RESPULES

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Tobramycin Inhalation Solution USP 300 mg/5ml

tobamist

Respules

Composition
Each 5 ml Respule contains
Tobramycin IP……..... 300 mg
Sodium Chloride IP ... 11.25 mg
DOSAGE FORM
Solution for inhalation
PHARMACOLOGY
Pharmacodynamics
Tobramycin is an aminoglycoside antibiotic and 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 a concentration equal to or slightly greater than inhibitory concentrations.
Pharmacokinetics
Tobramycin Solution for Inhalation contains tobramycin, a cationic polar molecule that does not readily cross the epithelial membranes. **Tobramycin Solution for Inhalation** is specifically formulated for administration by inhalation. When inhaled, tobramycin is concentrated in the airways.
Sputum Concentrations
Ten minutes after inhalation of the first 300 mg dose of inhaled tobramycin, the average concentration of tobramycin is 1,237 mcg/g in the sputum. Tobramycin does not accumulate in the sputum; after 20 weeks of therapy, the average concentration of inhaled tobramycin at ten minutes is 1,154 mcg/g in the sputum. High variability of tobramycin concentration in the sputum is observed. Two hours after inhalation, sputum concentrations declined to approximately 14% of the 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 in cystic fibrosis patients, was 0.95 mcg/mL. After 20 weeks of therapy on the inhaled tobramycin regimen, the average serum tobramycin concentration one hour after dosing was 1.05 mcg/mL.
Elimination
After intravenous (I.V.) administration, the elimination half-life of tobramycin from serum is approximately two hours. Assuming that tobramycin absorbed following inhalation behaves similarly to tobramycin following I.V. administration, systematically absorbed tobramycin is eliminated principally by glomerular filtration. Following administration of **Tobramycin Solution for Inhalation**, unabsorbed tobramycin is probably eliminated primarily in expectorated sputum.
INDICATIONS
Tobramycin Solution for Inhalation is indicated for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*. Safety and efficacy have not been demonstrated in patients below the age of 6 years, patients with a forced expiratory volume (FEV_1 <25% or >75% predicted, or patients colonized with *Burkholderia cepacia*.
DOSAGE AND ADMINISTRATION
The recommended dosage for both adults and paediatric patients, 6 years of age and older, is one single-use respule (300 mg) administered b.i.d for 28 days. Dosage is not adjusted by weight. The doses should be taken as close to 12 hours apart as possible; they should not be taken less than six hours apart.
Tobramycin Solution for Inhalation is inhaled while sitting or standing upright and breathing normally through the mouthpiece of a nebulizer. Nose clips may help the patient breathe through the mouth.
While taking several medications the recommended order is as follows:
Bronchodilator first, followed by chest physiotherapy, then other inhaled medications and, finally, **Tobramycin Solution for Inhalation**.
Treatment Schedule
Tobramycin Solution for Inhalation is taken in repeated cycles of 28 days on the drug followed by 28 days off the drug. **Tobramycin Solution for Inhalation** is to be administered twice a day during the 28-day period on the drug.
CONTRAINDICATIONS
Tobramycin Solution for Inhalation is contraindicated in patients with a known hypersensitivity to any aminoglycoside.
WARNINGS AND PRECAUTIONS
Drug Interactions
Inhaled tobramycin taken concomitantly with dornase alpha, beta-agonists, inhaled corticosteroids, other oral or parenteral anti-pseudomonal antibiotics demonstrated adverse experience profiles which were similar to those of the control group.
Concurrent and/or sequential use of **Tobramycin Solution for Inhalation** with other drugs with neurotoxic or ototoxic potential should be avoided. Some diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. **Tobramycin Solution for Inhalation** should not be administered concomitantly with ethacrynic acid, furosemide, urea or mannitol.
Other medicinal products that have been reported to increase the potential toxicity of parenterally administered aminoglycosides include:
