New Zealand Data Sheet

1 TOBRAMYCIN BNM

TOBRAMYCIN BNM 300 mg/5 mL solution for inhalation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL ampoule contains 300 mg tobramycin.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Tobramycin BNM is a solution for inhalation.

It is a sterile, clear, slightly yellow solution free from visible particles.

It has a pH of 4.0 to 5.0 and an osmolality of 150 to 200 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tobramycin BNM is indicated for the management of cystic fibrosis patients with *P. aeruginosa* infections. Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with FEV_1 <25% or >75% predicted, or patients colonised with *Burkholderia cepacia* (see Section 5.1 Pharmacodynamic properties: Clinical trials).

4.2 Dose and method of administration

Dose

Adults and paediatric patients 6 years of age and older
The recommended dosage for both adults and paediatric patients 6 years of age and older is one single-use ampoule (300 mg) administered twice daily for 28 days.

Dosage is not adjusted by weight. All patients should be administered 300 mg twice daily. The doses should be taken as close to 12 hours apart as possible; they should not be taken less than six hours apart.

Tobramycin BNM is inhaled while 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.

Tobramycin BNM is administered twice daily in alternating periods of 28 days. After 28 days of therapy, patients should stop Tobramycin BNM therapy for the next 28 days, then resume therapy for the next 28 days on/28 days off cycle.

Method of administration

Tobramycin BNM is for oral inhalation only and must not be administered by any other route.

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

Tobramycin BNM is not for subcutaneous, intravenous or intrathecal administration.

Tobramycin BNM should not be diluted or mixed with dornase alfa or other medications in the nebuliser.

During clinical studies, patients on multiple therapies were instructed to take them first, followed by Tobramycin.

4.3 Contraindications

Tobramycin BNM is contraindicated in patients with a known hypersensitivity to tobramycin, any aminoglycoside or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Tobramycin BNM is not for subcutaneous, intravenous or intrathecal administration.

Caution should be exercised when prescribing tobramycin to patients with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction. Patients receiving concomitant parenteral aminoglycoside therapy should be monitored as clinically appropriate.

Aminoglycosides can cause foetal harm when administered to a pregnant woman. Aminoglycosides cross the placenta, and streptomycin has been associated with several reports of total, irreversible, bilateral congenital deafness in paediatric patients exposed in utero. Patients who use tobramycin during pregnancy, or become pregnant while taking tobramycin should be apprised of the potential hazard to the foetus. See Section 4.6 Fertility, pregnancy and lactation: Pregnancy.

Ototoxicity

In clinical studies 4 (1%) patients reported mild to moderate hearing loss in clinical studies of up to 9 treatment cycles. Hearing loss was transient for 3 patients and ongoing at the end of study for one patient. Three of these patients had received IV aminoglycosides concomitantly to receiving tobramycin.

In postmarketing experience, some patients receiving tobramycin and extensive previous or concomitant parenteral aminoglycosides have reported hearing loss. Patients with hearing loss frequently reported tinnitus. Tinnitus is a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution (see Section 4.8 Undesirable effects). Ototoxicity, manifested as both auditory and vestibular toxicity, has been reported with parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness.

If a patient reports tinnitus or hearing loss during Tobramycin BNM therapy, the physician should refer them for audiological assessment.

If ototoxicity occurs in a patient receiving Tobramycin BNM, tobramycin therapy should be discontinued until tobramycin serum concentrations fall below 2 μg/mL.

Also see Section 4.4 Special warnings and precautions for use: Laboratory tests – Serum concentrations.

Nephrotoxicity

Nephrotoxicity was not seen during tobramycin clinical studies but has been associated with aminoglycosides as a class. Nephrotoxicity has been reported with the use of parenteral aminoglycosides. If nephrotoxicity occurs in a patient receiving Tobramycin BNM, tobramycin therapy should be discontinued until serum concentrations fall below 2 mcg/ml. Also see Section 4.4 Special warnings and precautions for use: Laboratory tests – Serum concentrations.

Laboratory tests of renal function should be monitored as clinically appropriate.

Muscular Disorders

Tobramycin BNM should be used cautiously in patients with muscular disorders, such as myasthenia gravis or Parkinson's disease, since aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.

