**ANNEX I**

**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.

See sections 4.4 and 5.1 regarding data in different age groups.

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

### 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. 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.

Special populations

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

*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 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 TOBI Podhaler in patients after organ transplantation. No recommendation for or against dose adjustment can be made for 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, however acute kidney injury (AKI) has been reported post-marketing with the use of inhaled tobramycin (see section 4.8). 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 (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** | |
| Oropharnygeal pain | Very common |
| Vomiting | Common |
| Diarrhoea | Common |
| Throat irritation | Common |
| Nausea | Common |
| Dysgeusia | Common |
| **Skin and subcutaneous tissue disorders** | |
| Rash | Common |
| **Musculoskeletal and connective tissue disorders** | |
| Musculoskeletal chest pain | Common |
| **Renal and urinary disorders** | |
| Acute kidney injury (AKI) | Not known |
| **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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 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. Haemodialysis 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*<br>*Haemophilus influenzae*<br>*Staphylococcus aureus* |
| Insusceptible | *Burkholderia cepacia*<br>*Stenotrophomonas maltophilia*<br>*Alcaligenes xylosoxidans* |

Clinical experience

The TOBI Podhaler Phase III clinical development programme 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 >6years 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 $\log_{10}$ 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
The European Medicines Agency has waived the obligation to submit the results of studies with TOBI Podhaler in one or more subsets of the paediatric population in treatment of pseudomonas aeruginosa pulmonary infection/colonisation in patients with cystic fibrosis (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 litres 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 litres/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

Capsule content
1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)
Calcium chloride
Sulfuric acid (for pH adjustment)

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

4 years

Discard the Podhaler device and its case 1 week after first use.

### 6.4 Special precautions for storage

TOBI Podhaler capsules must always be stored in the blister to protect from moisture and only removed immediately before use.

### 6.5 Nature and contents of container

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

The Podhaler inhalation device and its storage case are made from plastic materials (polypropylene).

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

56 capsules and 1 inhaler
224 (4 x 56) capsules and 5 inhalers (monthly multipack)
448 (8 x 56) capsules and 10 inhalers (2 x monthly multipack wrapped in foil)

Not all pack sizes may be marketed.

## 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

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/652/001-003

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 July 2011
Date of latest renewal: 18 February 2016

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

# ANNEX II

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

McDermott Laboratories Ltd T/A Mylan Dublin Respiratory
Unit 25, Baldoyle Industrial Estate
Grange Road, Baldoyle
Dublin 13, D13 N5X2
Ireland

Mylan Germany GmbH
Zweigniederlassung Bad Homburg v. d. Hoehe
Benzstrasse 1
61352 Bad Homburg v. d. Hoehe
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON OF UNIT PACK (INCLUDING BLUE BOX)**

## 1. NAME OF THE MEDICINAL PRODUCT

TOBI Podhaler 28 mg inhalation powder, hard capsules
tobramycin

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 28 mg tobramycin.

## 3. LIST OF EXCIPIENTS

Contains 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), calcium chloride and sulphuric acid (for pH adjustment).

## 4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsules

56 capsules + 1 inhaler

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use
Read the package leaflet before use.
For use only with the inhaler provided in the pack.
Always store inhaler in its case.
Do not swallow capsules.
4 capsules = 1 dose
Lift here to open.

*(To be displayed only on the inner lid of the outer carton of unit pack)*
Read the package leaflet before use.
4 capsules = 1 dose
Do not push the capsules through the foil.
Tear the perforations along the length then width: see Figures (a) and (b).
Then peel back the foil by rolling it back from the capsule card to reveal one capsule at a time, see Figures (c) and (d). Hold the foil close to where you are rolling back.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture and only remove immediately before use.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/652/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

TOBI Podhaler

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**WEEKLY INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)**

## 1. NAME OF THE MEDICINAL PRODUCT

TOBI Podhaler 28 mg inhalation powder, hard capsules
tobramycin

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 28 mg tobramycin.

## 3. LIST OF EXCIPIENTS

Contains 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), calcium chloride and sulphuric acid (for pH adjustment).

