SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TOBI Podhaler 28 mg inhalation powder, hard capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 28 mg tobramycin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder, hard capsule

Clear colourless capsules containing a white to almost white powder, with "MYL TPH" printed in blue on one part of the capsule and Mylan logo printed in blue on the other part of the capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TOBI Podhaler is indicated for the suppressive therapy of chronic pulmonary infection due to *Pseudomonas aeruginosa* in adults and children aged 6 years and older with cystic fibrosis.

4.2 Posology and method of administration

Posology

The dose of TOBI Podhaler is the same for all patients within the approved age range, regardless of age or weight. The recommended dose is 112 mg tobramycin (4 x 28 mg capsules), administered twice daily for 28 days. TOBI Podhaler is taken in alternating cycles of 28 days on treatment followed by 28 days off-treatment. The two doses (of 4 capsules each) should be inhaled as close as possible to 12 hours apart and not less than 6 hours apart.

Missed doses

In case of missed dose with at least 6 hours until the next dose, the patient should take the dose as soon as possible. Otherwise, the patient should wait for the next dose and not inhale more capsules to make up for the missed dose.

Duration of treatment

Treatment with TOBI Podhaler should be continued on a cyclical basis for as long as the physician considers the patient is gaining clinical benefit from the treatment with TOBI Podhaler taking into account that long-term safety data are not available for TOBI Podhaler. If clinical deterioration of pulmonary status is evident, additional or alternative anti-pseudomonal therapy should be considered. See also information on clinical benefit and tolerability in sections 4.4, 4.8 and 5.1.

Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with FEV1 (Forced Expiratory Volume in 1 second) <25% or >75% predicted, or patients colonized with Burkholderia cepacia.

Special populations

Elderly patients (≥ 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 TOBI Podhaler (see section 4.8).

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 2 mg/dL or more and blood urea nitrogen (BUN) 40 mg/dL 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 TOBI Podhaler. Caution should be exercised when prescribing TOBI Podhaler to patients with known or suspected renal dysfunction.

Please also refer to nephrotoxicity information in section 4.4.

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 Podhaler in patients after organ transplantation.

Paediatric population

The safety and efficacy of TOBI Podhaler in children aged under 6 years have not been established.

No data are available.

Method of administration

Inhalation use.

TOBI Podhaler is administered by inhalation using the Podhaler device (see section 6.6 for detailed instructions for use). It must not be administered by any other route or using any other inhaler.

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

TOBI Podhaler capsules must not be swallowed. Each TOBI Podhaler capsule should be inhaled with two breath-hold manoeuvres and checked to ensure it is empty.

Where patients are receiving several different inhaled medicinal products and chest physiotherapy, it is recommended that TOBI Podhaler is taken last.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Ototoxicity

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

Hearing loss and tinnitus were reported by patients in the TOBI Podhaler clinical studies (see section 4.8). Caution should be exercised when prescribing TOBI Podhaler to patients with known or suspected auditory or vestibular dysfunction.

In patients with any evidence of auditory dysfunction, or those with a predisposing risk, it may be necessary to consider audiological assessment before initiating TOBI Podhaler therapy.

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 TOBI Podhaler therapy the physician should consider referring them for audiological assessment.

See also “Monitoring of serum tobramycin concentrations” below.

Nephrotoxicity

Nephrotoxicity has been reported with the use of parenteral aminoglycosides. Nephrotoxicity was not observed during TOBI Podhaler clinical studies. Caution should be exercised when prescribing TOBI Podhaler to patients with known or suspected renal dysfunction.

Baseline renal function should be assessed. Urea and creatinine levels should be reassessed after every 6 complete cycles of TOBI Podhaler therapy.

See also section 4.2 and “Monitoring of serum tobramycin concentrations” below.

Monitoring of serum tobramycin concentrations

Patients with known or suspected auditory or renal dysfunction should be monitored for serum tobramycin concentrations. If oto- or nephrotoxicity occurs in a patient receiving TOBI Podhaler, tobramycin therapy should be discontinued until serum concentration falls below 2 μg/ml.

Serum concentrations greater than 12 μg/ml are associated with tobramycin toxicity and treatment should be discontinued if concentrations exceed this level.

