SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tymbrineb 300 mg/5 mL Nebuliser Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 5 ml contains 300 mg tobramycin as a single dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.

Clear to slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tymbrineb Nebuliser Solution 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

Tymbrineb Nebuliser Solution is for inhalation use and is not intended 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 tobramycin 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 tobramycin 300 mg twice daily.

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

Tymbrineb Dosing Regimen in Controlled Clinical Studies

Cycle 1		**Cycle 2**		**Cycle 3**	
28 days	28 days	28 days	28 days	28 days	28 days
Tymbrineb 300 mg twice daily plus standard care	Standard care only	Tymbrineb 300 mg twice daily plus standard care	Standard care only	Tymbrineb 300 mg twice daily plus standard care	Standard care only

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, in patients with forced expiratory volume in 1 second (FEV_1) <25% or >75% predicted, or in patients colonised with *Burkholderia cepacia*.

Therapy should be initiated by a physician experienced in the management of cystic fibrosis. Tobramycin treatment should be continued on a cyclical basis for as long as the physician considers the patient is gaining clinical benefit from the inclusion of tobramycin in their treatment regimen. If clinical deterioration of the 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 tobramycin. 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 metabolised, 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 in patients after organ transplantation.

Paediatric population

The safety and efficacy of tobramycin 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.

Tobramycin 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 tobramycin.

Maximum tolerated daily dose
The maximum tolerated daily dose of tobramycin has not been established.

4.3 Contraindications

Hypersensitivity to the active substance, or any other aminoglycoside or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General warnings
For information on fertility, pregnancy and lactation, see section 4.6.

Tobramycin 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 tobramycin concentrations

Serum tobramycin concentrations should be monitored in patients with known or suspected auditory or renal dysfunction. If oto- or nephrotoxicity occurs in a patient receiving Tymbrineb, therapy should be discontinued until serum concentration falls below 2 µg/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 tobramycin 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, Tymbrineb should be discontinued. Bronchospasm should be treated as medically appropriate.

Neuromuscular disorders

Tymbrineb 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

Nephrotoxicity has been reported with the use of parenteral aminoglycosides. Nephrotoxicity was not observed during clinical trials with tobramycin, however acute kidney injury (AKI) has been reported post-marketing with the use of inhaled tobramycin (see section 4.8).

This medicinal 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 µmol/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 tobramycin therapy (180 days of nebulised aminoglycoside therapy).

See also “Monitoring of serum tobramycin 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 tobramycin 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 tobramycin therapy. In patients with a predisposing risk of ototoxicity due to previous prolonged, systemic aminoglycoside therapy, it may be necessary to consider audiological assessment before initiating tobramycin therapy. The onset of tinnitus warrants caution as it is a sentinel symptom of ototoxicity.

Caution should be exercised when prescribing tobramycin 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. 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 tobramycin 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 tobramycin 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.

In clinical studies, patients taking tobramycin 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 tobramycin 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. Tobramycin 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

Tymbrineb 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 section 5.3). However, aminoglycosides can cause foetal harm (e.g. congenital

deafness) when high systemic concentrations are achieved in a pregnant woman. If tobramycin is used during pregnancy, or if the patient becomes pregnant while using tobramycin, she should be informed of the potential hazard to the foetus.

Breast-feeding
Systemic tobramycin is excreted in breast milk. It is not known whether inhaled tobramycin will result in serum concentrations high enough 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 breast-feeding or discontinue tobramycin 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

Tymbrineb has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Two parallel, 24-week, randomised, double-blind, placebo-controlled clinical studies were conducted with tobramycin 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 tobramycin 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 tobramycin; (12.8% tobramycin vs. 6.5% placebo) and (3.1% tobramycin vs. 0% placebo) respectively. These episodes of tinnitus were transient and resolved without discontinuation of tobramycin 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 tobramycin (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 tobramycin 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 tobramycin, occurring at a higher rate in the Tymbrineb 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 using the following convention (CIOMS III) is also provided for each adverse drug reaction: 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); not known (cannot be estimated from the available data) including isolated reports.

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
Renal and urinary disorders	
Acute kidney injury (AKI)	Not known
General disorders and administration site conditions	
Malaise	Common
Investigations	
Pulmonary function test decreased	Very common

As the duration of exposure to tobramycin 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 tobramycin: 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 isnot 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

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 section 4.4). Parenteral aminoglycosides have been associated with hypersensitivity, ototoxicity and nephrotoxicity (see sections 4.3 and 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 Tymbrineb Nebuliser Solution, toxicity is unlikely as tobramycin is poorly absorbed from an intact gastrointestinal tract.