Bronchospasm

Bronchospasm can occur with inhalation of medicinal products and has been reported with tobramycin. In clinical studies of tobramycin, changes in FEV_1 measured after the inhaled dose were similar in the tobramycin and placebo groups. Bronchospasm should be treated as medically appropriate.

Laboratory tests

Audiograms
Clinical studies of tobramycin did not identify hearing loss using audiometric tests which evaluated hearing up to 8000 Hz. Tinnitus may be a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution. Physicians should consider an audiogram for patients who show any evidence of auditory dysfunction, or who are at increased risk for auditory dysfunction.

Serum concentrations
In patients with normal renal function treated with tobramycin, serum tobramycin concentrations are approximately 1 mcg/mL one hour after dose administration and do not require routine monitoring.

Serum concentrations of tobramycin should be monitored in patients with known or suspected auditory or renal dysfunction. Patients treated with concomitant parenteral tobramycin should be monitored at the discretion of the treating physician.

The serum concentration of tobramycin should only be monitored through venipuncture and not finger prick blood sampling. Contamination of the skin of the fingers with tobramycin may lead to falsely increased measurements of serum levels of the drug. This contamination cannot be completely avoided by hand washing before testing.

Renal function
The clinical studies of tobramycin did not reveal any imbalance in the percentage of patients in the tobramycin and placebo groups who experienced at least a 50% rise in serum creatinine from baseline (see Section 4.8 Undesirable effects). Laboratory tests of urine and renal function should be conducted at the discretion of the treating physician.

Patients with renal impairment

Tobramycin is primarily excreted unchanged in the urine and renal function is expected to affect the exposure to tobramycin. See Section 4.4 Special warnings and precautions for use: Nephrotoxicity.

Patients with hepatic impairment

No studies have been performed on patients with hepatic impairment. As tobramycin is not metabolised, an effect of hepatic impairment on the exposure to tobramycin is not expected.

Paediatric population
The safety and efficacy of tobramycin have not been studied in paediatric patients under 6 years of age.

4.5 Interaction with other medicines and other forms of interaction

No clinical drug interaction studies have been performed with Tobramycin BNM. However, in clinical studies of tobramycin, patients taking tobramycin concomitantly with dornase alfa, [3-agonists, inhaled corticosteroids, other anti-pseudomonal antibiotics, or parenteral aminoglycosides demonstrated adverse experience profiles similar to the study population as a whole. Concurrent and/or sequential use of Tobramycin BNM with other drugs with neurotoxic, nephrotoxic, or ototoxic potential should be avoided. Some diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. Tobramycin BNM should not be administered concomitantly with ethacrynic acid, frusemide, urea, or intravenous mannitol.

4.6 Fertility, pregnancy and lactation

Fertility

No reproduction toxicology studies have been conducted with Tobramycin BNM administered by inhalation. Data in animals from subcutaneous administration of tobramycin did not reveal a problem or potential problem concerning fertility in either males or females.

Subcutaneous administration of up to 600 mg/m^2/day of tobramycin did not affect mating behaviour or cause impairment of fertility in male or female rats, although fertility of the offspring was not examined.

Pregnancy

Category D. There are no adequate data from the use of tobramycin administered by inhalation in pregnant women. No reproduction toxicology studies have been conducted with tobramycin. However, subcutaneous administration of tobramycin at doses of 600 or 220 mg/m^2/day during organogenesis was not teratogenic in rats or rabbits, respectively. Doses of tobramycin $\geq$ 440 mg/m^2/day were severely maternally toxic to rabbits and precluded the evaluation of teratogenicity. Aminoglycosides can cause foetal harm (e.g. congenital deafness) when administered to a pregnant woman and high systemic concentrations are achieved. Ototoxicity was not evaluated in offspring during nonclinical reproduction toxicity studies with tobramycin.

Treatment with Tobramycin BNM during pregnancy should be undertaken only if the benefits to the mother outweigh the risks to the foetus or baby. If Tobramycin BNM is used during pregnancy, or if the patient becomes pregnant while taking Tobramycin BNM, the patient should be assessed for the potential hazard to the foetus.

Aminoglycosides can cross the placenta. There is evidence of selective uptake of aminoglycosides by foetal kidney resulting in damage (probably reversible) to immature nephrons. Eighth cranial nerve damage has also been reported following in utero exposure to some of the aminoglycosides. Because of their chemical similarity, all aminoglycosides must be considered potentially nephrotoxic and ototoxic to the foetus. It should also be

noted that therapeutic blood concentrations in the mother do not equate with safety to the foetus.