The serum concentration of tobramycin should only be monitored through validated methods. Finger prick blood sampling is not recommended due to the risk of contamination of the sample.

Bronchospasm
Bronchospasm can occur with inhalation of medicinal products and has been reported with TOBI Podhaler in clinical studies. Bronchospasm should be treated as medically appropriate.

The first dose of TOBI Podhaler should be given under supervision, after using a bronchodilator if this is part of the current regimen for the patient. FEV_1 should be measured before and after inhalation of TOBI Podhaler.

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

Cough

Cough was reported with use of TOBI Podhaler in clinical studies. Based on clinical trial data the inhalation powder TOBI Podhaler was associated with a higher reported rate of cough compared with tobramycin nebuliser solution (TOBI). Cough was not related to bronchospasm. Children below the age of 13 years may be more likely to cough when treated with TOBI Podhaler compared with older subjects.

If there is evidence of continued therapy-induced cough with TOBI Podhaler, the physician should consider whether an approved tobramycin nebuliser solution should be used as an alternative treatment. Should cough remain unchanged, other antibiotics should be considered.

Haemoptysis

Haemoptysis is a complication in cystic fibrosis and is more frequent in adults. Patients with haemoptysis (>60 ml) were excluded from the clinical studies so no data exist on the use of TOBI Podhaler in these patients. This should be taken into account before prescribing TOBI Podhaler, considering the inhalation powder TOBI Podhaler was associated with a higher rate of cough (see above). The use of TOBI Podhaler in patients with clinically significant haemoptysis should be undertaken or continued only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.

Other precautions

Patients receiving concomitant parenteral aminoglycoside therapy (or any medication affecting renal excretion, such as diuretics) should be monitored as clinically appropriate taking into account the risk of cumulative toxicity. This includes monitoring of serum concentrations of tobramycin. 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 TOBI Podhaler therapy.

See also “Monitoring of serum tobramycin concentrations” above.

Caution should be exercised when prescribing TOBI Podhaler to patients with known or suspected neuromuscular disorders such as myasthenia gravis or Parkinson’s disease. Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.

The development of antibiotic-resistant *P. aeruginosa* and superinfection with other pathogens represent potential risks associated with antibiotic therapy. In clinical studies, some patients on TOBI Podhaler therapy showed an increase in aminoglycoside minimum inhibitory concentrations (MIC) for *P. aeruginosa* isolates tested. MIC increases observed were in large part reversible during off treatment periods.

There is a theoretical risk that patients being treated with TOBI Podhaler may develop *P. aeruginosa* isolates resistant to intravenous tobramycin over time (see section 5.1). Development of resistance during inhaled tobramycin therapy could limit treatment options during acute exacerbations; this should be monitored.

Data in different age groups

In a 6-month (3 treatment cycles) study of TOBI Podhaler versus tobramycin nebuliser solution, which included a majority of tobramycin-experienced adult patients with chronic pulmonary *P. aeruginosa* infection, the suppression of sputum *P. aeruginosa* density was similar across age groups in both arms; however the increase from baseline FEV_1 was larger in younger age groups (6 - <20) than in the adult subgroup (20 years and older) in both arms. See also section 5.1 for the profile of response of TOBI Podhaler compared to tobramycin nebuliser solution. Adult patients tended to discontinue more frequently for tolerability reasons with TOBI Podhaler than with the nebuliser solution. See also section 4.8.

If clinical deterioration of pulmonary status is evident, additional or alternative anti-pseudomonal therapy should be considered.

Observed benefits on lung function and *P. aeruginosa* suppression should be assessed in the context of the patient's tolerance of TOBI Podhaler.

Safety and efficacy have not been studied in patients with forced expiratory volume in 1 second (FEV_1) <25% or >80% predicted, or patients colonised with *Burkholderia cepacia*.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with TOBI Podhaler. Based on the interaction profile for tobramycin following intravenous and aerosolised administration, concurrent and/or sequential use of TOBI Podhaler is not recommended with other medicinal products with nephrotoxic or ototoxic potential.

