

For Inhalation Only by Nebulizer

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KITABIS® PAK safely and effectively. See full prescribing information for KITABIS PAK. KITABIS PAK (tobramycin inhalation solution), for oral inhalation use

Initial U.S. Approval: 1975

----- INDICATIONS AND USAGE KITABIS PAK contains tobramycin, an aminoglycoside antibacterial drug indicated for the

management of cystic fibrosis in adults and pediatric patients 6 years of age and older with Pseudomonas aeruginosa (1). ----- DOSAGE AND ADMINISTRATION ------

KITABIS PAK is a co-packaging of tobramycin inhalation solution with a PARI LC PLUS® Reusable Nebulizer (2.1).

- Administer tobramycin inhalation solution as one single-use ampule (300 mg/5 mL)
- twice a day by oral inhalation in alternating periods of 28 days on drug, followed by 28 days off drug (2.1). • Dosage is not adjusted by weight (2.1).
- Take doses as close to 12 hours apart as possible; but not less than 6 hours apart (2.1).
- Administer each 300 mg dose using the PARI LC PLUS Reusable Nebulizer and DeVilbiss $^{\!@}$ Pulmo-Aide $^{\!@}$ compressor (2.2).
- ------ DOSAGE FORMS AND STRENGTHS -• Inhalation Solution: 300 mg in a single-use 5 mL ampule (3). ------ CONTRAINDICATIONS
- Known hypersensitivity to any aminoglycoside (4).
- ----- WARNINGS AND PRECAUTIONS -----
- Bronchospasm: Can occur with inhalation of tobramycin inhalation solution. Treat
- as medically appropriate, if it occurs (5.1).
- Ototoxicity: Tinnitus and hearing loss have been reported in patients receiving tobramycin inhalation solution. If noted, manage as medically appropriate, including potentially discontinuing tobramycin inhalation solution (5.2).
- Nephrotoxicity: Has been associated with aminoglycosides as a class. If nephrotoxicity develops, manage the patient as medically appropriate, including potentially discontinuing tobramycin inhalation solution (5.3). Neuromuscular Disorders: Aminoglycosides may aggravate muscle weakness because
- of a potential curare-like effect on neuromuscular function. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but mechanical assistance may be necessary (5.4).

----- ADVERSE REACTIONS ------The most common adverse reactions (> 5%) in patients treated with tobramycin inhalation solution were cough, pharyngitis, and increased sputum (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact PARI at 1-844 KITABIS (1-844-548-2247) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch ----- DRUG INTERACTIONS -----

Concurrent and/or sequential use with other drugs with neurotoxic, nephrotoxic or ototoxic potential should be avoided (7.1).

Concomitant administration with ethacrynic acid, furosemide, urea, or intravenous mannitol is not recommended due to possible enhancement of aminoglycoside toxicity (7.2). See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 05/2016 **FULL PRESCRIBING INFORMATION: CONTENTS***

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- **FULL PRESCRIBING INFORMATION**

INDICATIONS AND USAGE KITABIS PAK (co-packaging of tobramycin inhalation solution and PARI LC PLUS Reusable

Nebulizer) is indicated for the management of cystic fibrosis in adults and pediatric patients

6 years of age and older with *P. aeruginosa*. 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 colonized with Burkholderia cepacia [see Clinical Studies (14)]. DOSAGE AND ADMINISTRATION **Dosing Information** KITABIS PAK is a co-packaging of tobramycin inhalation solution ampules with a PARI LC PLUS Reusable Nebulizer. Administer as follows: One single-use ampule

(300 mg/5 mL) of tobramycin inhalation solution twice a day by oral inhalation in

- alternating periods of 28 days on drug, followed by 28 days off drug. The 300 mg/5 mL dose of tobramycin inhalation solution is the same for all patients regardless of age or weight.
- The doses should be taken as close to 12 hours apart as possible; they should not be taken less than 6 hours apart. **Administration of Tobramycin Inhalation Solution**

Each dose of tobramycin inhalation solution is administered by oral inhalation using only the co-packaged PARI LC PLUS Reusable Nebulizer (Model No. 022B81-T) included in the

KITABIS PAK, along with a DeVilbiss Pulmo-Aide air compressor (Model No. 5650D). Tobramycin inhalation solution is *not* for subcutaneous, intravenous or intrathecal Prior to administration, read the Patient Information/Instructions for Use for KITABIS PAK

instructions for use and care of the DeVilbiss Pulmo-Aide air compressor. The entire tobramycin inhalation solution treatment should take approximately 15 minutes to complete. Continue treatment until all the tobramycin inhalation solution has been delivered, and there is no longer any mist being produced.

for detailed information on how to use KITABIS PAK and follow the manufacturer's

Tobramycin inhalation solution should not be diluted or mixed with other drugs including dornase alfa in the nebulizer. Instruct patients on multiple therapies to take their medications prior to inhaling the tobramycin inhalation solution, or as directed by their physician.