Breastfeeding

It is not known if Tobramycin BNM will reach sufficient concentrations after administration by inhalation to be excreted in human breast milk. Because of the potential for ototoxicity and nephrotoxicity in infants, a decision should be made whether to terminate nursing or discontinue treatment with Tobramycin BNM, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable effects

Adverse Events in Clinical Trials

Tobramycin was generally well tolerated during two placebo-controlled clinical studies in 258 cystic fibrosis patients ranging in age from 6 to 48 years. Patients received tobramycin in alternating periods of 28 days on and 28 days off drug in addition to their standard cystic fibrosis therapy for a total of 24 weeks.

Voice alteration and tinnitus were the only adverse experiences reported by significantly more tobramycin treated patients. Thirty-three patients (13%) treated with tobramycin complained of voice alteration compared to 17 (7%) placebo patients. Voice alteration was more common in the on-drug periods.

Eight patients from the tobramycin group (3%) reported tinnitus compared to no placebo patients. All episodes were transient, resolved without discontinuation of the tobramycin treatment regimen, and were not associated with loss of hearing in audiograms. Tinnitus is one of the sentinel symptoms of cochlear toxicity and patients with this symptom should be carefully monitored for high frequency hearing loss. The numbers of patients reporting vestibular adverse experiences such as dizziness were similar in the tobramycin and placebo groups.

Nine (3%) patients in the tobramycin group and nine (3%) patients in the placebo group had increases in serum creatinine of at least 50% over baseline. In all nine patients in the Tobramycin BNM group, creatinine decreased at the next visit.

Table 1 lists the percentage of patients with treatment-emergent adverse experiences that occurred in $\geq$ 5% of patients during the 48 weeks of the open-label extension. The table also presents the corresponding data from the 24-week placebo-controlled studies, where one group of patients received placebo and the other group received tobramycin during the first three cycles of therapy.

Table 1: Percentage of patients with treatment-emergent adverse events occurring in ≥ 5% of patients in any group.

	During the open label extension[a]		During the placebo-controlled studies	
ADVERSE EVENT	**9 cycles (n=192)**	**6 cycles (n=204)**	**3 cycles (n=258)**	**Placebo (n =262)**
Respiratory System				
Cough Increased	50	48	46	47
Pharyngitis	48	44	38	39
Sputum Increased	44	38	38	40
Dyspnoea	42	34	34	39
Rhinitis	38	33	35	34
Lung Disorder	34	36	31	31
Haemoptysis	31	27	19	24
Asthma	28	24	16	20
Lung Function Decreased	29	23	16	15
Sputum Discoloration	25	19	21	20
Upper Respiratory Infection	14	10	5	8
Sinusitis	7	14	8	9
Voice Alteration	12	6	13	7
Epistaxis	8	8	7	7
Lower Respiratory Tract Infection	7	9	6	8
Respiratory Disorder	6	9	2	6
Hyperventilation	9	5	5	10
Hypoxia	6	6	5	4
Nasal Polyp	4	5	4	2
Laryngitis	5	3	4	3
Body as a Whole				
Fever	40	46	33	44
Asthenia	44	38	36	39
Chest Pain	37	35	26	30
Headache	29	34	27	32
Abdominal Pain	21	27	13	24
Pain	18	24	8	13
Back Pain	10	6	7	8
Chills	7	6	3	2
Accidental Injury	5	6	2	3
Malaise	3	7	6	5
Flu Syndrome	4	5	1	2
Digestive System				
Anorexia	29	28	19	28
Vomiting	18	22	14	22
Nausea	16	19	11	16
Diarrhoea	17	13	6	10
Dyspepsia	5	5	4	4
Oral Moniliasis	6	3	2	1

Hemic and Lymphatic System Lymphadenopathy	8	7	4	2
Metabolic & nutritional disorders				
Weight Loss	16	20	10	15
Skin and Appendages				
Rash	10	12	5	6
Sweating	6	5	2	4
Special Senses				
Ear Pain	8	9	7	9
Ear Disorder	4	7	2	4
Otitis Media	5	2	3	3
Hemic and Lymphatic System				
Lymphadenopathy	8	7	4	2
Nervous System				
Dizziness	6	6	6	8
Somnolence	6	6	2	4
Musculoskeletal System				
Myalgia	6	5	5	3

[a]Patients with newly occurring or worsening adverse events since Week 24.
The 6-Cycle group received placebo during the controlled study (first 3 cycles).
The 9-Cycle group received tobramycin during both the controlled study and the open label extension.