Concomitant use of TOBI Podhaler with diuretic compounds (such as ethacrynic acid, furosemide, urea or intravenous mannitol) is not recommended. Such compounds can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

See also information on previous and concomitant use of systemic aminoglycosides and diuretics in section 4.4.

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).

In clinical studies, patients receiving TOBI Podhaler continued to take dornase alfa, bronchodilators, inhaled corticosteroids and macrolides, no evidence of drug interactions with these medicines was identified.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of tobramycin via inhalation in pregnant women. Animal studies with tobramycin do not indicate a teratogenic effect (see section 5.3). However, aminoglycosides can cause foetal harm (e.g. congenital deafness) when high systemic concentrations are achieved in a pregnant woman. Systemic exposure following inhalation of TOBI Podhaler is very low, however TOBI Podhaler should not be used during pregnancy unless

clearly necessary, i.e. when the benefits to the mother outweigh the risks to the foetus. Patients who use TOBI Podhaler during pregnancy, or become pregnant while taking TOBI Podhaler, should be informed of the potential hazard to the foetus.

Breast-feeding

Tobramycin is excreted in human breast milk after systemic administration. The amount of tobramycin excreted in human breast milk after administration by inhalation is not known, though it is estimated to be very low considering the low systemic exposure. Because of the potential for ototoxicity and nephrotoxicity in infants, a decision should be made whether to terminate breast-feeding or discontinue treatment with TOBI Podhaler, taking into account the importance of the treatment to the mother.

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

TOBI Podhaler has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in the main safety, active-controlled clinical study with TOBI Podhaler versus tobramycin nebuliser solution in cystic fibrosis patients with *P. aeruginosa* infection were cough, productive cough, pyrexia, dyspnoea, oropharyngeal pain, dysphonia and haemoptysis.

In the placebo-controlled study with TOBI Podhaler, the adverse reactions for which reported frequency was higher with TOBI Podhaler than with placebo were pharyngolaryngeal pain, dysgeusia and dysphonia.

The vast majority of adverse reactions reported with TOBI Podhaler were mild or moderate, and severity did not appear to differ between cycles or between the entire study and on-treatment periods.

Tabulated summary of adverse reactions

Adverse drug reactions in Table 1 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); not known: frequency cannot be estimated from the available data.

The frequencies in Table 1 are based on the reporting rates from the active-controlled study.

Table 1 Adverse reactions

Adverse reactions	Frequency category
Ear and labyrinth disorders	
Hearing loss	Common
Tinnitus	Common

Vascular disorders	
Haemoptysis	Very common
Epistaxis	Common
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	Very common
Dysphonia	Very common
Productive cough	Very common
Cough	Very common
Wheezing	Common
Rales	Common
Chest discomfort	Common
Nasal congestion	Common
Bronchospasm	Common
Aphonia	Common
Sputum discoloured	Not known
Gastrointestinal disorders	
Oropharyngeal pain	Very common
Vomiting	Common
Diarrhoea	Common
Throat irritation	Common
Nausea	Common
Dysgeusia	Common
Skin and subcutaneous tissue disorders	
Rash	Common
Musculoskeletal, connective tissue and bone disorders	
Musculoskeletal chest pain	Common
General disorders and administration site conditions	
Pyrexia	Very common
Malaise	Not known

Description of selected adverse drug reactions

Cough was the most frequently reported adverse reaction in both clinical studies. However, no association was observed in either clinical study between the incidence of bronchospasm and cough events.

In the active-controlled study, audiology testing was performed in selected centres accounting for about a quarter of the study population. Four patients in the TOBI Podhaler treatment group experienced significant decreases in hearing which were transient in three patients and persistent in one case.

In the active-controlled open-label study, patients aged 20 years and older tended to discontinue more frequently with TOBI Podhaler than with the nebuliser solution; discontinuations due to adverse events accounted for about half of the discontinuations with each formulation. In children under 13 years of age, discontinuations were more frequent in the TOBI nebuliser solution arm whereas in patients aged 13 to 19, discontinuation rates with both formulations were similar.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

4.9 Overdose

Adverse reactions specifically associated with overdose of TOBI Podhaler have not been identified.