Tobramycin inhalation solution should not be used if it is cloudy, if there are particles in the solution, or if it has been stored at room temperature for more than 28 days. DOSAGE FORMS AND STRENGTH Inhalation solution: 300 mg/5 mL in a single-use ampule

CONTRAINDICATIONS Tobramycin inhalation solution is contraindicated in patients with a known hypersensitivity to any aminoglycoside.

WARNINGS AND PRECAUTIONS 5 **Bronchospasm** 5.1

Bronchospasm can occur with inhalation of tobramycin inhalation solution. In clinical studies with tobramycin inhalation solution, changes in FEV₁ measured after the inhaled dose were similar in tobramycin inhalation solution and placebo groups. Bronchospasm that occurs during the use of tobramycin inhalation solution should be treated as medically appropriate.

Transient tinnitus occurred in eight tobramycin inhalation solution treated patients versus no placebo patients in the clinical studies. Tinnitus may be a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants further clinical investigation. In postmarketing experience, patients receiving tobramycin inhalation solution have reported

hearing loss. Ototoxicity, manifested as both auditory and vestibular toxicity, has been reported with parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness. Patients with known or suspected auditory or vestibular dysfunction should be closely monitored when taking tobramycin inhalation solution. Monitoring might include obtaining audiometric evaluations and serum tobramycin levels. If ototoxicity is noted, the patient should be managed as medically appropriate, including potentially discontinuing tobramycin inhalation solution [see Adverse Reactions (6.2)]. Nephrotoxicity Nephrotoxicity was not seen during clinical studies with tobramycin inhalation solution but has been associated with aminoglycosides as a class. Patients with known or suspected renal dysfunction or taking concomitant nephrotoxic drugs along with tobramycin inhalation solution should have serum concentrations of tobramycin and laboratory measurements of

the patient should be managed as medically appropriate, including potentially discontinuing tobramycin inhalation solution.

Neuromuscular Disorders Aminoglycosides, including tobramycin, may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function. Neuromuscular blockade, respiratory failure, and prolonged respiratory paralysis may occur more commonly in patients with underlying neuromuscular disorders, such as myasthenia gravis or Parkinson's disease. Prolonged respiratory paralysis may also occur in patients receiving neuromuscular blocking agents. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but mechanical assistance may be necessary.

renal function obtained at the discretion of the treating physician. If nephrotoxicity develops,

Aminoglycosides can cause fetal 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 pediatric patients exposed

Embryo-Fetal Toxicity

in utero. The risk with inhaled tobramycin is less well characterized. Patients who use tobramycin inhalation solution during pregnancy, or become pregnant while taking tobramycin inhalation solution should be apprised of the potential hazard to the fetus. **Concomitant Use of Systemic Aminoglycosides** Patients receiving concomitant tobramycin inhalation solution and parenteral aminoglycoside therapy should be monitored as clinically appropriate for toxicities associated with aminoglycosides as a class. Serum tobramycin levels should be monitored.

ADVERSE REACTIONS The following serious adverse reactions are described below and elsewhere in the labeling: • Bronchospasm [see Warnings and Precautions (5.1)]

• Ototoxicity [see Warnings and Precautions (5.2)] **Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Tobramycin

inhalation solution was studied in two clinical studies in 258 cystic fibrosis patients ranging

Eight patients from the tobramycin inhalation solution group (3%) reported tinnitus

compared to no placebo patients. All episodes were transient, resolved without

discontinuation of the tobramycin inhalation solution treatment regimen, and were

in age from 6 to 48 years. Patients received tobramycin inhalation solution 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. Adverse reactions reported in these studies are described below: The most frequent adverse reactions in the tobramycin inhalation arm were cough,

not associated with loss of hearing in audiograms.