## 4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsules

56 capsules + 1 inhaler
Component of a multipack. Not to be sold separately.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use
Read the package leaflet before use.
For use only with the inhaler provided in the pack.
Always store inhaler in its case.
Do not swallow capsules.
4 capsules = 1 dose
Lift here to open.

*(To be displayed only on the inner lid of the intermediate carton of multipack)*
Read the package leaflet before use.
4 capsules = 1 dose
Do not push the capsules through the foil.
Tear the perforations along the length then width: see Figures (a) and (b).
Then peel back the foil by rolling it back from the capsule card to reveal one capsule at a time, see Figures (c) and (d). Hold the foil close to where you are rolling back.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture and only remove immediately before use.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

| | |
|---|---|
| EU/1/10/652/002 | monthly multipack |
| EU/1/10/652/003 | 2 x monthly multipack wrapped in foil |

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

TOBI Podhaler

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)**

## 1. NAME OF THE MEDICINAL PRODUCT

TOBI Podhaler 28 mg inhalation powder, hard capsules
tobramycin

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 28 mg tobramycin.

## 3. LIST OF EXCIPIENTS

Contains 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), calcium chloride and sulphuric acid (for pH adjustment).

## 4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsules

Multipack: 224 capsules (4 packs of 56 + 1 inhaler) + reserve inhaler

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use
Read the package leaflet before use.
For use only with the inhaler provided in the pack.
Always store inhaler in its case.
Do not swallow capsules.
Lift here to open.
1 reserve inhaler inside. Use this if your weekly inhaler is not functioning correctly, is wet, or has dropped on the ground.

*(To be displayed only on the inner lid of the outer carton of multipack)*
Read the package leaflet before use.
Do not use each inhaler and its case for longer than 1 week.
Please discard inhaler and its case after 1 week of use.
FOUR capsules are required for ONE complete dose.
4 capsules = 1 dose

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture and only remove immediately before use.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/652/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

TOBI Podhaler

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**MONTHLY INTERMEDIATE CARTON OF MULTIPACK COMPRISING 2 MONTHLY PACKS, EACH CONTAINING 4 WEEKLY PACKS) (WITHOUT BLUE BOX)**

## 1. NAME OF THE MEDICINAL PRODUCT

TOBI Podhaler 28 mg inhalation powder, hard capsules
tobramycin

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 28 mg tobramycin.

## 3. LIST OF EXCIPIENTS

Contains 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), calcium chloride and sulphuric acid (for pH adjustment).

## 4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsules

224 capsules + 5 inhalers
Monthly pack. Component of a multipack. Not to be sold separately.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use
Read the package leaflet before use.
For use only with the inhaler provided in the pack.
Always store inhaler in its case.
Do not swallow capsules.
Lift here to open.
1 reserve inhaler inside. Use this if your weekly inhaler is not functioning correctly, is wet, or has dropped on the ground.

*(To be displayed only on the inner lid of the outer carton of multipack)*
Read the package leaflet before use.
Do not use each inhaler and its case for longer than 1 week.
Please discard inhaler and its case after 1 week of use.
FOUR capsules are required for ONE complete dose.
4 capsules = 1 dose

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture and only remove immediately before use.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/652/003

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

TOBI Podhaler

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**WRAPPER LABEL ON MULTIPACKS WRAPPED IN FOIL COMPRISING 2 MONTHLY PACKS, EACH CONTAINING 4 WEEKLY PACKS) (INCLUDING BLUE BOX)**

## 1. NAME OF THE MEDICINAL PRODUCT

TOBI Podhaler 28 mg inhalation powder, hard capsules
tobramycin

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 28 mg tobramycin.

## 3. LIST OF EXCIPIENTS

Contains 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), calcium chloride and sulphuric acid (for pH adjustment).