The maximum tolerated daily dose of TOBI Podhaler has not been established. Tobramycin serum concentrations may be helpful in monitoring overdosage. In case of signs of acute toxicity, immediate withdrawal of TOBI Podhaler and testing of renal function are recommended.

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

Hemodialysis may be helpful in removing tobramycin from the body.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, 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.

Sputum from cystic fibrosis exhibits an inhibitory action on the local biological activity of inhaled aminoglycosides. This necessitates sputum concentrations of tobramycin after inhalation to be about ten-fold above the minimum inhibitory concentration (MIC) or higher for *P. aeruginosa* suppression. In the active-controlled study, at least 89% of patients had *P. aeruginosa* isolates with MICs at least 15 times lower than mean post-dose sputum concentration, both at baseline and at the end of the third active treatment cycle.

Susceptibility

In the absence of conventional susceptibility breakpoints for the inhaled route of administration, caution must be exercised in defining organisms as susceptible or insusceptible to inhaled tobramycin.

The clinical significance of changes in MICs of tobramycin for *P. aeruginosa* has not been clearly established in the treatment of cystic fibrosis patients. Clinical studies with inhaled tobramycin solution (TOBI) have shown a small increase in tobramycin, amikacin and gentamicin Minimum Inhibitory Concentrations for *P. aeruginosa* isolates tested. In the open label extensions, each additional 6 months of treatment resulted in incremental increases similar in magnitude to that observed in the 6 months of placebo-controlled studies.

Resistance to tobramycin involves different mechanisms. The main resistance mechanisms are drug efflux and drug inactivation by modifying enzymes. The unique characteristics of chronic *P.*

aeruginosa infections in CF patients, such as anaerobic conditions and high frequency of genetic mutations, may also be important factors for reduced susceptibility of *P. aeruginosa* in CF patients.

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 Podhaler therapy as follows:

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

Clinical experience

The TOBI Podhaler Phase III clinical development program consisted of two studies and 612 treated patients with a clinical diagnosis of CF, confirmed by quantitative pilocarpine iontophoresis sweat chloride test or well-characterised disease causing mutations in each cystic fibrosis transmembrane regulator (CFTR) gene, or abnormal nasal transepithelial potential difference characteristic of CF.

In the placebo controlled study, patients were aged 6 - ≤22 years with an FEV_1 at screening of between 25% and 84% of predicted normal values for their age, sex and height based upon Knudson criteria. In the active controlled studies, all patients were aged >6 years old (range 6-66 years) with an FEV_1 % predicted at screening of between 24% and 76%. In addition, all patients were infected with *P. aeruginosa* as demonstrated by a positive sputum or throat culture (or bronchoalveolar lavage) within 6 months prior to screening, and also in a sputum culture taken at the screening visit.

In a randomised, double-blind, placebo-controlled, multicentre study, TOBI Podhaler 112 mg (4 x 28 mg capsules) was administered twice daily, for three cycles of 28 days on-treatment and 28 days off-treatment (a total treatment period of 24 weeks). Patients who were randomised to the placebo treatment group received placebo during the first treatment cycle and TOBI Podhaler in the subsequent two cycles. Patients in this study had no exposure to inhaled tobramycin for at least 4 months prior to study start.

TOBI Podhaler significantly improved lung function compared with placebo, as shown by the relative increase in percent predicted FEV_1 of about 13% after 28 days of treatment. The improvements in lung function achieved during the first treatment cycle were maintained during the two subsequent cycles of treatment with TOBI Podhaler.

When patients in the placebo treatment group were switched from placebo to TOBI Podhaler at the start of the second treatment cycle, they experienced a similar improvement from baseline in percent predicted FEV_1. Treatment with TOBI Podhaler for 28 days resulted in a statistically significant reduction in *P. aeruginosa* sputum density (mean difference with placebo about 2.70 $\log_{10}$ in colony forming units/CFUs).

In a second open-label, multicentre study, patients received treatment with either TOBI Podhaler (112 mg) or tobramycin 300 mg/5 ml nebuliser solution (TOBI), administered twice daily for three cycles. A majority of the patients were tobramycin-experienced adults with chronic pulmonary *P. aeruginosa* infection.