Postmarketing Experience

Some patients receiving tobramycin and extensive previous or concomitant parenteral aminoglycosides have reported hearing loss during postmarketing surveillance (see Section 4.4 Special warnings and precautions for use).

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)
The following adverse drug reactions have been derived from postmarketing experience with tobramycin via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Ear and labyrinth disorders
Hearing loss

Skin and subcutaneous tissue disorders
Hypersensitivity, pruritus, urticaria, rash

Nervous system disorders
Aphonia, dysgeusia

Respiratory, thoracic, and mediastinal disorders
Bronchospasm, oropharyngeal pain, sputum increased, chest pain

General disorders and administration site conditions
Decreased appetite

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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Signs and symptoms

In the event of inadvertent administration of tobramycin by the IV route, signs and symptoms of parenteral tobramycin overdosage may occur that include dizziness, tinnitus, vertigo, loss of high-tone hearing acuity, respiratory distress or failure, renal impairment, and neuromuscular blockade. Administration by inhalation results in low systemic bioavailability of tobramycin.

In the event of accidental oral ingestion of Tobramycin BNM, systemic toxicity is unlikely as tobramycin is not significantly absorbed following oral administration.

The maximum tolerated daily dose of tobramycin has not been established. Tobramycin serum concentrations may be helpful in monitoring overdose.

Treatment

In all cases of suspected overdosage and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

In the case of any overdosage, the possibility of drug interactions with alterations in drug disposition should be considered.
Acute toxicity should be treated with immediate withdrawal of Tobramycin BNM and baseline tests of renal function should be undertaken.

Haemodialysis may be helpful in removing tobramycin from the body.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

TOBRAMYCIN BNM is specifically formulated for administration by inhalation. When inhaled, tobramycin is concentrated in the airways.

Microbiology

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.

Tobramycin has *in vitro* activity against a wide range of gram-negative organisms including *Pseudomonas aeruginosa*. It is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Susceptibility Testing

A single sputum sample from a cystic fibrosis patient may contain multiple morphotypes of *Pseudomonas aeruginosa* and each morphotype may have a different level of *in vitro* susceptibility to tobramycin. Treatment for 6 months with tobramycin in two clinical studies did not affect the susceptibility of the majority of *P. aeruginosa* isolates tested; however, increased MICs were noted in some patients. The clinical significance of this information has not been clearly established in the treatment of *P. aeruginosa* in cystic fibrosis patients. For additional information regarding the effects of tobramycin on *P. aeruginosa* MIC values and bacterial sputum density, please refer to the section 5.1 Pharmacodynamic properties: Clinical trials.

The *in vitro* antimicrobial susceptibility test methods used for parenteral tobramycin therapy can be used to monitor the susceptibility of *P. aeruginosa* isolated from cystic fibrosis patients. If decreased susceptibility is noted, the results should be reported to the clinician. Susceptibility breakpoints established for parenteral administration of tobramycin do not apply to aerosolised administration of tobramycin. The relationship between in vitro susceptibility test results and clinical outcome with tobramycin therapy is not clear.

Clinical Trials

Two identically designed, double-blind, randomised, placebo-controlled, parallel group, 24-week clinical studies were conducted in 520 cystic fibrosis patients aged ≥ 6 years who had baseline FEV_1 % predicted between 25% and 75% and were positive for *P. aeruginosa*.

Patients with a baseline creatinine of > 0.18 mmol/L or who had *Burkholderia cepacia* isolated from sputum were excluded. A cyclical treatment regimen consisting of 28 days on therapy followed by 28 days off therapy was used in these studies. This cycle was repeated twice for a total of three cycles. Patients received either tobramycin (300 mg) or placebo (saline with 1.25 mg quinine) twice daily, delivered by aerosol using a hand-held PARI LC PLUS Reusable Nebuliser with a DeVilbiss Pulmo-Aide Compressor.