## 4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsules

Multipack: 448 capsules (2 packs of 224 + 5 inhalers)

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use
Read the package leaflet before use.
For use only with the inhaler provided in the pack.
Always store inhaler in its case.
Do not swallow capsules.
Lift here to open.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture and only remove immediately before use.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/652/003

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

TOBI Podhaler

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

TOBI Podhaler 28 mg inhalation powder, hard capsules
tobramycin

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

Inhalation use only. Do not swallow.
Use capsule immediately after removal from blister.
Do not push capsule through foil.
4 capsules = 1 dose

# B. PACKAGE LEAFLET

**Package leaflet: Information for the user**

**TOBI Podhaler 28 mg inhalation powder, hard capsules**
tobramycin

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What TOBI Podhaler is and what it is used for

**What TOBI Podhaler is**
TOBI Podhaler contains a medicine called tobramycin which is an antibiotic. This antibiotic belongs to a class called aminoglycosides.

**What TOBI Podhaler is used for**
TOBI Podhaler is used in patients aged 6 years and older who have cystic fibrosis to treat lung infections caused by bacteria called *Pseudomonas aeruginosa.*

For the best results from this medicine, please use it as this leaflet instructs you.

**How TOBI Podhaler works**
TOBI Podhaler is a powder for inhalation that is filled into capsules. When you inhale TOBI Podhaler, the antibiotic can enter directly into your lungs to fight against the bacteria causing the infection and to improve your breathing.

**What is *Pseudomonas aeruginosa***
It is a very common bacterium that infects the lungs of nearly everyone with cystic fibrosis at some time during their lives. Some people do not get this infection until later on in their lives, while others get it very young. It is one of the most damaging bacteria for people with cystic fibrosis. If the infection is not properly fought, it will continue to damage your lungs, causing further problems to your breathing.

## 2. What you need to know before you take TOBI Podhaler

**Do not take TOBI Podhaler**
- **if you are allergic** to tobramycin, to any type of aminoglycoside antibiotic, or to any of the other ingredients of this medicine (listed in section 6).

If this applies to you, **tell your doctor without taking TOBI Podhaler**.
If you think you may be allergic, ask your doctor for advice.

**Warnings and precautions**
Tell your doctor if you have ever had any of the following conditions:
- hearing problems (including noises in the ears and dizziness), or your mother has had hearing problems after taking an aminoglycoside
- certain gene variants (a change in the gene) related to hearing abnormalities inherited from your mother
- kidney problems
- unusual difficulty in breathing with wheezing or coughing, chest tightness
- blood in your sputum (the substance you cough up)
- muscle weakness that lasts or becomes worse over time, a symptom mostly related to conditions such as myasthenia or Parkinson's disease.

If any of these apply to you, **tell your doctor before taking TOBI Podhaler**.

If you are aged 65 years or older, your doctor may perform additional tests to decide if TOBI Podhaler is right for you.

Inhaling medicines can cause chest tightness and wheezing and this can happen immediately after inhalation of TOBI Podhaler. Your doctor will supervise your first dose of TOBI Podhaler and check your lung function before and after dosing. Your doctor may ask you to use other appropriate medicines before taking TOBI Podhaler.

Inhaling medicines can also cause cough and this can happen with TOBI Podhaler. Talk to your doctor if the cough is persistent and is a burden for you.

Strains of *Pseudomonas* can become resistant to treatment with an antibiotic over time. This means that TOBI Podhaler may not work as well as it should over time. Talk to your doctor if you are concerned about this.

If you are taking tobramycin or another aminoglycoside antibiotic by injection, it can sometimes cause hearing loss, dizziness and kidney damage.

**Children**
TOBI Podhaler should not be given to children less than 6 years old.

**Other medicines and TOBI Podhaler**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You should not take the following medicines while you are taking TOBI Podhaler:
- Furosemide or ethacrynic acid, diuretics
- Other medicines with diuretic properties such as urea or intravenous mannitol
- Other medicines which may harm your kidneys or hearing.

The following medicines can increase the chances of harmful effects occurring if they are given to you while you are also receiving **injections** of tobramycin or other aminoglycoside antibiotic:
- Amphotericin B, cefalotin, polymyxins (used to treat microbial infections), ciclosporin, tacrolimus (used to reduce the activity of immune system). These medicines may harm the kidneys.
- Platinum compounds such as carboplatin and cisplatin (used to treat some forms of cancer). These medicines may harm the kidneys or hearing.
- Anticholinesterases such as neostigmine and pyridostigmine (used to treat muscle weakness), or botulinum toxin. These medicines may cause muscle weakness to appear or become worse.