- pharyngitis, and increased sputum (see Table 1). Thirty-three patients (13%) treated with tobramycin inhalation solution complained of voice alteration compared to 17 (7%) placebo patients. Voice alteration was more common in the on-drug periods.
- Table 1 lists the percent of patients with selected adverse reactions that occurred in > 5% of tobramycin inhalation solution patients during the two Phase III studies. Table 1: Percent of Patients with Selected Adverse Reactions Occurring in > 5% of **Tobramycin Inhalation Solution Patients**

Adverse Reaction TOBRAMYCIN **Placebo Inhalation Solution** (n=262)(n=258)

46.1 Cough Increased 47.3 Pharyngitis 38.0 39.3 Snutum Increased 376 30.7

33.7	38.5				
19.4	23.7				
16.3	15.3				
12.8	6.5				
6.6	6.9				
5.4	6.1				
¹ Includes reported decreases in pulmonary function tests or decreased lung volume on chest radiograph associated with intercurrent illness or study drug administration.					
	19.4 16.3 12.8 6.6 5.4				

Selected adverse reactions that occurred in less than or equal to 5% of patients treated with tobramycin inhalation solution: Ear and labyrinth disorders

Musculoskeletal and connective tissue disorders

Infections and infestations Laryngitis **Postmarketing Experience** The following adverse reactions have been identified during post approval use of tobramycin

Tinnitus

Myalgia

inhalation solution. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Ear and labyrinth disorders Hearing loss: Some of these reports occurred in patients with previous or concomitant treatment with systemic aminoglycosides. Patients with hearing loss frequently reported tinnitus. [see Warnings and Precautions (5.2)]

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

Respiratory, thoracic, and mediastinal disorders Bronchospasm [see Warnings and Precautions (5.1)], oropharyngeal pain

Aphonia, dysgeusia

DRUG INTERACTIONS Drugs with Neurotoxic, Nephrotoxic or Ototoxic Potential Concurrent and/or sequential use of tobramycin inhalation solution with other drugs

with ethacrynic acid, furosemide, urea, or intravenous mannitol.

with neurotoxic, nephrotoxic, or ototoxic potential should be avoided if possible.

7.2 **Diuretics** Some diuretics can enhance aminoglycoside toxicity by altering aminoglycoside concentrations in serum and tissue. Tobramycin inhalation solution should not be administered concomitantly

(continued on back)

Patient Information KITABIS® PAK (Ki TAH biss Pak) (tobramycin inhalation solution) for oral inhalation

Read this Patient Information before you start using KITABIS PAK and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

PARI LC PLUS® Reusable Nebulizer used to treat adults and children 6 years of age and older with cystic fibrosis who have a bacterial infection called Pseudomonas aeruginosa. KITABIS PAK contains an antibacterial medicine called tobramycin (an aminoglycoside).

and effective: in children under 6 years of age

- than 75% predicted in people who are colonized with a bacterium called
- when used for more than 3 cycles
- Who should not use KITABIS PAK?
- Do not use KITABIS PAK if you are allergic to tobramycin,

any of the ingredients in KITABIS PAK, or to any other aminoglycoside antibacterial medicine. What should I tell my healthcare provider before using

Before you use KITABIS PAK, tell your healthcare provider

have or have had hearing problems (including noises in

- have dizziness

- have or have had breathing problems such as wheezing. coughing, or chest tightness
- have had an organ transplant are pregnant or plan to become pregnant. See "What are

more information.

new medicine.

How should I use KITABIS PAK?

medicine in KITABIS PAK (tobramycin inhalation solution) passes into your breast milk. Tell your healthcare provider about all the medicines you take,

are breastfeeding or plan to breastfeed. It is not known if the

herbal supplements. serious side effects.

other medicines that may harm your nervous system, kidneys, or hearing

healthcare provider if you should take:

"water pills" (diuretics) such as Edecrin (ethacrynic acid), Lasix (furosemide), or mannitol

these medicines, if you are not sure. Know the medicines you take. Keep a list of them and show it

to your healthcare provider and pharmacist when you get a

this Patient Information leaflet about the right way to use KITABIS PAK. Use KITABIS PAK exactly as your healthcare provider

