1.5.5.1 Clean Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

TOBI® 300 mg/5 ml (nebuliser solution)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each 5 ml solution contains tobramycin 300 mg

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Clear slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Long-term management of chronic pulmonary colonisation by *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients aged 6 years and older.

1.5.5.1 Clean Professional Information for medicines for human use

4.2 Posology and method of administration

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

Posology

- The recommended dose for adults and children is one ampoule twice daily for 28 days.
- The dose interval should be as close as possible to 12 hours and not less than 6 hours.
- After 28 days of therapy, patients should stop TOBI therapy for the next 28 days.
- A cycle of 28 days of active therapy and 28 days of rest from treatment should be maintained.
- Dosage is not adjusted for weight.
- All patients should receive one ampoule of TOBI (300 mg of tobramycin) twice daily.

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

1.5.5.1 Clean Professional Information for medicines for human use

TOBI Dosing Regimen in Controlled Clinical Studies

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

Safety and efficacy have been assessed in controlled and open label studies for up to 96 weeks (12 cycles) but have not been studied in patients under the age of 6 years, patients with forced expiratory volume in 1 second (FEV1) <25 % or >75 % predicted, or patients colonised with *Burkholderia cepacia.*

Therapy should be initiated by a doctor experienced in the management of cystic fibrosis. Treatment with TOBI should be continued on a cyclical basis for as long as the doctor considers the patient is gaining clinical benefit from the inclusion of TOBI in their treatment regimen. If clinical deterioration of pulmonary status is evident, additional anti-pseudomonal therapy should be considered. Clinical studies have shown that a microbiological report indicating in vitro drug resistance does not necessarily preclude a clinical benefit for the patient.

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

1.5.5.1 Clean Professional Information for medicines for human use

Method of administration

- The contents of one ampoule should be emptied in the nebuliser and administered by inhalation over approximately a 15-minute period using a hand-held PARI LC PLUS reusable nebuliser with a suitable compressor.
- Suitable compressors are those which, when attached to a PARI LC Plus nebuliser, deliver a flow rate of 4-6 L/min and/or a back pressure of 110-217 kPa. The manufacturers' instructions for the care and use of the nebuliser and compressor should be followed.
- TOBI is inhaled whilst the patient is sitting or standing upright and breathing normally through the mouthpiece of the nebuliser.
- Nose clips may help the patient breathe through the mouth.
- The patient should continue their standard regimen of chest physiotherapy.
- The use of appropriate bronchodilators should continue as thought clinically necessary.
- Where patients are receiving several different respiratory therapies, it is recommended that they are taken in the following order, bronchodilator, chest physiotherapy, other inhaled medicines and finally TOBI.

4.3 Contraindications

- Administration of TOBI is contraindicated in any patient with known hypersensitivity to any aminoglycoside or to any of the excipients.
- Pregnancy and lactation.

1.5.5.1 Clean Professional Information for medicines for human use

4.4 Special warnings and precautions for use

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

Monitoring of serum tobramycin concentrations

The serum concentration of tobramycin should only be monitored through venipuncture and not finger prick blood sampling, which is a non-validated dosing method. It has been observed that contamination of the skin of the fingers from the preparation and nebulisation of TOBI may lead to falsely increased serum levels of the medicine. This contamination cannot be completely avoided by hand washing before testing.

Bronchospasm

Bronchospasm may occur with inhalation of medicines and has been reported with nebulised tobramycin. The first dose of TOBI should be given under supervision, using a pre-nebulisation bronchodilator if this is part of the current regimen for the patient. FEV1 should be measured before and after nebulisation. If there is evidence of therapy-induced bronchospasm in a patient not receiving a bronchodilator the test should be repeated, on a separate occasion, using a bronchodilator. Evidence of bronchospasm in the presence of bronchodilator therapy may indicate an allergic response. If an allergic response is suspected

1.5.5.1 Clean Professional Information for medicines for human use

TOBI should be discontinued. Bronchospasm should be treated as medically appropriate.

Neuromuscular disorders

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

Nephrotoxicity

Although nephrotoxicity has been associated with parenteral tobramycin therapy, there was no evidence of nephrotoxicity during clinical trials with TOBI.