If you are taking one or more of the above medicines, discuss with your doctor before you take TOBI Podhaler.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

It is not known whether inhaling this medicine when you are pregnant causes side effects.

When they are given by an injection, tobramycin and other aminoglycoside antibiotics can cause harm to an unborn child, such as deafness.

If you are breast feeding, you should talk to your doctor before taking this medicine.

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

## 3. How to take TOBI Podhaler

Always take TOBI Podhaler exactly as your doctor has told you. Check with your doctor if you are not sure.

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.

**How much TOBI Podhaler to take**
Inhale the content of 4 capsules twice a day (4 capsules in the morning and 4 capsules in the evening), using the Podhaler device.
The dose is the same for everyone aged 6 years and older. Do not exceed the recommended dose.

**When to take TOBI Podhaler**
Taking your capsules at the same time each day will help you remember when to take them. Inhale the content of 4 capsules twice a day as follows:
- 4 capsules in the morning to be inhaled using the Podhaler device.
- 4 capsules in the evening to be inhaled using the Podhaler device.
- It is best to leave close to 12 hours between doses, but this must be at least 6 hours

If you are taking several different inhaled treatments and following other therapies for cystic fibrosis, you should take TOBI Podhaler after all of these are done. Please check the order of medications with your doctor.

**How to take TOBI Podhaler**
- For inhalation use only.
- Do not swallow the capsules
- Only use the capsules with the inhaler provided in this pack. The capsules should remain in the capsule card until you need to use them.
- When you start a new weekly pack of capsules, use the new inhaler that is supplied in the pack. Each inhaler is only used for 7 days.
- Please read the instructions at the end of this leaflet for more information about how to use the inhaler.

**How long to take TOBI Podhaler**
After you have taken TOBI Podhaler for 28 days, you then have a 28-day break, during which you do not inhale any TOBI Podhaler. You then start another course.
It is important that you keep using the product twice each day during your 28 days on treatment and that you keep to the 28-day on, 28-day off cycle.

| ON TOBI Podhaler | OFF TOBI Podhaler |
|---|---|
| Take TOBI Podhaler twice a day, every day for 28 days | Do not take any TOBI Podhaler for the next 28 days |

**Repeat cycle**

Continue taking TOBI Podhaler as your doctor tells you.
If you have questions about how long to take TOBI Podhaler for, talk to your doctor or your pharmacist.

**If you take more TOBI Podhaler than you should**
If you inhale too much TOBI Podhaler, tell your doctor as soon as possible. If TOBI Podhaler is swallowed, don't worry but tell your doctor as soon as possible.

**If you forget to take TOBI Podhaler**
If you forget to take TOBI Podhaler and there are at least 6 hours to your next dose, take your dose as soon as you can. Otherwise, wait for your next dose. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

People with cystic fibrosis have many symptoms of the disease. These may still happen while taking TOBI Podhaler, but should not be any more frequent or seem worse than before.

If your underlying lung disease seems worse while taking TOBI Podhaler, **tell your doctor straight away**.

**Some side effects can be serious**
- Unusual difficulty in breathing with wheezing or coughing and chest tightness (common).

If you experience any of these, **stop taking TOBI Podhaler and tell your doctor straight away**.

- Coughing up blood (very common)
- Decreasing hearing (ringing in the ears is a potential warning sign of hearing loss), noises (such as hissing) in the ears (common).
- Low urine volume, vomiting, confusion and swelling in the legs, ankles or feet, as these may be signs of sudden decrease in kidney function (not known)

If you experience any of these, **tell your doctor straight away**.