See the step-by-step Instructions for Use at the end of

- tells you to. Ask your healthcare provider or pharmacist if you are not sure. The usual dose of KITABIS PAK for adults and children
- 6 years of age and over is: 1 ampule of tobramycin inhalation solution inhaled by mouth in the morning and 1 ampule of tobramycin inhalation solution inhaled by mouth in the evening using your PARI LC PLUS® Reusable Nebulizer with
- Each dose of KITABIS PAK should be used as close to 12 hours apart as possible.
- Do not use your dose of KITABIS PAK less than 6 hours apart. After using KITABIS PAK for 28 days, you should stop using it for 28 days. After you have stopped using KITABIS PAK for 28 days, you should start using KITABIS PAK again for 28 days. It is important that you keep to the
 - including dornase alfa (Pulmozyme®) in your nebulizer.
- If you are taking other medicines inhaled through your mouth (bronchodilators), your healthcare provider will tell you how to take your medicine the right way.
- What are the possible side effects of KITABIS PAK? KITABIS PAK can cause serious side effects, including:

severe breathing problems (bronchospasm). Tell your healthcare provider right away if you get any of these symptoms of bronchospasm while using KITABIS PAK:

 coughing and chest tightness hearing loss or ringing in the ears (ototoxicity). Tell your

you develop vertigo, dizziness, or difficulty with balance.

worsening kidney problems (nephrotoxicity). Your

healthcare provider may do a blood test and urine test

- to check how your kidneys are working while you are using KITABIS PAK. worsening muscle weakness. The medicine in KITABIS PAK (tobramycin inhalation solution) is in a class of medicines
- gravis or Parkinson's disease). The medicine in KITABIS PAK (tobramycin inhalation solution) is in a class of medicines which may cause harm to an unborn baby.
- productive cough shortness of breath
 - coughing up blood worsening of lung problems or cystic fibrosis

bothers you or that does not go away. These are not all of the possible side effects of KITABIS PAK. For

General information about the safe and effective use of KITABIS PAK. Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use KITABIS PAK for a condition for which it was not prescribed.

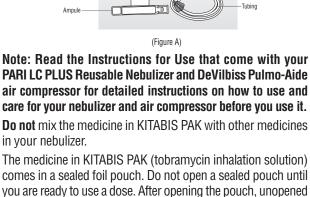
What are the ingredients in KITABIS PAK? Active ingredient: tobramycin Inactive ingredients: sodium chloride, sulfuric acid, and sodium hydroxide (for pH adjustment)

Follow the instructions below for using KITABIS PAK which contains tobramycin inhalation solution and the PARI LC PLUS Reusable Nebulizer (PARI LC PLUS). If you have any questions, ask your healthcare provider or pharmacist.

(tobramycin inhalation solution)

nose clip (optional, not pictured)

clean, lint-free towel



ampules should be returned to and stored in the pouch.

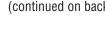
Getting ready:

Inspiratory Valve Cap, Mouthpiece with Valve, and Tubing on a clean, dry surface or towel (See Figure B). Nebulizer Cup or "Bottom"

Open the PARI LC PLUS package. Place the PARI LC PLUS

parts including Top and Bottom (Nebulizer Cup) Assembly,

(Figure B)



KITABIS PAK contains a prescription medicine and a

It is not known if tobramycin inhalation solution is safe in people who have an FEV_1 less than 25% or greater

Burkholderia cepacia

KITABIS PAK? if you:

your ears)

have or have had kidney problems have or have had problems with muscle weakness such as myasthenia gravis or Parkinson's disease

the possible side effects of KITABIS PAK?" below for

including prescription and over-the-counter, vitamins, and

Using KITABIS PAK with certain other medicines can cause If you are using KITABIS PAK, you should discuss with your

Ask your healthcare provider or pharmacist for a list of

- a DeVilbiss® Pulmo-Aide® air compressor. Each dose of KITABIS PAK should take about 15 minutes
- 28-day on, 28-day off cycle. Do not mix the medicine in KITABIS PAK with other medicines
- If you inhale too much of the medicine in KITABIS PAK, tell your healthcare provider right away.
- shortness of breath with wheezing healthcare provider right away if you have hearing loss or hear noises in your ears (such as ringing or hissing), or if
- that can cause muscle weakness to get worse in people who already have problems with muscle weakness (myasthenia
- The most common side effects of KITABIS PAK include: cough sore throat
- changes in your voice (hoarseness) altered taste
- more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Tell your healthcare provider about any side effect that

Do not give KITABIS PAK to other people, even if they have the same symptoms that you have. It may harm them. This leaflet summarizes the most important information

about KITABIS PAK. If you would like more information, talk

with your healthcare provider. You can ask your healthcare

provider or pharmacist for information about KITABIS PAK

For more information, go to www.KITABIS.com or call 1-844-

that is written for health professionals.

KITABIS (548-2247).

