TIOCAP®

(TIOTROPIUM)

ٹائیوکیپ

COMPOSITION
TioCap 18mcg
Each capsule contains:
Tiotropium bromide monohydrate Ph. Eur. equivalent
to Tiotropium.....18mcg
(As per Innovator's Specs.)

DESCRIPTION
Each hard gelatin TioCap capsule contains a dry powder consisting of 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate (which may contain milk proteins).

The contents of TioCap capsules are intended for oral inhalation only, and are intended for administration only with the AirCare device.

The active component of TioCap is tiotropium. The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1α, 2β, 4β, 5α, 7β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.02,4]nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound.

Tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of $C_{19}H_{22}NO_4S_2Br \cdot H_2O$.

The AirCare device is an inhalation device used to inhale the dry powder contained in the TioCap capsule. The dry powder is delivered from the AirCare device at flow rates as low as 20 L/min. Under standardized in vitro testing, the AirCare device delivers a mean of 10.4 mcg tiotropium when tested at a flow rate of 39 L/min for 3.1 seconds (2 L total).

CLINICAL PHARMACOLOGY
Mechanism of Action
Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3-receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical in vitro as well as in vivo studies, prevention of methacholine-induced bronchoconstriction effects was dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

Pharmacodynamics
Cardiac Electrophysiology
In a multicenter, randomized, double-blind trial using tiotropium dry powder for inhalation that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30 to 60 msec was higher in the tiotropium group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs. 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical studies with tiotropium did not detect an effect of the drug on QTc intervals.

The effect of tiotropium dry powder for inhalation on QT interval was also evaluated in a randomized, placebo- and positive-controlled crossover study in 53 healthy volunteers. Subjects received tiotropium dry powder for inhalation 18 mcg, 54 mcg (3 times the recommended dose), or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Relative to placebo, the maximum mean change from baseline in study-specific QTc interval was 3.2 msec and 0.8 msec for tiotropium dry powder for inhalation 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of ≥60 msec.

Pharmacokinetics
Tiotropium is administered by dry powder inhalation. Some of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy. A dedicated pharmacokinetic study in patients with COPD evaluating once-daily tiotropium delivered from the RESPIMAT inhaler (5 mcg) and as inhalation powder (18 mcg) from the HANDIHALER device resulted in a similar systemic exposure between the two products.

Absorption
Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Food is not expected to influence the absorption of tiotropium. Maximum tiotropium plasma concentrations were observed 7 minutes after inhalation.

Distribution
Tiotropium is 72% bound to plasma protein and had a volume of distribution of 32 L/kg after intravenous administration to young healthy volunteers. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not readily penetrate the blood-brain barrier.

Metabolism
The extent of metabolism is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, neither of which binds to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. In vitro studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations did not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Excretion
Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74%). After dry powder inhalation to COPD patients at steady state, urinary excretion was 7% (1.3mcg) of the unchanged dose over 24 hours. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine.

The terminal half-life of tiotropium in COPD patients following once daily inhalation of 5 mcg tiotropium was approximately 25 hours. Total clearance was 880 mL/min after intravenous administration in young healthy volunteers. After chronic once-daily dry powder inhalation by COPD patients, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

Specific Populations
Geriatric Patients
As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (365 mL/min in COPD patients < 65 years to 271 mL/min in COPD patients ≥ 65 years) This did not result in a corresponding increase in AUC0-6,ss or Cmax,ss values.

Renally Impaired Patients
Following once daily inhaled administrations of tiotropium to steady-state in COPD patients, mild renal impairment (CLCR 50-80 ml/min) resulted in slightly higher AUC0-6,ss (between 1.8-30% higher) and similar Cmax, ss values compared to patients with normal renal function(CLCR >80 ml/min).

In COPD patients with moderate to severe renal impairment (CLCR <50 ml/min), the intravenous administration of tiotropium resulted in doubling of the total exposure (82% higher AUC0-4h) and 52% higher Cmax) compared to COPD patients with normal renal function, which was confirmed by plasma concentrations after dry powder inhalation.

Hepatically Impaired Patients
Liver insufficiency is not expected to have any relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and simple non-enzymatic ester cleavage to pharmacologically inactive products.

Paediatric Patients
No data is available.

INDICATIONS
TioCap (tiotropium bromide inhalation powder) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. TioCap is indicated to reduce exacerbations in COPD patients.

DOSAGE AND ADMINISTRATION
For oral inhalation only. Do not swallow TioCap capsules, as the intended effects on the lungs will not be obtained. The contents of the TioCap capsules should only be used with the AirCare® device
The recommended dose of TioCap is two inhalations of the powder contents of one TioCap capsule, once-daily, with the AirCare device. Do not take more than one dose in 24 hours.