All patients received study drug in addition to standard treatment recommended for cystic fibrosis patients, which included oral and parenteral anti-pseudomonal therapy, 132-agonists, sodium cromoglycate, inhaled steroids, and airway clearance techniques. In addition, approximately 77% of patients were concurrently treated with dornase alfa.

The randomised clinical studies were followed by a 48-week open label extension where all patients who chose to continue received up to 6 cycles of tobramycin therapy following the same regimen of 28 days on and 28 days off. Thus, patients who continued into the open label extension received a total exposure of either up to 9 cycles or up to 6 cycles, depending on their original assignment in the controlled studies.

In each of the two placebo-controlled studies, tobramycin treated patients experienced significant improvement in pulmonary function. Improvement was demonstrated in the tobramycin group in Study 1 by an average increase in FEV_1% predicted of about 11% relative to baseline (Week 0) during 24 weeks compared to no average change in placebo patients. The study with tobramycin treated patients had an average increase of about 7% compared to an average decrease of about 1% in placebo patients.

Three hundred and ninety six (396) patients from the controlled studies participated in the open label extension. Of these, a total of 192 patients received up to 9 cycles of tobramycin, 3 cycles during the controlled studies and 6 cycles during the open label extension. At the end of cycle 9, in these patients FEV_1% predicted was 1.7% above baseline (measured at the start of the controlled trials). A total of 204 patients received placebo for 3 cycles followed by 6 cycles of tobramycin. Whilst on placebo, these patients experienced a mean 2.9% decrease in FEV_1% predicted from baseline. After 6 cycles of tobramycin, FEV_1% predicted had improved to 1% below baseline.

P. aeruginosa density in sputum was measured during the 24-week placebo-controlled studies. Tobramycin therapy resulted in a significant reduction in the number of *P. aeruginosa* colony forming units (CFUs) in sputum during the on-drug periods. Sputum bacterial density returned to baseline during the off-drug periods. Reductions in sputum bacterial density were smaller in each successive cycle. *P. aeruginosa* density in sputum was not measured during the open label extension.

During the 24 weeks of the placebo-controlled studies, patients treated with tobramycin were hospitalised for an average of 5.1 days compared to 8.1 days for placebo patients. Patients treated with tobramycin required an average of 9.7 days of parenteral anti-pseudomonal antibiotic treatment compared to 14.1 days for placebo patients. During the 24 weeks of treatment, 40% of tobramycin patients and 53% of placebo patients were treated with parenteral anti-pseudomonal antibiotics. Over the subsequent 48 weeks of the open-label extension, patients were hospitalised for a mean of 11.1 days. Patients were treated with parenteral anti-pseudomonal antibiotics for a mean of 22.4 days and 60.6% of patients were treated with parenteral anti-pseudomonal antibiotics.

The relationship between in vitro susceptibility test results and clinical outcome with tobramycin therapy is not clear. However, four tobramycin patients who began the clinical trial with *P. aeruginosa* isolates having MIC values 2:128 I-Ig/mL did not experience an

improvement in FEV, or a decrease in sputum bacterial density during the first 24 weeks of therapy.

For patients given 9 cycles of active treatment the proportion of patients with isolates of *P. aeruginosa* with an MIC ≥ 16 µg/mL increased from 13.7% at baseline 5 to 29.8% at the end of cycle 9. The proportion of patients with isolates of *P. aeruginosa* with MIC ≥ 128 µg/mL increased from 2.1% at baseline to 9.2% at the end of cycle 9.

During the open-label extension, susceptibility testing of other aminoglycosides (amikacin and gentamicin) indicated a shift toward increasing MIC values similar in magnitude to that seen for tobramycin. The MIC values for ciprofloxacin, aztreonam, ceftazidime and ticarcillin remained unchanged.

Treatment for 18 months (9 cycles) with tobramycin in clinical studies demonstrated a trend to decreasing *in vitro* susceptibility of *P. aeruginosa* isolates. The clinical significance of this information has not been clearly established in the treatment of *P. aeruginosa* in cystic fibrosis patients.

Pediatric clinical study

In a double-blind, randomised, placebo-controlled trial, 51 patients aged 3 months to less than 7 years with a confirmed diagnosis of CF and an early colonisation with P. aeruginosa (defined as: either first positive culture overall or first positive culture after at least a 1-year history of negative cultures) were treated with tobramycin 300 mg/5 mL or placebo, both inhaled via a nebulizer (PARI LC Plus®) twice daily for 28 days. Patients who were treated with anti-pseudomonal therapy in the previous year were excluded.