Instructions for Use KITABIS PAK (Ki TAH biss Pak)

contain 4 single-use tobramycin inhalation solution ampules. You will need the following supplies (See Figure A): • 1 tobramycin inhalation solution ampule PARI LC PLUS Reusable Nebulizer DeVilbiss Pulmo-Aide (Pulmo-Aide) air compressor

tubing to connect the nebulizer and compressor

Each KITABIS PAK carton (28-day supply) contains 56 tobramycin

inhalation solution ampules packed in 14 foil pouches that each



Preparing your KITABIS PAK dose:

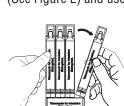
Step 1: Wash your hands with soap and water (See Figure C).



Step 2: Open the foil pouch (See Figure D).

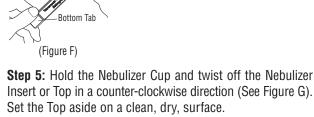


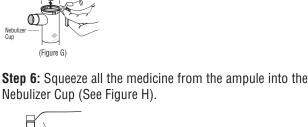
Step 3: Separate 1 ampule by gently pulling apart starting at the TOP of the ampules and continue down to the bottom tabs (See Figure E) and use it right away.

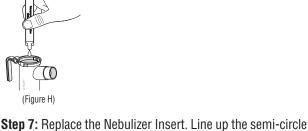


Step 4: Hold the bottom tab on the KITABIS PAK ampule with

1 hand (See Figure F). With your other hand, hold the top of the ampule and twist off the top of the ampule (See Figure F). • Do not squeeze the ampule until you are ready to squeeze all of the medicine into the Nebulizer Cup.



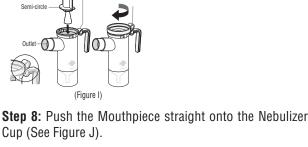




tight and the alignment rings are lined up (See Figure I).

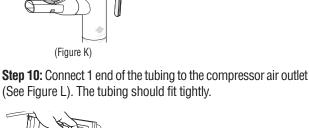
on the Nebulizer Insert with the Nebulizer Outlet and twist

on the Nebulizer Insert in a clock-wise direction until it is

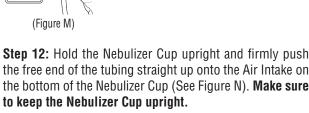


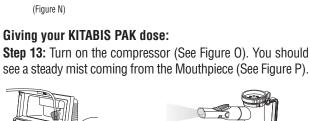


Valve Cap should fit tightly.

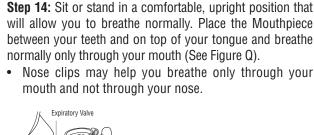


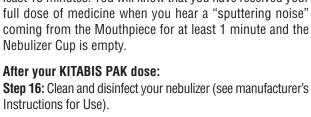






(Figure 0) (Figure P)





least 15 minutes. You will know that you have received your full dose of medicine when you hear a "sputtering noise" coming from the Mouthpiece for at least 1 minute and the Nebulizer Cup is empty.

Step 15: Keep breathing in your KITABIS PAK dose for at

Care and Use of your DeVilbiss Pulmo-Aide compressor: Follow the manufacturer's instructions for care and use of your compressor.

How should I store KITABIS PAK?

· Store tobramycin inhalation solution in the refrigerator between 36°F to 46°F (2°C to 8°C) until needed. You may store the tobramycin inhalation solution in the

foil pouches (opened or unopened) at room temperature

between 66°F to 77°F (20°C to 25°C) for up to 28 days.

Do not use tobramycin inhalation solution after the

- expiration date stamped on the ampule. Keep tobramycin inhalation solution in the foil pouch and out of the light. Tobramycin inhalation solution is normally slightly yellow, but may get darker with age if unrefrigerated. The color
- **Do not** use tobramycin inhalation solution if it is cloudy, has particles in the solution, or if it has been stored at room temperature for more than 28 days. Throw the applicable ampule(s) away in your household trash and

change does not change how the medicine works.

get a new ampule. Keep KITABIS PAK and all medicines out of the reach of children.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Additional Information PARI LC PLUS® Reusable Nebulizer: 1-800-327-8632 DeVilbiss® Pulmo-Aide® Air Compressor: 1-800-338-1988

KITABIS PAK: 1-844-KITABIS (548-2247) Manufactured by:

Catalent Pharma Solutions, LLC

Woodstock, IL 60098 Distributed by:

PARI Respiratory Equipment, Inc.