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

Current clinical practice suggests baseline renal function should be assessed. Serum urea and creatinine levels should be reassessed after every 6 complete cycles of TOBI therapy (180 days of nebulised aminoglycoside therapy). If there is evidence of nephrotoxicity, TOBI therapy should be discontinued until trough serum concentrations fall below 2 µg /mL. Patients receiving concomitant parenteral aminoglycoside therapy should be monitored as clinically appropriate taking into account the risk of cumulative toxicity.

1.5.5.1 Clean Professional Information for medicines for human use

Ototoxicity

Ototoxicity, manifested as both auditory and vestibular toxicity, has been reported with tobramycin. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness.

Auditory toxicity, as measured by complaints of hearing loss or by audiometric evaluations, did not occur with TOBI therapy during controlled clinical studies.

In open label studies and post-marketing experience, some patients with a history of prolonged previous or concomitant use of intravenous aminoglycosides have experienced hearing loss.

Doctors should consider the potential for aminoglycosides to cause vestibular and cochlear toxicity and carry out appropriate assessments of auditory function during TOBI therapy. In patients with a predisposing risk due to previous prolonged, systemic aminoglycoside therapy it may be necessary to consider audiological assessment before initiating TOBI therapy.

The onset of tinnitus warrants caution as it is a sentinel symptom of ototoxicity. If a patient reports tinnitus of hearing loss during aminoglycoside therapy the doctor should consider referring them for audiological assessment. Patients receiving concomitant parenteral aminoglycoside therapy should be monitored as clinically appropriate taking into account the risk of cumulative toxicity.

1.5.5.1 Clean Professional Information for medicines for human use

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, consider alternative treatments other than aminoglycosides.

Microbial Resistance

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

4.5 Interaction with other medicines and other forms of Interaction

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

Concurrent and/or sequential use of TOBI with other medicines with nephrotoxic or ototoxic potential should be avoided.

1.5.5.1 Clean Professional Information for medicines for human use

Some diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. TOBI should not be administered concomitantly with furosemide, urea or mannitol.

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

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

Platinum compounds (risk of increased nephrotoxicity and ototoxicity).

Anticholinesterases, botulinum toxin (neuromuscular effects).

4.6 Fertility, pregnancy and lactation

Pregnancy

TOBI should not be used during pregnancy or lactation (*see section 4.3*).

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

1.5.5.1 Clean Professional Information for medicines for human use

Breastfeeding

Systemic tobramycin is excreted in breast milk. It is not known if administration of TOBI will result in serum concentrations high enough for tobramycin to be detected in breast milk.

Because of the potential for ototoxicity and nephrotoxicity with tobramycin in infants TOBI should not be used in breastfeeding.

4.7 Effects on ability to drive and use machines

TOBI can cause a ringing or buzzing noise in one or both ears that may be constant or come and go, often associated with hearing loss or can cause dizziness and may affect mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

Summary of the safety profile

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

The most commonly (≥ 10 %) reported adverse events in the placebo-controlled studies with TOBI were cough, pharyngitis, productive cough, asthenia, rhinitis, dyspnoea, pyrexia, lung disorder, headache, chest pain, sputum discoloured,

haemoptysis, anorexia, pulmonary function test decreased, asthma, vomiting, abdominal pain, dysphonia, nausea, and weight loss.

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

Tabulated list of adverse reactions

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

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

1.5.5.1 Clean Professional Information for medicines for human use

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

Body system	**Undesirable effects**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Infections and Infestations:					Fungal infection, oral moniliasis
Blood and the lymphatic system disorders:					Lymphadeno pathy
Psychiatric disorders:					Somnolence
Nervous system disorders:				Headache, pain, dizziness, taste perversion	

1.5.5.1 Clean Professional Information for medicines for human use

Ear and labyrinth disorders:		Tinnitus		Hearing loss,	Ear disorder, ear pain
Respiratory, thoracic and mediastinal disorders:	Lung disorder, rhinitis, dysphonia, sputum discoloured	Laryngitis	Dyspnoea, increased cough, pharyngitis	Chest pain, chest tightness, cough, shortness of breath, increased sputum, haemoptysis, epistaxis, asthma, decreased lung function	Hyperventilation, hypoxia, sinusitis
Gastrointestinal disorders:					Abdominal pain, diarrhoea
Musculoskeletal, connective tissue and bone disorders:		Myalgia		Asthenia	Back pain
General disorders and administrative site conditions:		Malaise		Fever	
Investigations:	Decreased lung function				

As the duration of exposure to TOBI increased over the two open-label extension studies, the incidence of productive cough and pulmonary function test

decreased appeared to increase; however, the incidence of dysphonia appeared to decline.