In the event of inadvertent administration of Tymbrineb Nebuliser Solution 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 tobramycin 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 tobramycin 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 around 10 and 25-fold above the Minimum Inhibitory Concentration (MIC) for, respectively, *P. aeruginosa* growth suppression and bactericidal activity. In controlled clinical trials, 97% of patients receiving inhaled tobramycin achieved sputum concentrations 10 fold the highest *P. aeruginosa* MIC cultured from the patient and 95% of patients receiving inhaled tobramycin 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, 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 µg/mL at baseline showed improved lung function following treatment with inhaled tobramycin. Patients with a *P. aeruginosa* isolate with a MIC ≥128 µg/mL at baseline are less likely to show a clinical response. However, 7 of 13 patients (54%) in the placebo-controlled trials who acquired isolates with MICs ≥128 µg/mL while using inhaled tobramycin 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 µg/mL and the MIC90 increased from 8 to 32 µg/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 inhaled tobramycin therapy as follows:

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

In clinical studies, treatment with inhaled tobramycin showed a small but clear increase in tobramycin, amikacin and gentamycin MIC 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 for up to 18 months with inhaled tobramycin were at a greater risk for acquiring *B. cepacia, S. maltophilia* or *A. xylosoxidans,* than would be expected in patients not treated with tobramycin. *Aspergillus* species were more frequently recovered from the sputum of patients who received tobramycin; 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 and 18 years of age and 10 patients above 18 years of age) with early (non-chronic) *P. aeruginosa* infection were treated for 28 days with tobramycin. 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 tobramycin 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 tobramycin 300 mg/5 mL or 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 tobramycin and 25 patients to placebo. The primary outcome was based on the proportion of patients free from *P. aeruginosa* colonisation 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 tobramycin 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 tobramycin.
The use of tobramycin 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, randomised, 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 tobramycin therapy on an outpatient basis using a hand-held PARI LC PLUS™ Reusable Nebuliser with a DeVilbiss® Pulmo-Aide® compressor.

In each study, tobramycin-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 FEV1 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 tobramycin experienced fewer hospitalisation 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 tobramycin for 48, 72 and 96 weeks respectively. The rate of lung function decline was significantly lower following initiation of tobramycin therapy than that observed among patients receiving placebo during the double blind randomised 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 tobramycin treatment (p=0.0001).

5.2 Pharmacokinetic properties

Absorption

Tobramycin is a cationic polar molecule that does not readily cross epithelial membranes. 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 may vary because of individual differences in nebuliser performance and airway pathology.

Sputum concentrations

Ten minutes after the first inhalation of tobramycin 300 mg, the average sputum concentrations of tobramycin was 1,237 µg/g (range: 35 to 7,414 µg/g). Tobramycin does not accumulate in sputum; after 20 weeks of therapy with the tobramycin regimen, the average sputum concentration of tobramycin 10 minutes after inhalation was 1,154 µg/g (range: 39 to 8,085 µg/g). High variability of sputum tobramycin concentrations was observed. Two hours after inhalation, sputum concentration declined to approximately 14% of the 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 tobramycin by CF patients, was 0.95 µg/mL (range: below limit of quantitation [BLQ] - 3.62 µg/mL). After 20 weeks of therapy, the mean serum tobramycin concentration, 1 hour after dosing, was 1.05 µg/mL (range: BLQ - 3.41 µg/mL). For comparison, the peak concentrations after intravenous or intramuscular administration of a single tobramycin dose of 1.5 to 2 mg/kg typically range from 4 to 12 µg/mL.

Distribution

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

Biotransformation
Tobramycin is not metabolised 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 300 mg single dose of tobramycin 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 µmol/L) or more or blood urea nitrogen (BUN) 40 mg/dL or more were not included in clinical studies.

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

5.3 Preclinical safety data

Pre-clinical 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 40 mg/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
Sulfuric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

3 years

The foil pouches (intact or opened) may be stored at up to 25 °C for up to 28 days.

The contents of the whole ampoule should be used immediately after opening (see section 6.6).

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Store in the original package in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

Tymbrineb solution may be slightly yellow and some variability in colour may be observed; this does not indicate loss of activity providing the solution has been stored as recommended.

6.5 Nature and contents of container

Tymbrineb Nebuliser Solution is supplied in 5 mL single-dose low density polyethylene ampoules.

4 ampoules are packed and sealed in a foil pouch. Each carton comprises 14 (56 ampoules), 28 (112 ampoules) or 42 (168 ampoules) foil pouches.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product 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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited,

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WF10 5HX,

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1437

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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