2412 PARI Way, Midlothian, VA 23112

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Pregnancy Pregnancy Category D [see Warnings and Precautions (5.5)]

Aminoglycosides can cause fetal harm (e.g., congenital deafness) when administered to a pregnant woman. No adequate and well-controlled studies of tobramycin inhalation solution have been conducted in pregnant women. If tobramycin inhalation solution is used during pregnancy, or if the patient becomes pregnant while taking tobramycin inhalation solution, the patient should be apprised of the potential hazard to the fetus.

No reproduction toxicology studies have been conducted with tobramycin inhalation solution. However, subcutaneous administration of tobramycin at doses of 100 or 20 mg/kg/day during organogenesis was not teratogenic in rats or rabbits, respectively. Doses of tobramycin ≥ 40 mg/kg/day were severely maternally toxic to rabbits and precluded the evaluation of teratogenicity. Ototoxicity was not evaluated in offspring during nonclinical reproduction toxicity studies with tobramycin. 8.3 **Nursing Mothers**

It is not known if tobramycin inhalation solution will reach sufficient concentrations after

administration by inhalation to be excreted in human breast milk. Because of the potential for ototoxicity and nephrotoxicity in nursing infants from tobramycin inhalation solution, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Pediatric Use

patients under 6 years of age. Geriatric Use

over. Tobramycin is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function [see Warnings and Precautions (5.3)]. OVERDOSAGE

dizziness, tinnitus, vertigo, loss of high-tone hearing acuity, respiratory failure, and neuromuscular blockade. Administration by inhalation results in low systemic bioavailability of tobramycin. Tobramycin is not significantly absorbed following oral administration. Tobramycin serum concentrations may be helpful in monitoring overdosage. DESCRIPTION

Nebulizer (PARI LC PLUS). Tobramycin inhalation solution is a sterile, clear, slightly yellow, non-pyrogenic, aqueous solution with the pH and salinity adjusted specifically for administration by a compressed air driven PARI LC PLUS Reusable Nebulizer. The chemical formula for tobramycin is $C_{18}H_{37}N_5O_9$ and the molecular weight is 467.52. Tobramycin is O-3-amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 4)-O-[2,6-diamino-2,3,6-trideoxy- α -D-*ribo*hexopyranosyl- $(1\rightarrow 6)$]-2-deoxy-L-streptamine. The structural formula for tobramycin is:

pH to 6.0. Nitrogen is used for sparging. The formulation contains no preservatives. The inhalation solution has an osmolality in the range 135 to 200 mOsmol/kg. The PARI LC PLUS Reusable Nebulizer has the following performance characteristics with tobramycin inhalation solution [measured using Next Generation Impactor (NGI) at 15 L/min continuous flow, standard conditions (50%RH, 23°C)]: (1) Delivered Dose: 174 mg;

(2) Fine Particle Dose (< 5µm): 97 mg; (3) Nebulization Time: 13 min.; (4) Mass Median Aerodynamic Diameter: 4.3 μm; (5) Geometric Standard Deviation (GSD): 2.2 μm.

CLINICAL PHARMACOLOGY

Mechanism of Action

Tobramycin is an antibacterial drug [see Clinical Pharmacology (12.4)]. **Pharmacokinetics** Tobramycin inhalation solution contains tobramycin, a cationic polar molecule that does not readily cross epithelial membranes. The bioavailability of tobramycin inhalation solution may vary because of individual differences in nebulizer performance and airway pathology. Following administration of tobramycin inhalation solution, tobramycin remains concentrated primarily in the airways.

Sputum Concentrations: Ten minutes after inhalation of the first 300 mg dose of tobramycin inhalation solution, 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 inhalation solution regimen, the average concentration of tobramycin at ten minutes after inhalation was 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 inhalation solution by cystic fibrosis patients

was 0.95 mcg/mL. After 20 weeks of therapy on the tobramycin inhalation solution regimen, the average serum tobramycin concentration one hour after dosing was 1.05 mcg/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

inhalation solution administration, is likely eliminated primarily in expectorated sputum.