**Other side effects may include:**
Very common (may affect more than 1 in 10 people)
- Shortness of breath
- Cough, productive cough, voice alteration (hoarseness)
- Sore throat
- Fever

Common (may affect up to 1 in 10 people)
- Wheezing, rales (crackles)

- Chest discomfort, chest pain from muscles or skeletal origins
- Blocked nose
- Nosebleed
- Vomiting, nausea
- Diarrhoea
- Rash
- Disturbed sense of taste.
- Loss of voice

Not known (frequency cannot be estimated from the available data)
- Generally feeling unwell
- Discoloration of the substance you cough up (sputum)

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store TOBI Podhaler

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the box or capsule card.
- Store in the original packaging in order to protect from moisture.

**Once removed from the capsule card (blister), a capsule should be used immediately.**

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What TOBI Podhaler contains**
- The active substance is tobramycin. One capsule contains 28 mg tobramycin.
- The other ingredients are DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), calcium chloride, sulfuric acid (for pH adjustment).

**What TOBI Podhaler looks like and contents of the pack**
TOBI Podhaler inhalation powder, hard capsules consist of a white to almost white powder for inhalation filled into clear colourless hard capsules with “MYL TPH” imprinted in blue ink on one part of the capsule and the Mylan logo imprinted in blue on the other part of the capsule.

TOBI Podhaler is supplied in monthly packs containing 4 weekly cartons and a reserve Podhaler device in its storage case.

Each weekly carton contains 7 blisters (capsule cards) of 8 capsules each, and a Podhaler device in its storage case.

The following pack sizes are available:
56 inhalation powder, hard capsules and 1 inhaler (weekly pack)
224 (4 x 56) inhalation powder, hard capsules and 5 inhalers (monthly multipack)
448 (8 x 56) inhalation powder, hard capsules and 10 inhalers (2 x monthly multipack wrapped in foil)

Not all pack sizes may be available in your country.

**Marketing Authorisation Holder**
Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ireland

**Manufacturer**
McDermott Laboratories Ltd T/A Mylan Dublin Respiratory
Unit 25, Baldoyle Industrial Estate
Grange Road, Baldoyle
Dublin 13, D13 N5X2
Ireland

Mylan Germany GmbH
Zweigniederlassung Bad Homburg v. d. Hoehe
Benzstrasse 1
61352 Bad Homburg v. d. Hoehe
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
Viatris
Tél/Tel: +32 2 658 61 00