Treatment with both TOBI Podhaler and tobramycin 300 mg/5 ml nebuliser solution (TOBI) resulted in relative increases from baseline to day 28 of the third treatment cycle in percent

predicted FEV_1 of 5.8% and 4.7%, respectively. The improvement in percent predicted FEV_1 was numerically greater in the TOBI Podhaler treatment group and was statistically non-inferior to TOBI nebuliser solution. Although the magnitude of improvements in lung function was smaller in this study, this is explained by the previous exposure of this patient population to treatment with inhaled tobramycin. Over half of the patients in both the TOBI Podhaler and TOBI nebuliser solution treatment groups received new (additional) anti-pseudomonal antibiotics (64.9% and 54.5% respectively, the difference consisting mainly of oral ciprofloxacin use). The proportions of patients requiring hospitalisation for respiratory events were 24.4% with TOBI Podhaler and 22.0% with TOBI nebuliser solution.

A difference in FEV_1 response by age was noted. In the patients aged <20 years the increase from baseline percent predicted FEV_1 was larger: 11.3% for TOBI Podhaler and 6.9% for the nebuliser solution after 3 cycles. A numerically lower response in patients aged ≥20 years was observed: the change from baseline FEV_1 observed in the patients aged ≥20 years was smaller (0.3% with TOBI Podhaler and 0.9% with TOBI nebuliser solution).

Furthermore, an improvement of 6% in percent predicted FEV_1 was obtained in about 30% versus 36% of the adult patients in the TOBI Podhaler and TOBI nebuliser solution group respectively.

Treatment with TOBI Podhaler for 28 days resulted in a statistically significant reduction in *P. aeruginosa* sputum density (-1.61 log10 CFUs), as did the nebuliser solution (-0.77 $\log_{10}$ CFUs). Suppression of sputum *P. aeruginosa* density was similar across age groups in both arms. In both studies, there was a trend for a recovery of *P. aeruginosa* density after the 28 days off-treatment period, which was reversed after a further 28 days on-treatment.

In the active-controlled study, administration of a TOBI Podhaler dose was faster with a mean difference of approximately 14 minutes (6 minutes vs. 20 minutes with the nebuliser solution). Patient-reported convenience and overall treatment satisfaction (as collected through a patient-reported outcomes questionnaire) were consistently higher with TOBI Podhaler compared with tobramycin nebuliser solution in each cycle.

For safety results see section 4.8.

Paediatric population

See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

The systemic exposure to tobramycin after inhalation of TOBI Podhaler is expected to be primarily from the inhaled portion of the medicinal product as tobramycin is not absorbed to any appreciable extent when administered via the oral route.

Serum concentrations

After inhalation of a 112 mg single dose (4 x 28 mg capsules) of TOBI Podhaler in cystic fibrosis patients, the maximum serum concentration (C_{max}) of tobramycin was 1.02 ± 0.53 µg/ml (mean ± SD) and the median time to reach the peak concentration (T_{max}) was one hour. In comparison, after inhalation of a single dose of tobramycin 300 mg/5 ml nebuliser solution (TOBI), C_{max} was 1.04 ± 0.58 µg/ml and median T_{max} was one hour. The extent of systemic exposure (AUC) was also similar for the 112 mg TOBI Podhaler dose and the 300 mg tobramycin nebuliser solution dose. At the end of a 4-week dosing cycle of TOBI Podhaler (112 mg twice daily), maximum serum concentration of tobramycin 1 hour after dosing was 1.99 ± 0.59 µg/ml.

Sputum concentrations

After inhalation of a 112 mg single dose (4 x 28 mg capsules) of TOBI Podhaler in cystic fibrosis patients, sputum C_{max} of tobramycin was 1047 ± 1080 µg/g (mean ± SD). In comparison, after inhalation of a single 300 mg dose of tobramycin nebuliser solution (TOBI), sputum C_{max} was 737.3 ± 1028.4 µg/g. The variability in pharmacokinetic parameters was higher in sputum as compared to serum.

