4.2 Posology and method of administration).

Clinical efficacy

Two identically designed, double-blind, randomized, placebo-controlled, parallel group, 24-week clinical studies (Study 1 and Study 2) were conducted in cystic fibrosis patients with P. aeruginosa to support original registration which took place in 1999. These studies enrolled 520 subjects who had a baseline FEV1 of between 25% and 75% of their predicted normal value. Patients who were less than six years of age, or who had a baseline creatinine of > 2 mg/dL, or who had Burkholderia cepacia isolated from sputum were excluded. In these clinical studies, 258 patients received TOBI therapy on an outpatient basis using a hand-held PARI LC PLUS™ Reusable Nebulizer with a DeVilbiss® Pulmo-Aide® compressor.
In each study, TOBI-treated patients experienced significant improvement in pulmonary function and significant reduction in the number of *P. aeruginosa* colony forming units (CFUs) in sputum during the on-drug periods. The mean FEV_1 remained above baseline in the 28-day off-drug periods, although it reversed somewhat on most occasions. Sputum bacterial density returned to baseline during the off-drug periods. Reductions in sputum bacterial density were smaller in each successive cycle. Patients treated with TOBI experienced fewer hospitalization days and required fewer days of parenteral anti-pseudomonal antibiotics on average, compared with placebo patients.

In open label extensions to the studies 1 and 2, there were 396 patients of the 464 who completed either of the two 24 week double blind studies. In total, 313, 264 and 120 patients completed treatment with TOBI for 48, 72 and 96 weeks respectively. The rate of lung function decline was significantly lower following initiation of TOBI therapy than that observed among patients receiving placebo during the double blind randomized treatment period. The estimated slope in the regression model of lung function decline was -6.52% during the blinded placebo treatment and -2.53% during TOBI treatment ($p=0.0001$).

5.2 Pharmacokinetic properties

Absorption
Tobramycin is acatinic polar molecule that does not readily cross epithelial membranes. The systemic exposure to tobramycin after inhalation of TOB I 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 TOBI may vary because of individusl differences in nebulizer performance and airway pathology.

Sputum concentrations:
Ten minutes after inhalation of the first 300 mg dose of TOBI, the average sputum concentration of tobramycin was 1,237 microgram/g (range: 35 to 7,414 microgram/g). Tobramycin does not accumulate in sputum; after 20 weeks of therapy with the TOBI regimen, the average sputum concentration of tobramycin 10 minutes after inhalation was 1,154 microgram/g (range: 39 to 8,085 microgram/g). High variability of sputum tobramycin concentrations was observed. Two hours after inhalation, sputum concentrations declined to approximately 14% of tobramycin levels measured at 10 minutes after inhalation.

Serum concentrations:
The mean serum concentration of tobramycin 1 hour after inhalation of a single 300 mg dose of TOBI by CF patients was 0.95 microgram/mL (range: below limit of quantitation [BLQ] – 3.62 microgram/mL). After 20 weeks of therapy on the TOBI regimen, the mean serum tobramycin concentration 1 hour after dosing was 1.05 microgram/mL (range: BLQ- 3.41microgram/mL).For comparison. the peak concentrations after intravenous or intramuscular administration of a single tobramycin dose of 1.5 to 2mg/kg typically range from 4 to 12 microgram/mL.

Distribution
Following administration of TOBI, tobramycin remains concentrated primarily in the airways. Less than 10% of tobramycin is bound to plasma proteins.

Biotransformation

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

Elimination

The elimination of tobramycin administered by the inhalation route has not been studied.
Following intravenous administration, tobramycin is eliminated principally by glomerular filtration of the unchanged compound. The apparent terminal half-life of tobramycin in serum after inhalation of a 300mg single dose of TOBI was 3 hours in cystic fibrosis patients.

Renal function is expected to affect the exposure to tobramycin, however data are not available as patients with serum creatinine 2 mg/dL (176,8 micromol/L) or more or blood urea nitrogen (BUN) 40 mg/dL or more were not included in clinical studies.

Unabsorbed tobramycin following TOBI administration is probably eliminated primarily in expectorated sputum.

5.3 Preclinical safety data

Nonclinical data reveal that the main hazard for humans, based on studies of safety pharmacology, repeated dose toxicity, genotoxicity, or toxicity to reproduction, consists of renal toxicity and ototoxicity. In repeated dose toxicity studies, target organs of toxicity are the kidneys and vestibular/cochlear functions. In general, toxicity is seen at higher systemic tobramycin levels than are achievable by inhalation at the recommended clinical dose.
Carcinogenicity studies with inhaled tobramycin do not increase the incidence of any variety of tumour. Tobramycin showed no genotoxic potential in a battery of genotoxicity tests.
No reproduction toxicology studies have been conducted with tobramycin administered by inhalation, but subcutaneous administration at doses of 100 mg/kg/day in rats and the maximum tolerated dose of 20 mg/kg/day in rabbits, during organogenesis, was not teratogenic. Teratogenicity could not be assessed at higher parenteral doses (greater than or equal to 40mg/kg/day) in rabbits as they induced maternal toxicity and abortion. Ototoxicity was not evaluated in offspring during nonclinical reproduction toxicity studies with tobramycin. Based on available data from animals a risk of toxicity (e.g. ototoxicity) at prenatal exposure levels cannot be excluded.
Subcutaneous administration of up to 100 mg/kg of tobramycin did not affect mating behaviour or cause impairment of fertility in male or female rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Sulphuric acid and sodium hydroxide for pH adjustment

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with any other medicinal product in the nebuliser.

6.3 Shelf life

3 years.

For single use. The contents of the whole ampoule should be used immediately after opening (see section 6.6).
Discard any remaining contents.

6.4 Special precautions for storage

Store under refrigeration at 2-8°C. Store in the original package in order to protect from light.
After removal from the refrigerator, or if refrigeration is unavailable, TOBI pouches (intact or opened) may be stored at up to 25°C for up to 28 days.

TOBI solution is normally slightly yellow, but some variability in colour may be observed, which does not indicate loss of activity if the product has been stored as recommended.

6.5 Nature and contents of container

TOBI is supplied in 5 ml single-use low density polyethylene ampoules. One outer carton contains a total of 56, 112 or 168 ampoules comprising 4, 8 or 12 sealed foil pouches, respectively. Each foil pouch contains 14 ampoules packed in a plastic tray.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

TOBI is a sterile, non-pyrogenic, aqueous preparation for single use only. As it is preservative-free, the contents of the whole ampoule should be used immediately after opening and any unused solution discarded. Opened ampoules should never be stored for re-use.

7 MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23355/045/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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