**България**
Майлан ЕООД
Тел.: +359 2 44 55 400

**Česká republika**
Viatris CZ s.r.o.
Tel: +420 222 004 400

**Danmark**
Viatris ApS
Tlf.: +45 28 11 69 32

**Deutschland**
Viatris Healthcare GmbH
Tel: +49 800 0700 800

**Eesti**
Viatris OÜ
Tel: + 372 6363 052

**Ελλάδα**
Viatris Hellas Ltd
Τηλ: +30 210 0100002

**España**
Viatris Pharmaceuticals, S.L.
Tel: +34 900 102 712

**Lietuva**
Viatris UAB
Tel: +370 5 205 1288

**Luxembourg/Luxemburg**
Viatris
Tél/Tel: +32 2 658 61 00

**Magyarország**
Viatris Healthcare Kft.
Tel.: +36 1 465 2100

**Malta**
V.J. Salomone Pharma Ltd
Tel: +356 21 22 01 74

**Nederland**
Mylan Healthcare B.V.
Tel: +31 20 426 3300

**Norge**
Viatris AS
Tlf: +47 66 75 33 00

**Österreich**
Viatris Austria GmbH
Tel: + 43 1 86 390

**Polska**
Viatris Healthcare Sp. z o.o.
Tel.: +48 22 546 64 00

**France**
Viatris Santé
Tél: +33 1 40 80 15 55

**Hrvatska**
Viatris Hrvatska d.o.o.
Tel: +385 1 23 50 599

**Ireland**
Viatris Limited
Tel: +353 1 8711600

**Ísland**
Icepharma hf.
Sími: + 354 540 8000

**Italia**
Viatris Italia S.r.l.
Tel: +39 02 612 46921

**Κύπρος**
GPA Pharmaceuticals Ltd
Τηλ: +357 22863100

**Latvija**
Viatris SIA
Tel: +371 676 055 80

**Portugal**
Viatris Healthcare, Lda.
Tel: +351 214 127 200

**România**
BGP PRODUCTS SRL
Tel: +40 372 579 000

**Slovenija**
Viatris d.o.o.
Tel: +386 1 236 31 80

**Slovenská republika**
Viatris Slovakia s.r.o.
Tel: +421 2 32 199 100

**Suomi/Finland**
Viatris Oy
Puh/Tel: +358 20 720 9555

**Sverige**
Viatris AB
Tel: +46 8 630 19 00

**This leaflet was last revised in**

**Other sources of information**

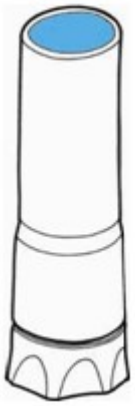
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

## INSTRUCTIONS FOR USE OF THE PODHALER DEVICE

Please read the following instructions carefully to learn how to use and care for your Podhaler device.

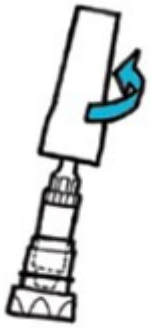
**Inside your TOBI Podhaler weekly pack**
Each weekly carton of TOBI Podhaler contains:

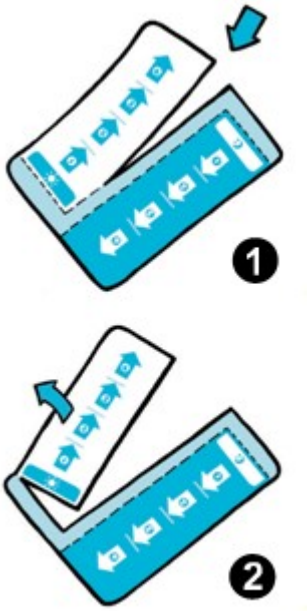
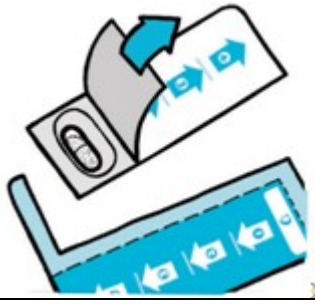
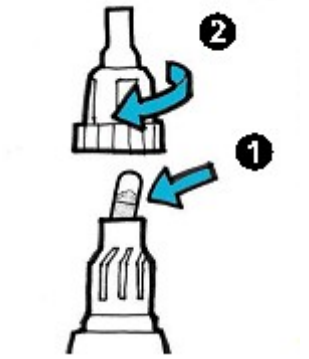
- 1 inhaler (the Podhaler device) and its storage case.
- 7 capsule cards (one card for each day of the week).
- Each capsule card contains 8 capsules (corresponding to a daily dose: content of 4 capsules to be inhaled in the morning and content of 4 capsules to be inhaled in the evening).

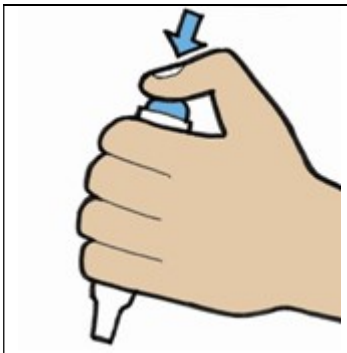
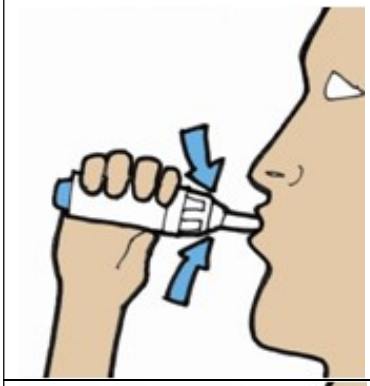
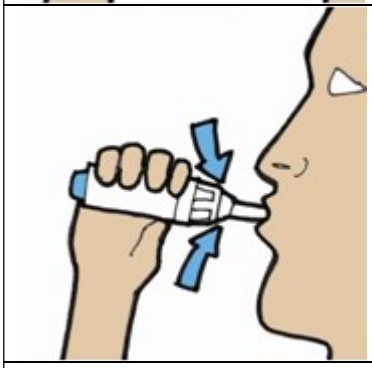
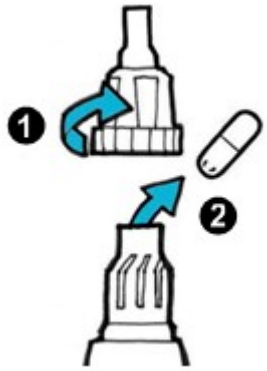
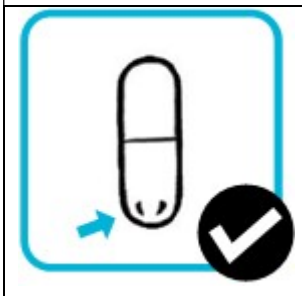
| | | |
|---|---|---|
|  |  |  |
| **Capsule card** | **Inhaler** | **Storage case** |