This was a crossover trial in which 26 patients were allocated to the group receiving tobramycin in the first treatment period and placebo in the crossover treatment period, and 25 patients were allocated to the group receiving placebo in the first treatment period and tobramycin in the crossover treatment period.

The primary outcome was the proportion of patients free from P. aeruginosa colonisation assessed by sputum/throat swab culture after completion of a 28-day treatment period which was 84.6% and 24% (p <0.001) for the tobramycin and placebo groups, respectively.

The safety and efficacy of tobramycin in children < 6 years of age is not established. tobramycin is not indicated for use in pediatric patients less than 6 years of age.

5.2 Pharmacokinetic properties

Tobramycin BNM contains tobramycin, a cationic polar molecule that does not readily cross epithelial membranes. The bioavailability of tobramycin may vary because of individual differences in nebuliser performance and airway pathology. Following administration of Tobramycin BNM, tobramycin remains concentrated primarily in the airways.

Sputum Concentrations

Ten minutes after inhalation of the first 300 mg dose of tobramycin, the average concentration of tobramycin was 1237 mcg/g (ranging from 35 to 7414 mcg/g) in sputum. Tobramycin does not accumulate in sputum. After 20 weeks of therapy with the tobramycin regimen, the average concentration of tobramycin at ten minutes after inhalation as 1154 mcg/g (ranging from 39 to 8085 mcg/g) in sputum. High variability of tobramycin concentration in sputum was observed. Two hours after inhalation, sputum concentrations declined to approximately 14% of tobramycin levels at ten minutes after inhalation.

Serum Concentrations

The average serum concentration of tobramycin one hour after inhalation of a single 300 mg dose of tobramycin by cystic fibrosis patients was 0.95 mcg/mL. After 20 weeks of therapy on the tobramycin regimen, the average serum tobramycin concentration one hour after dosing was 1.05 g/mL.

Elimination

The elimination half-life of tobramycin from serum is approximately 2 hours after intravenous (IV) administration. Assuming tobramycin absorbed following inhalation behaves similarly to tobramycin following IV administration, systemically absorbed tobramycin is eliminated principally by glomerular filtration. Unabsorbed tobramycin, following tobramycin administration, is probably eliminated primarily in expectorated sputum.

5.3 Preclinical safety data

Animal Toxicology

Bronchoepithelial hyperplasia and chronic interstitial inflammation around terminal bronchioles occurred in studies in rats after daily inhalational exposures to tobramyin for 6 months. Progression of the hyperplastic lesions is currently uncertain and this will be assessed further in a 2 year inhalational study in progress.

Carcinogenicity

A two-year rat inhalation toxicology study to assess the carcinogenic potential of tobramycin has been completed. Rats were exposed to tobramycin for up to 1.5 hours per day for 95 weeks. Serum levels of tobramycin of up to 35 µg/mL were measured in rats. There was no drug-related increase in the incidence of any variety of tumour.

Genotoxicity

Tobramycin has been evaluated for genotoxicity in a battery of assays for gene mutations and chromosomal damage. Tobramycin was negative in the bacterial reverse mutation and the mouse lymphoma forward mutation assays. Tobramycin did not induce chromosomal

aberrations in Chinese hamster ovary cells and was negative in the mouse micronucleus test.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide
Sulphuric acid
Water for injections.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Tobramycin BNM should be stored under refrigeration at 2 to 8°C.

For single use. As it is preservative-free, the contents of the whole Tobramycin BNM ampoule should be used immediately after opening and any unused solution discarded. Opened Tobramycin BNM ampoules should never be stored for re-use.

After removal from the refrigerator, or if refrigeration is unavailable, Tobramycin BNM pouches (intact or unopened) may be stored up to 25°C for up to 28 days.

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

6.5 Nature and contents of container

Tobramycin BNM is supplied in 5 ml single-use low density polyethylene (LDPE) ampoules.

One carton contains 56 ampoules with 8 sealed foil pouches. Each foil pouch contains 7 ampoules.

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

BNM Group
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Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

15 August 2019

10 DATE OF REVISION OF TEXT

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