Amphotericin B, cefalotin, ciclosporin, tacrolimus, polymyxins (risk of increased nephrotoxicity); Platinum compounds (risk of increased nephrotoxicity and ototoxicity); Anticholinesterases, botulinum toxin (neuromuscular effects). Caution should be exercised when prescribing **Tobramycin Solution for Inhalation** 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 have been associated with several reports of total, irreversible, bilateral congenital deafness in paediatric patients exposed *in utero*. Patients who use **Tobramycin Solution for Inhalation** during pregnancy, or become pregnant while using it should be apprised of the potential hazard to the foetus.
Ototoxicity
Ototoxicity, manifested as both auditory and vestibular toxicity, has been reported with parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness. Auditory toxicity, as measured by complaints of hearing loss or by audiometric evaluations, did not occur with Tobramycin Solution for Inhalation 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. Physicians should consider the potential for aminoglycosides to cause vestibular and cochlear toxicity and carry out appropriate assessments of auditory function during Tobramycin Solution for Inhalation therapy. In patients with a predisposing risk due to previous prolonged, systemic aminoglycoside therapy, it may be necessary to consider audiological assessment before initiating Tobramycin Solution for Inhalation therapy. The onset of tinnitus warrants caution as it is a sentinel symptom of ototoxicity. If a patient reports tinnitus or hearing loss during aminoglycoside therapy the physician 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.
Nephrotoxicity
Although nephrotoxicity has been associated with parenteral aminoglycoside therapy, there was no evidence of nephrotoxicity during clinical trials with Tobramycin Solution for Inhalation.
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 the clinical studies.
Current clinical practice suggests baseline renal function should be assessed. Urea and creatinine levels should be reassessed after every 6 complete cycles of Tobramycin Solution for Inhalation therapy (180 days of nebulised aminoglycoside therapy). If there is evidence of nephrotoxicity, all tobramycin therapy should be discontinued until trough serum concentrations fall below 2 mcg/mL. Tobramycin Solution for Inhalation therapy may then be resumed at the physician's discretion. Patients receiving concomitant parenteral aminoglycoside therapy should be monitored as clinically appropriate taking into account the risk of cumulative toxicity.
Neuromuscular Disorders
Tobramycin **Solution for Inhalation** 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 the neuromuscular function.
Bronchospasm
Bronchospasm can occur with inhalation of medicinal products and has been reported with nebulised tobramycin. The first dose of Tobramycin should be given under supervision, using a pre-nebulisation bronchodilator if this is a part of the current regimen for the patient. FEV_1 should be measured before and after nebulisation. If there is evidence of therapy-induced bronchospasm in a patient not receiving a bronchodilator the test should be repeated, on a separate occasion, using a bronchodilator. Evidence of bronchospasm in the presence of bronchodilator therapy may indicate an allergic response. If an allergic response is suspected, Tobramycin should be discontinued. Bronchospasm should be treated as medically appropriate.
Haemoptysis
Inhalation of nebulised solutions may induce a cough reflex. The use of Tobramycin Solution for Inhalation in patients with active, severe haemoptysis should be undertaken only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.
Microbial Resistance
In clinical studies, some patients on tobramycin solution for inhalation showed an increase in aminoglycoside minimum inhibitory concentrations for *P. aeruginosa* isolates tested. There is a theoretical risk that patients being treated with nebulised tobramycin may develop *P. aeruginosa* isolated resistant to intravenous tobramycin.
Renal Impairment
There are no data in this population to support a recommendation for or against dose adjustment with Tobramycin Solution for Inhalation. Please also refer to nephrotoxicity information.
Hepatic Impairment
No studies have been performed on patients with hepatic impairment. As Tobramycin is not metabolized, an effect of hepatic impairment on the exposure of Tobramycin is not expected.
Pregnancy