For administration of TioCap, a capsule is placed into the center chamber of the AirCare device. The TioCap capsule is pierced by pressing and releasing the piercing button on the side of the AirCare device. The tiotropium formulation is dispersed into the air stream when the patient inhales through the mouthpiece.

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given TioCap should be monitored closely for anticholinergic effects.

Using the AirCare device:
TioCap capsules should only be used with AirCare device. Do not ingest TioCap capsules. Detailed instructions for use are given at the end of this patient information leaflet.

Dosage adjustment
Geriatric
Geriatric patients can use tiotropium bromide at the recommended dose.

Renal impairment
Renally impaired patients can use tiotropium bromide at the recommended dose. For patients with moderate to severe impairment (creatinine clearance ≤ 50 ml/min)

Hepatic impairment
Hepatically impaired patients can use tiotropium bromide at the recommended dose.

Pediatric dosage
COPD
There is no relevant use in the paediatric population (below 18 years).

Cystic fibrosis
The safety and efficacy of TioCap in children and adolescents has not been established. No data are available.

CONTRAINDICATIONS
TioCap is contraindicated in patients with a hypersensitivity to tiotropium or any components of this product. In clinical trials and postmarketing experience with TioCap, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported.

WARNING AND PRECAUTIONS
Not for Acute Use
TioCap is intended as a once-daily maintenance treatment for COPD and should not be used for relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm.

Immediate Hypersensitivity Reactions
Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue, or throat), rash, bronchospasm, anaphylaxis, or itching, may occur after administration of TioCap. If such a reaction occurs, therapy with TioCap should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to TioCap. In addition, TioCap should be used with caution in patients with severe hypersensitivity to milk proteins.
Paradoxical Bronchospasm
Inhaled medicines, including TioCap, may cause paradoxical bronchospasm. If this occurs, it should be treated immediately with an inhaled short-acting beta2-agonist such as albuterol. Treatment with TioCap should be stopped and other treatments considered.

Worsening of Narrow-Angle Glaucoma
TioCap should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Worsening of Urinary Retention
TioCap should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

ADVERSE REACTIONS
The frequencies assigned to the undesirable effects listed below are based on crude incidence rates of adverse drug reactions (i.e. events attributed to tiotropium) observed in the tiotropium group (9,647 patients) from 28 pooled placebo-controlled clinical trials with treatment periods ranging from four weeks to four years.

Frequency is defined using the following convention:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data)

System Organ Class / MedDRA Preferred Term	**Frequency**
Metabolism and nutrition disorders	
Dehydration	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Taste disorders	Uncommon
Insomnia	Rare
Eye disorders	
Vision blurred	Uncommon
Glaucoma	Rare
Intraocular pressure increased	Rare
Cardiac disorders	
Atrial fibrillation	Uncommon
Supraventricular tachycardia	Rare
Tachycardia	Rare
Palpitations	Rare
Respiratory, thoracic and mediastinal disorders	
Pharyngitis	Uncommon
Dysphonia	Uncommon
Cough	Uncommon
Bronchospasm	Rare

Epistaxis	Rare
Laryngitis	Rare
Sinusitis	Rare
Gastrointestinal disorders	
Dry Mouth	Common
Gastrooesophageal reflux disease	Uncommon
Constipation	Uncommon
Oropharyngeal candidiasis	Uncommon
Intestinal obstruction, including ileus paralytic	Rare
Gingivitis	Rare
Glossitis	Rare
Dysphagia	Rare
Stomatitis	Rare
Nausea	Rare
Dental caries	Not known
Skin and subcutaneous tissue disorders, immune system disorders	
Rash	Uncommon
Urticaria	Rare
Pruritus	Rare
Hypersensitivity (including immediate reactions)	Rare
Angioedema	Rare
Anaphylactic reaction	Not known
Skin infection, skin ulcer	Not known
Dry skin	Not known
Musculoskeletal and connective tissue disorders	
Joint swelling	Not known
Renal and urinary disorders	
Dysuria	Uncommon
Urinary retention	Uncommon
Urinary tract infection	Rare

Description of selected adverse reactions
In controlled clinical studies, the commonly observed undesirable effects were anticholinergic undesirable effects such as dry mouth which occurred in approximately 4% of patients.

In 28 clinical trials, dry mouth led to discontinuation in 18 of 9,647 tiotropium treated patients (0.2 %).

Serious undesirable effects consistent with anticholinergic effects include glaucoma, constipation and intestinal obstruction including ileus paralytic as well as urinary retention.

DRUG INTERACTIONS
Although no formal drug interaction studies have been performed, tiotropium bromide inhalation powder has been used concomitantly with other drugs without clinical evidence of drug interactions. These include sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, commonly used in the treatment of COPD.