Tobramycin is an aminoglycoside antibacterial produced by Streptomyces tenebrarius. It acts primarily by disrupting protein synthesis, leading to altered cell permeability, progressive disruption of the cell envelope, and eventual cell death. Tobramycin has in vitro activity against Gram-negative bacteria including P. aeruginosa. It is bactericidal in vitro at peak concentrations equal to or slightly greater than the

Interpretive criteria for inhaled antibacterial products are not defined. In vitro antimicrobial

susceptibility test methods used to determine the susceptibility for parenteral tobramycin therapy can be used to monitor the susceptibility of P. aeruginosa isolated from cystic fibrosis patients.^(1,2,3) The relationship between in vitro susceptibility test results and clinical outcome with tobramycin inhalation solution therapy is not clear. A single sputum sample

from a cystic fibrosis patient may contain multiple morphotypes of *P. aeruginosa* and each morphotype may require a different concentration of tobramycin to inhibit its growth in vitro. Patients should be monitored for changes in tobramycin susceptibility. NONCLINICAL TOXICOLOGY Carcinogenesis, Mutagenesis, Impairment of Fertility A two-year rat inhalation toxicology study to assess carcinogenic potential of tobramycin inhalation solution has been completed. Rats were exposed to tobramycin inhalation solution for up to 1.5 hours per day for 95 weeks. The clinical formulation of the drug was used for this carcinogenicity study. Serum levels of tobramycin of up to 35 mcg/mL

were measured in rats, in contrast to the average 1 mcg/mL levels observed in cystic

fibrosis patients in clinical trials. There was no drug-related increase in the incidence

 $\label{lem:conditionally} Additionally, to bramycin has been evaluated for genotoxicity in a battery of in vitro and in (x,y) and the substitution of the property of the$ vivo tests. The Ames bacterial reversion test, conducted with 5 tester strains, failed to show

a significant increase in revertants with or without metabolic activation in all strains. Tobramycin was negative in the mouse lymphoma forward mutation assay, did not induce chromosomal aberrations in Chinese hamster ovary cells, and was negative in the mouse micronucleus test Subcutaneous administration of up to 100 mg/kg of tobramycin did not affect mating behavior or cause impairment of fertility in male or female rats. **CLINICAL STUDIES**

Two identically designed, double-blind, randomized, placebo-controlled, parallel group, 24-week clinical studies (Study 1 and Study 2) at a total of 69 cystic fibrosis centers in the United States were conducted in cystic fibrosis patients with *P. aeruginosa* with tobramycin

inhalation solution. Subjects who were less than 6 years of age, had a baseline creatinine

of > 2 mg/dL, or had B. cepacia isolated from sputum were excluded. All subjects had baseline FEV₁% predicted between 25% and 75%. In these clinical studies, 258 patients received tobramycin inhalation solution therapy on an outpatient basis (see Table 2) using a PARI LC PLUS nebulizer along with a DeVilbiss Pulmo-Aide compressor. Table 2: Dosing Regimens in Clinical Studies Cycle 1 Cycle 2 Cycle 3 28 days 28 days 28 days 28 days 28 days 28 days TOBRAMYCIN No drug TOBRAMYCIN No drug TOBRAMYCIN No drug TOBRAMYCIN

Inhalation

Inhalation Inhalation Inhalation

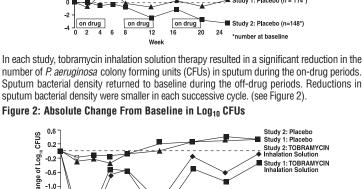
	regimen n=258	300 mg BID	300 mg BID	300 mg	
	Placebo regimen n=262	Placebo BID	Placebo BID	Placebo BID	
All patients received either tobramycin inhalation solution or placebo (saline with 1.25 mg quinine for flavoring) in addition to standard treatment recommended for cystic fibrosis patients, which included oral and parenteral anti-pseudomonal therapy, Beta 2-agonists cromolyn, inhaled steroids, and airway clearance techniques. In addition, approximately 77% of patients were concurrently treated with dornase alfa.					
	In each study, tobramycin inhalation solution-treated patients experienced significant				

relative to baseline (Week 0) during 24 weeks compared to no average change in placebo patients. In Study 2, tobramycin inhalation solution-treated patients had an average increase of about 7% compared to an average decrease of about 1% in placebo patients. Figure 1 shows the average relative change in FEV₁% predicted over 24 weeks for both studies. Figure 1: Relative Change From Baseline in FEV₁% Predicted

improvement in pulmonary function. Improvement was demonstrated in the tobramycin

inhalation solution group in Study 1 by an average increase in FEV $_1\%$ predicted of about 11 %

10 Study 1: TOBRAMYCIN Study 2: TOBRAMYCIN



of 5.1 days compared to 8.1 days for placebo patients. Patients treated with tobramycin inhalation solution required an average of 9.6 days of parenteral anti-pseudomonal antibiotic treatment compared to 14.1 days for placebo patients. During the 6 months of treatment, 40% of tobramycin inhalation solution patients and 53% of placebo patients were treated with parenteral anti-pseudomonal antibiotics. The relationship between in vitro susceptibility test results and clinical outcome with tobramycin inhalation solution therapy is not clear. However, 4 tobramycin inhalation solution patients who began the clinical trial with *P. aeruginosa* isolates having MIC values \geq 128 μ g/mL did not experience an improvement in FEV₁ or a decrease in sputum bacterial density. **REFERENCES**

on drug

on drug

Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.