Aminoglycosides can cause foetal harm (e.g. congenital deafness) when administered to a pregnant woman. If **Tobramycin Solution for Inhalation** is used during pregnancy, or if the patient becomes pregnant while using it, the patient should be apprised of the potential hazard to the foetus.
Lactation
It is not known if **Tobramycin Solution for Inhalation** will reach sufficient concentrations after administration by inhalation so as to be excreted into human breast milk. Because of the potential for ototoxicity and nephrotoxicity in infants, a decision should be made whether to terminate nursing or discontinue **Tobramycin Solution for Inhalation.**
Paediatric Use
Safety and efficacy of tobramycin have not been studied in paediatric patients below 6 years of age.
Elderly patients (≥65 years)
There are insufficient data in this population to support a recommendation for or against dose adjustment.
UNDESIRABLE EFFECTS
Inhaled tobramycin is generally well-tolerated. Dysphonia and tinnitus are more common in the on-drug periods. However, all the episodes are transient and resolved without discontinuation of the regimen, and are not associated with permanent loss of hearing on audiogram testing.
Additional undesirable effects, some of which are common sequelae of the underlying disease, but where a casual relationship to tobramycin solution for inhalation could not be excluded were: sputum discoloured, respiratory tract infection, myalgia, nasal polyps and otitis media.
The undesirable effects that have been reported during post-marketing surveillance include: laryngitis, oral candidiasis, fungal infection, lymphadenopathy, hypersensitivity, anorexia, headache, dizziness, aphonia, somnolence, tinnitus, hearing loss, ear disorder, ear pain, dysphonia, dyspnoea, cough, pharyngitis, bronchospasm, chest discomfort, lung disorder, productive cough, haemoptysis, epistaxis, rhinitis, sinusitis, dysguesia, nausea, mouth ulceration, vomiting, diarrhoea, abdominal pain, rash, urticaria, pruritus, back pain, asthenia, pyrexia, chest pain, pain, malaise and pulmonary function test decreased.
OVERDOSAGE
Signs and symptoms of acute toxicity from overdosage of I.V. tobramycin might include dizziness, tinnitus, vertigo, loss of high-tone hearing acuity, respiratory distress and/or neuromuscular blockade and renal impairment. Administration by inhalation results in the low systemic bioavailability of tobramycin. Symptoms of aerosol overdose may include severe hoarseness. Tobramycin is not significantly absorbed following oral administration. Tobramycin serum concentrations may be helpful in monitoring overdosage. In the case of any overdosage, the possibility of drug interactions with alterations in the drug disposition should be considered.
INCOMPATIBILITY
Do not mix **Tobramycin Solution for Inhalation** with any other medicinal products in the nebulizer.
STORAGE AND HANDLING INSTRUCTIONS
Tobramycin Solution for Inhalation respule pouches should be stored under refrigeration at 2–8°C/36–46°F. Upon removal from the refrigerator, or if refrigeration is unavailable, the pouches (opened or unopened) may be stored at room temperature (up to 25°C/77°F) for up to 28 days.
Tobramycin Solution for Inhalation should not be used beyond the expiration date stamped on the respule when stored under refrigeration (2–8°C/36–46°F) or beyond 28 days when stored at room temperature (25°C/77°F).
Tobramycin Solution for Inhalation respules should not be exposed to intense light. The solution in the respule is slightly yellow, but may darken with age if not stored in the refrigerator; however, the colour change does not indicate any change in the quality of the product as long as it is stored as per the recommended storage conditions.
SHELF LIFE : See on pack
PACKAGING INFORMATION
Tobramycin Solution for Inhalation Respule of 5 mL
INFORMATION FOR PATIENTS
How to Administer
This information is not intended to replace consultation with your physician about properly taking the medication or using the inhalation equipment.
Tobramycin Solution for Inhalation is specially formulated for inhalation using a PARI LC PLUS™ reusable nebulizer and a DeVilbiss Pulmo-Aide® air compressor. **Tobramycin Solution for Inhalation** can be taken at home, school, or at work. Given below are instructions on how to use the DeVilbiss Pulmo-Aide® air-compressor and PARI LC PLUS™ reusable nebulizer to administer **Tobramycin Solution for Inhalation**:
You will need the following supplies:

i. **Tobramycin Solution for Inhalation** plastic respule (vial)
ii. DeVilbiss Pulmo-Aide® air compressor
iii. PARI LC PLUS™ reusable nebulizer
iv. Tubing to connect the nebulizer and compressor
v. Clean paper or cloth towels
vi. Nose clips (optional)

It is important that your nebulizer and compressor function properly before starting your **Tobramycin Solution for Inhalation** therapy.
Preparing* Tobramycin Solution for Inhalation *for Inhalation

1. Wash your hands thoroughly with soap and water.
2. **Tobramycin Solution for Inhalation** is packaged as five respules per foil pouch. Separate one respule by gently pulling apart at the bottom tabs. Store all the remaining respules in the refrigerator as directed.

3. Lay out the contents of a PARI LC PLUS™ reusable nebulizer package on a clean, dry paper or cloth towel. You should have the following parts:

i. Nebulizer top and bottom (nebulizer cup) assembly
ii. Inspiratory valve cap
iii. Mouthpiece with valve
iv. Tubing

4. Remove the nebulizer top from the nebulizer cup by twisting the nebulizer top counter-clockwise, and then lifting. Place the nebulizer top on the clean paper or cloth towel. Stand the nebulizer cup upright on the towel.
5. Connect one end of the tubing to the compressor air outlet. The tubing should fit snugly. Plug in your compressor to an electrical outlet.
6. Open the **Tobramycin Solution for Inhalation** respule by holding the bottom tab with one hand and twisting off the top of the respule with the other hand. Be careful not to squeeze the respule until you are ready to empty its contents into the nebulizer cup.

7. Squeeze all the contents of the respule into the nebulizer cup.

8. Replace the nebulizer top. Note: In order to insert the nebulizer top into the nebulizer cup, the semi-circle halfway down the stem of the nebulizer top should face the nebulizer outlet.
9. Attach the mouthpiece to the nebulizer outlet. Then firmly push the inspiratory valve cap in place on the nebulizer top. Note: The inspiratory valve cap should fit snugly.
10. Connect the free end of the tubing to the air intake on the bottom of the nebulizer, making sure to keep the nebulizer upright. Press the tubing on the air intake firmly.

Tobramycin Solution for Inhalation Treatment

1. Turn on the compressor.
2. Check for a steady mist from the mouthpiece. If there is no mist, check all the tubing connections and confirm that the compressor is working properly.
3. Sit or stand in an upright position that will allow you to breathe normally.
4. Place the mouthpiece between your teeth and on top of your tongue and breathe normally only through your mouth. Nose clips may help you breathe through your mouth and not through your nose. Do not block the airflow with your tongue.

5. Continue treatment until all your **Tobramycin Solution for Inhalation** is over and there is no longer any mist being produced. You may hear a sputtering sound when the nebulizer cup is empty. The entire **Tobramycin Solution for Inhalation** treatment should take approximately 15 minutes to complete.
   Note: If you are interrupted, need to cough or rest during your **Tobramycin Solution for Inhalation** treatment, turn off the compressor to save your medication. Turn the compressor back on when you are ready to resume your therapy.
6. **Follow the nebulizer cleaning and disinfecting instructions after completing therapy to reduce the risk of infection, illness or injury from contamination.**

Follow the manufacturer's instructions regarding the care and use of the compressor.
Tobramycin Solution for Inhalation is supplied as a single-use respule and is administered by inhalation, using a hand-held PARI LC PLUS™ reusable nebulizer with a DeVilbiss Pulmo-Aide® compressor. **Tobramycin Solution for Inhalation** is not for subcutaneous, I.V. or intrathecal administration.

Last updated: January 2012

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PACKAGING DEVELOPMENT

Product Name: Tobamist respules	**Material No.:** 21076086	**Version:** 01	**Item:** Leaflet	**Co-ordinator:** Shilpa	**Artist:** Shashikant	**Date:** 31/01/2019
Colours: BLUE WOOL TEST VALUE 5-8 (LIGHT FASTENING DATA) Pantone 4495 C				**INK:** Oil based Ink from DIC OR MICRO		
Design: Folded	**Reference:** 21059938			**Software:** Illustrator CC		
Fonts: ------	**Links:-**					
Actual Size: 150 x 280 mm	**Size after folding:** 75 x 70 mm	**Pharmacode: 4620_MINI_**	**Grain Direction :** Parallel to length			**Screen : # __**
Material: 54 GSM Maplitho Paper			**Varnish:-**	**Artwork Print Size:** ☐ actual ☐ scaled		
Path: F:\Jobs\OTC\Shilpa\Iran\Tobamist\21076086 Tobamist respules Leaflet Iran.ai						

- **Instructions / Remark: -**
- Any deviation must be brought to the notice of packaging development co-ordinator immediately.
- For any clarification, please contact packaging development co-ordinator immediately.
  NO CHANGES IN ARTWORK SHOULD BE DONE BY THE PRINTER
- The printer should verify the e-proof against the approved artwork before submitting for approval and the e-proof should have printer details .

Checked by	Artist	Cordinator	file loaded in Server	Section Head
Pharma Code	☐	☐		
2D Code	☐	☐		
QR Code	☐	☐		
Bar Code	☐	☐		
Artwork	☐	☐		
Spell check	☐	☐		