Use of LABA or ICS was not found to alter the exposure to tiotropium.

The co-administration of tiotropium bromide with other anticholinergic-containing drugs has not been studied and is therefore not recommended.

USE IN SPECIAL POPULATIONS
Pregnancy
There is a very limited amount of data from the use of tiotropium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses. As a precautionary measure, it is preferable to avoid the use of TioCap during pregnancy.

Breast-feeding
It is unknown whether tiotropium bromide is excreted in human breast milk. Despite studies in rodents which have demonstrated that excretion of tiotropium bromide in breast milk occurs only in small amounts, use of TioCap is not recommended during breast-feeding. Tiotropium bromide is a long-acting compound. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with TioCap should be made taking into account the benefit of breast-feeding to the child and the benefit of TioCap therapy to the woman.

Pediatrics
See section Dose adjustment.

Elderly
See section Dose adjustment.

Renal impairment
See section Dose adjustment.

Hepatic impairment
See section Dose adjustment.

OVER DOSAGE
High doses of tiotropium bromide may lead to anticholinergic signs and symptoms.

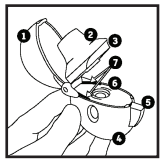
However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 340 microgram tiotropium bromide in healthy volunteers. Additionally, no relevant adverse effects, beyond dry mouth, were observed following 7 day dosing of up to 170 microgram tiotropium bromide in healthy volunteers. In a multiple dose study in COPD patients with a maximum daily dose of 43 microgram tiotropium bromide over four weeks no significant undesirable effects have been observed.

Acute intoxication by inadvertent oral ingestion of tiotropium bromide capsules is unlikely due to low oral bioavailability.

PRESENTATION
TioCap 18mcg: Pack of 6 capsules.

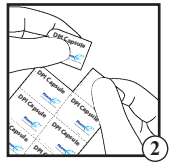
INSTRUCTION ON HOW TO USE CAPSULE

Components of AirCare Device:
1. Dust Cap
2. Mouthpiece
3. Mouthpiece grip
4. Base
5. Piercing button
6. Capsule chamber
7. Air intake vents



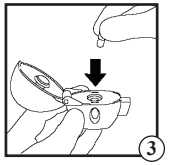
Open the dust cap by pulling it upwards and lift the mouthpiece with help of the mouthpiece grip.

ایئر کیئر ڈیوائس کے ڈسٹ کیپ کو کھولیں اور ماؤتھ پیس گرپ کی مدد سے ماؤتھ پیس کو اوپر کھینچیے۔



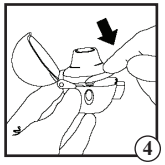
Remove the capsule from the blister right before use. Do not store the capsule in the AirCare device.

استعمال سے پہلے کیپسول بلسٹر میں سے نکالیں۔ کیپسول کو ایئر کیئر ڈیوائس میں اسٹور نہ کریں۔



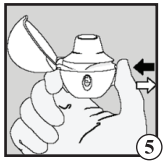
Insert the capsule in the capsule chamber of the AirCare device.

کیپسول کو ایئر کیئر ڈیوائس کے کیپسول چیمبر میں ڈالیں۔



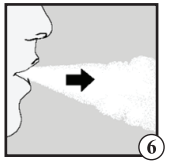
Close the mouthpiece until you hear a click, but leave the dust cap open.

جب تک کلک کی آواز نہ سُنائی دے تب تک ماؤتھ پیس کو بند کریں، لیکن ڈسٹ کیپ کو کھلا رہنے دیں۔



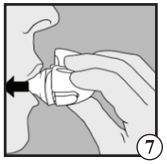
Hold the AirCare device with the mouthpiece upright. Press the piercing button once completely and release. This is how you make holes in the capsule so that you get medicine when you breathe in.

ایئر کیئر ڈیوائس کو سیدھا پکڑیں۔ کیپسول پنچر کرنے والے بٹن کو ایک دفعہ مکمل طور پر دبائیں اور چھوڑ دیں۔ اس طرح آپ کیپسول میں سوراخ کرتے ہیں تاکہ سانس لینے پر آپ کو دوا مل جائے۔



Breathe out completely. Do not breathe (exhale) into the mouthpiece of the AirCare device at any time.

مکمل طور پر سانس باہر نکالیں۔ کبھی بھی ایئر کیئر ڈیوائس کے ماؤتھ پیس میں پھونک نہ ماریں۔



Raise the AirCare device to your mouth and close your lips tightly around the mouthpiece. Keep your head in an upright position. Breathe in slowly and deeply so that you hear or feel the capsule vibrate. Breathe in as much as you can and hold your breath as long as possible. At the same time, remove the AirCare device from your mouth. Breathe normally again.
Repeat steps 6 & 7, in order to empty the capsule completely.