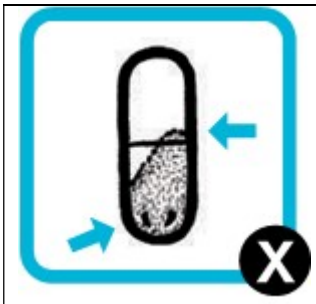
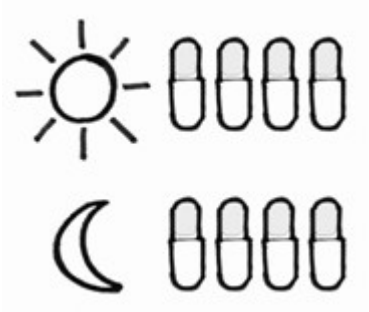
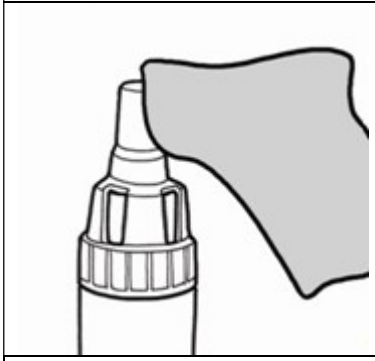
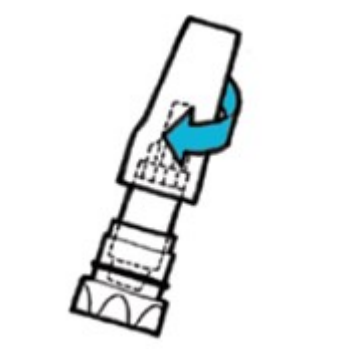
**How to inhale your medicine with the Podhaler device**

- **Only use Podhaler device contained in this pack.** Do not use TOBI Podhaler capsules with any other device, and do not use the Podhaler device to take any other medicine.
- When you start a new weekly pack of capsules, use the new Podhaler device that is supplied in the pack. Each Podhaler device is only used for 7 days. Ask your pharmacist how to dispose of medicines and inhalers no longer required.
- **Do not swallow the capsules.** The powder in the capsules is for you to inhale.
- Always keep the capsules in the capsule card until when you need to use them. Do not take the capsules out of the card in advance.
- Store the Podhaler device in its tightly closed case when not in use.

| | |
|---|---|
|  | 1. Wash and **fully dry your** hands. |
|  | 2. • Just before use, remove the inhaler from its case by holding the base and twisting off the top of the case in an anti-clockwise direction.<br>• Set the top of the case aside.<br>• Look at the inhaler to make sure it is not damaged or dirty.<br>• Stand the inhaler upright in the base of the case. |

| | |
|---|---|
|  | 3. • Hold the body of the inhaler and unscrew the mouthpiece in an anti-clockwise direction.<br>• Set the mouthpiece aside on a clean, dry surface. |
|  | 4. Tear along the perforations of the capsule card lengthwise then widthwise, as indicated in pictures (1) and (2). |
|  | 5. • Peel back the foil from the capsule card to reveal one capsule only.<br>• Remove the capsule from the card. |
|  | 6. • Put the capsule into the inhaler chamber straightaway (1).<br>• Replace the mouthpiece.<br>• Screw the mouthpiece on firmly until it stops. Do not overtighten (2). |