Suite 2500, Wayne, Pennsylvania 19087, USA, 2014.

How Supplied

16

16.1

HOW SUPPLIED / STORAGE AND HANDLING

2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard - Eleventh Edition. CLSI document M02-A11, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012. 3. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fourth Informational Supplement, CLSI document M100-S24, Clinical and Laboratory Standards Institute, 950 West Valley Road,

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Ninth Edition.

CLSI document M07-A9, Clinical and Laboratory Standards Institute, 950 West Valley Road,

Storage 16.2 Tobramycin inhalation solution should be stored under refrigeration at 2-8°C/36-46°F. Upon removal from the refrigerator, or if refrigeration is unavailable, tobramycin inhalation solution pouches (opened or unopened) may be stored at room temperature (up to 25°C/77°F) for up to 28 days. Tobramycin inhalation solution should not be used beyond the expiration date stamped on the ampule when stored under refrigeration

(2-8°C/36-46°F) or beyond 28 days when stored at room temperature (25°C/77°F).

Tobramycin inhalation solution ampules should not be exposed to intense light. The solution

in the ampule is slightly yellow, but may darken with age if not stored in the refrigerator;

however, the color change does not indicate any change in the quality of the product as

KITABIS PAK co-packaged kit (NDC 24492-850-56) is available in cartons containing one

reusable PARI LC PLUS nebulizer (Model No.: 022B81-T) and 14 tobramycin inhalation solution pouches. Each pouch contains four 300 mg/5 ml ampules of tobramycin inhalation

solution for a total of 56 ampules in each carton. Each carton constitutes a 28 day supply.

long as it is stored within the recommended storage conditions. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use). **Instructions for Administration** Instruct patients to read the *Instructions for Use* before starting KITABIS PAK. Instruct patients to use the tobramycin inhalation solution in KITABIS PAK only with the PARI LC PLUS

solution can cause a narrowing of the airway [see Warnings and Precautions (5.1)].

Difficulty Breathing

Reusable Nebulizer included in the KITABIS PAK.

Advise patients to inform their physician if they experience ringing in the ears, dizziness, or any changes in hearing because tobramycin inhalation solution has been associated with hearing loss [see Warnings and Precautions (5.2)]. Kidney Damage Advise patients to inform their physician if they have any history of kidney problems

because tobramycin inhalation solution is in a class of drugs that have caused kidney

antibacterial drugs that have caused harm to the fetus [see Warnings and Precautions (5.5)].

Advise patients to inform their physicians if they experience shortness of breath or

wheezing after administration of tobramycin inhalation solution. Tobramycin inhalation

damage [see Warnings and Precautions (5.3)]. Advise patients to talk with their physician if they want to become pregnant while on tobramycin inhalation solution because tobramycin inhalation solution is in a class of

Advise patients to talk with their physician before using tobramycin inhalation solution while nursing a baby [see Use in Specific Populations (8.3)]. **Additional Information**

Catalent Pharma Solutions, LLC Woodstock, IL 60098

850D5601 Rev C 05/2016

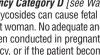
Nursing Mothers

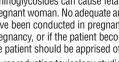
Manufactured by:

PARI LC PLUS® Reusable Nebulizer: 1-800-327-8632 DeVilbiss® Pulmo-Aide® Air Compressor: 1-800-338-1988 KITABIS PAK: 1-844-KITABIS (548-2247)



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The safety and efficacy of tobramycin inhalation solution have not been studied in pediatric Clinical studies of tobramycin inhalation solution did not include patients aged 65 years and

Signs and symptoms of acute toxicity from overdosage of IV tobramycin might include

KITABIS PAK contains tobramycin inhalation solution, USP and the PARI LC PLUS Reusable

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12.1

Mechanism of Action

Susceptibility Testing

minimum inhibitory concentration.