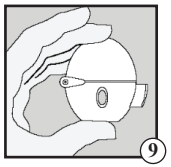
ایئر کیئر ڈیوائس کو اپنے منہ کی طرف اٹھائیں اور اپنے ہونٹوں سے ماؤتھ پیس کو مضبوطی سے پکڑیں۔ اپنے سر کو سیدھا رکھیں۔ آہستہ اور گہری سانس لیں یہاں تک کہ آپکو کیپسول ہلتی ہوئی محسوس ہو یا سنائی دے۔ جتنا ہو سکے سانس لیں اور اپنی سانس کو جتنی دیر ہو سکے روکے رکھیں۔ ساتھ ہی ایئر کیئر ڈیوائس کو منہ سے ہٹالیں۔ پھر حسب معمول سانس لیں۔ کیپسول کو مکمل طور پر خالی کرنے کے لیے اقدامات 6 اور 7 کو دہرائیں۔

کیپسول استعمال کرنے کا طریقہ

ایئر کیئر ڈیوائس کے کمپونینٹ
۱ - ڈسٹ کیپ
۲ - ماؤتھ پیس
۳ - ماؤتھ پیس کا گرپ
۴ - بیس
۵ - کیپسول پنچر کرنے کا بٹن
۶ - کیپسول کا چیمبر
۷ - ہوا کے داخل ہونے کا راستہ

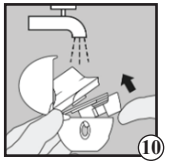
After taking your dose, open the mouthpiece. Tip out the used capsule and throw it away.

اپنی دوا لینے کے بعد، ماؤتھ پیس کو کھولیں۔ استعمال شدہ کیپسول نکال کر پھینک دیں۔



Close the mouthpiece and dust cap for storing your AirCare device.

ایئر کیئر ڈیوائس کو اسٹور کرنے سے پہلے ماؤتھ پیس اور ڈسٹ کیپ کو بند کر دیں۔



Clean the AirCare device once a month. Open the dust cap and mouthpiece. Then open the base by lifting the piercing button. Rinse the AirCare device with warm water and check if any powder buildup or capsule fragments remain. Dry the AirCare device thoroughly by tipping excess of water out on a paper towel and air-dry afterwards, leaving the dust cap, mouthpiece and base open.
Do not use detergents or a dishwasher to clean the AirCare device. It takes 24 hours to air dry, so clean it immediately after use so that it will be ready for your next dose. Do not use a hair dryer to dry the AirCare device. Do not use the AirCare device when it is wet. If needed, you may clean the outside of the mouthpiece with a clean damp cloth.

ایئر کیئر ڈیوائس کو مہینے میں ایک مرتبہ صاف کریں۔ ڈسٹ کیپ اور ماؤتھ پیس کھولیں۔ پھر پنچر کرنے والے بٹن کو اٹھا کر بیس کو کھولیں۔ ایئر کیئر ڈیوائس کو نیم گرم پانی سے کھنگال لیں اور چیک کر لیں کہ پاؤڈر یا کیپسول کے ذرات رہ نہ گئے ہوں۔ ایئر کیئر ڈیوائس میں موجود پانی کو ٹیشو پیپر تولیے پر نکال لیں۔ ڈسٹ کیپ، ماؤتھ پیس اور بیس کو کھلا رکھیں اور ہوا میں خشک ہونے دیں۔ ایئر کیئر ڈیوائس کی صفائی کے لئے ڈیٹرجینٹ یا ڈش واشر کا استعمال نہ کریں۔ ایئر کیئر ڈیوائس 24 گھنٹے میں ہوا میں خشک ہوتا ہے، اس لیے اسے استعمال کے فوراً بعد صاف کریں تاکہ یہ آپ کی اگلی خوراک کے لیے تیار ہو۔ ایئر کیئر ڈیوائس کو خشک کرنے کے لیے ہیئر ڈرائر کا استعمال نہ کریں۔ ایئر کیئر ڈیوائس گیلا ہونے کی صورت میں استعمال نہ کریں۔ ماؤتھ پیس کا بیرونی حصہ گیلے کپڑے سے صاف کیا جا سکتا ہے۔

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
Capsules are intended for use through Aircare only and are not to be swallowed.
For suspected adverse drug reaction, email us at reports@pharmevo.biz

For more information on our products call PharmAssist helpline 0800-82222 Monday to Friday 9:00 am to 6:00 pm or email us at : pharmassist@pharmevo.biz

ہدایات:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔
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