Distribution

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

Biotransformation

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

Elimination

Tobramycin is eliminated from the systemic circulation primarily by glomerular filtration of the unchanged compound. The apparent terminal half-life of tobramycin in serum after inhalation of a 112 mg single dose of TOBI Podhaler was approximately 3 hours in cystic fibrosis patients and consistent with the half-life of tobramycin after inhalation of tobramycin 300 mg/5 ml nebuliser solution (TOBI).

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

5.3 Preclinical safety data

Non-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 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. However, subcutaneous administration of tobramycin during organogenesis was not teratogenic nor embryotoxic. Severely maternally toxic doses to female rabbits (i.e. nephrotoxicity) lead to spontaneous abortions and death. Based on available data from animals a risk of toxicity (e.g. ototoxicity) at prenatal exposure levels cannot be excluded.

Subcutaneous administration 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

Hypromellose, sulfuric acid, DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), purified water, carrageenan (E407), calcium chloride, potassium chloride, carnauba wax, blue ink (shellac,

indigo carmine aluminium lake (E132), N-butyl alcohol, titanium dioxide (E171), propylene glycol (E1520), isopropyl alcohol).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Discard the Podhaler device and its case 1 week after first use.

6.4 Special precautions for storage

Store below 30°C. TOBI Podhaler capsules must always be stored in the original package in order to protect from moisture and only removed immediately before use. Store the inhaler in its tightly closed case when not in use.

6.5 Nature and contents of container

The hard capsules are supplied in PVC/PA/Alu/PVC- PET/Alu blisters.

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

Pack sizes

224 (4 x 56) capsules and 5 inhalers (monthly multipack)

6.6 Special precautions for disposal and other handling

Only TOBI Podhaler capsules are to be used in the Podhaler device. No other inhaler may be used.

TOBI Podhaler capsules must always be stored in the blister (capsule card), and only removed immediately before use. Each Podhaler device and its case are used for seven days and then discarded and replaced. Store the Podhaler device in its tightly closed case when not in use.

Basic instructions for use are given below, more detailed instructions are available from the patient leaflet.

1. Wash and fully dry hands.
2. Just before use, remove the Podhaler device from its case. Briefly inspect the inhaler to make sure it is not damaged or dirty.
3. Holding the body of the inhaler, unscrew and remove the mouthpiece from the inhaler body. Set the mouthpiece aside on a clean, dry surface.
4. Separate the morning and evening doses from the capsule card.
5. Peel back the foil from the capsule card to reveal one TOBI Podhaler capsule and remove it from the card.
6. Immediately insert the capsule into the inhaler chamber. Replace the mouthpiece and screw it on firmly until it stops. Do not overtighten.
7. To puncture capsule, hold the inhaler with the mouthpiece down, press the button firmly with your thumb as far as it will go, then release the button.

8. Fully exhale away from the inhaler.
9. Place mouth over the mouthpiece creating a tight seal. Inhale the powder deeply with a single continuous inhalation.
10. Remove inhaler from mouth, and hold breath for approximately 5 seconds, then exhale normally away from the inhaler.
11. After a few normal breaths away from the inhaler, perform a second inhalation from the same capsule.
12. Unscrew mouthpiece and remove the capsule from the chamber.
13. Inspect the used capsule. It should appear punctured and empty.
    - If the capsule is punctured but still contains some powder, place it back into the inhaler and take another two inhalations from the capsule. Reinspect capsule.
    - If the capsule appears to be unpunctured, place it back into the inhaler, press the button firmly as far as it goes and take another two inhalations from the capsule. After this if the capsule is still full and appears to be unpunctured, replace the inhaler with the reserve inhaler and try again.
14. Discard the empty capsule.
15. Repeat, starting at step 5, for the remaining three capsules of the dose.
16. Replace the mouthpiece and screw it on firmly until it stops. When the full dose (4 capsules) has been inhaled, wipe mouthpiece with a clean dry cloth.
17. Place inhaler back in storage case and close tightly. The inhaler should never be washed with water.

See also section 4.2.

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

7. MARKETING AUTHORISATION HOLDER:

Dexcel Ltd.
1 Dexcel Street, Or Akiva, 3060000, Israel

8. MARKETING AUTHORISATION NUMBER

147-05-33412-00

Revised in September 2023 according to MOH guidelines.