Overall, the incidence of adverse events related to the following MedDRA System Organ Class (SOC) decreased with increasing exposure to TOBI: Respiratory, thoracic, and mediastinal disorders, Gastrointestinal disorders, and General disorders and administration site conditions.

Adverse reactions derived from spontaneous reports

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

Frequency unknown:

- **Nervous system disorders:**

  Aphonia (voice alteration (including hoarseness), dysgeusia (taste perversion)
- **Ear and labyrinth disorders:**

  Hearing loss
- **Respiratory, thoracic, and mediastinal disorders:**

  Bronchospasm, oropharyngeal pain
- **Skin and subcutaneous tissue disorders:**

  Hypersensitivity, pruritus, urticaria, rash

1.5.5.1 Clean Professional Information for medicines for human use

- **Metabolism and Nutrition Disorders:**

  Decreased appetite

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

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

1.5.5.1 Clean Professional Information for medicines for human use

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

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

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

Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group and ATC code:

Aminoglycoside Antibacterials, ATC Code: J01GB01

Pharmacodynamic effects:

1.5.5.1 Clean Professional Information for medicines for human use

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.

Established susceptibility breakpoints for parenteral administration of tobramycin are inappropriate in the aerolised administration of the medicines. Cystic fibrosis (CF) sputum exhibits an inhibitory action on the local biological activity of nebulised tobramycin. This necessitates sputum concentrations of aerosolised tobramycin to be some ten and twenty-five fold above the Minimum Inhibitory Concentration (MIC) for, respectively, P. aeruginosa growth suppression and bactericidal activity.

***Susceptibility*:**

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

1.5.5.1 Clean Professional Information for medicines for human use

5.2 Pharmacokinetic properties

Absorption and distribution:

Sputum concentrations: Ten minutes after inhalation of the first 300 mg dose of TOBI, the average sputum concentration of tobramycin was 1,237 µg/g (range: 35 to 7,414 µg/g).

Tobramycin does not accumulate in sputum; after 20 weeks of therapy with the TOBI regimen, the average sputum concentration of tobramycin 10 minutes after inhalation was 1,154 µg/g (range: 39 to 8,085 µg/g), however, high variability of sputum tobramycin concentrations was observed. Two hours after inhalation, sputum concentrations declined to approximately 14 % of tobramycin levels measured at 10 minutes after inhalation.

Serum concentrations:

The median serum concentration of tobramycin 1 hour after inhalation of a single 300 mg dose of TOBI by CF patients was 0.95 µg/ml (range: below limit of quantitation [BLQ] – 3.62 µg/ml). After 20 weeks of therapy on the TOBI regimen, the median serum tobramycin concentration 1 hour after dosing was 1.05 µg/ml (range: BLQ-3.41 µg/ml).

1.5.5.1 Clean Professional Information for medicines for human use

Elimination:

The elimination of tobramycin administered by the inhalation route has not been studied. Unabsorbed tobramycin following TOBI administration is probably eliminated primarily in expectorated sputum.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Sodium hydroxide (pH adjustment)

Sulfuric acid (pH adjustment)

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at 2 - 8 °C.

DO NOT FREEZE.

Store in the original package in order to protect from light.

1.5.5.1 Clean Professional Information for medicines for human use

After removal from the refrigerator, or if refrigeration is unavailable, TOBI pouches (intact or opened) may be stored at up to 25 °C for up to 28 days. TOBI solution is slightly yellow, but some variability in colour may be observed, which does not indicate loss of activity if the product has been stored as recommended.

6.5 Nature and contents of container

TOBI ® is supplied in 5 ml single-use low density polyethylene ampoules in packs of 56.

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

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd

4 Brewery Street

Isando

Republic of South Africa

8 REGISTRATION NUMBER(S)

A40/20.1.1/0522

1.5.5.1 Clean Professional Information for medicines for human use

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 April 2008

10 DATE OF REVISION OF TEXT

TBA