| | |
|---|---|
|  | 7. • Hold the inhaler **with the mouthpiece pointing down**<br>• Pierce the capsule by pressing firmly the blue button with your thumb as far as it will go, then release the button.<br>• You are now ready to inhale the capsule in 2 separate breaths (Steps 8 and 9). |
|  | 8. **Inhale the capsule – 1st breath**:<br>Before putting the mouthpiece in your mouth, breathe out fully, away from the inhaler.<br>Place your mouth over the mouthpiece – to make a tight seal.<br>Inhale the powder deeply with a single breath.<br>Remove the inhaler from your mouth, and hold your breath for about 5 seconds.<br>Then breathe out normally, away from the inhaler. |
|  | 9. **Inhale the capsule – 2nd breath**:<br>• Take a few normal breaths away from the inhaler.<br>• When you are ready, take your 2nd breath by repeating Step 8, using the same capsule. |
|  | 10. Unscrew mouthpiece (1) and remove the capsule from the chamber (2). |
|  | 11. **Look at the used capsule. It should appear pierced and empty.** If it is empty, discard the capsule. |

| | |
|---|---|
|  | If the capsule is pierced but still contains some powder:<br>• Put the capsule back into the inhaler chamber (step 6). Put the pierced side of the capsule in first.<br>• Replace the mouthpiece and repeat steps 8,9 and 10. |
|  | If the capsule does not look pierced:<br>• Put the capsule back into the inhaler chamber (step 6)<br>• Replace the mouthpiece and repeat Steps 7, 8 and 9.<br>• After this if the capsule is still full and appears not to be pierced, replace the inhaler with the reserve inhaler and repeat Steps 2, 3, 6, 7, 8, 9 and 10. |
|  | 12. Take the other 3 capsules in the same way.<br>• So for each remaining capsule, repeat steps 5,6, 7, 8, 9, 10 and 11.<br>• Discard all the empty capsules. |
|  | 13. • Replace the mouthpiece and screw it on firmly until it stops. When the full dose (4 capsules) has been inhaled, wipe mouthpiece with a clean dry cloth.<br>• **Do not wash the inhaler with water**. |
|  | 14. • Place inhaler back in storage case<br>• Twist the top of the case in a clockwise direction until it is closed tighly. |

**REMEMBER:**

- For inhalation use only.
- **Do not swallow TOBI Podhaler capsules.**
- **Only use the inhaler contained in this pack.**
- Always keep the TOBI Podhaler capsules in the capsule card. Only remove a capsule just before you are going to use it. Do not store the capsules in the inhaler.
- Always keep the TOBI Podhaler capsules and device in a dry place.

- Never place a TOBI Podhaler capsule directly into the mouthpiece of the device.
- Always hold the device with the mouthpiece pointing down when piercing the capsule.
- Do not press the piercing button more than once at a time.
- Never blow into the mouthpiece of the device.
- Never wash the Podhaler device with water. Keep it dry and store it in its case.

**Additional information**

Occasionally, very small pieces of the capsule can get past the screen and get into your mouth.

- If this happens, you may be able to feel these pieces on your tongue.
- It is not harmful if these pieces are swallowed or inhaled.
- The chances of the capsule breaking into pieces will be increased if the capsule is accidentally pierced more than once or if the device is not held with the mouthpiece pointing down during step 7.

# ANNEX IV

# SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

**Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for tobramycin (inhalation powder, capsules), the scientific conclusions of PRAC are as follows:

In view of available data on nephrotoxicity from the literature, including in some cases a close temporal relationship and a positive de-challenge, the PRAC considers that a causal relationship between tobramycin (inhalation powder, capsules) and acute kidney injury (AKI) is at least a reasonable possibility. The PRAC concluded that the product information of products containing tobramycin (inhalation powder, capsules) should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

**Grounds for the variation to the terms of the marketing authorisation(s)**

On the basis of the scientific conclusions for tobramycin (inhalation powder, capsules) the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing tobramycin (inhalation powder, capsules) is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.