Gentrop™ 18mcg
(Tiotropium Bromide)
Dry Powder Capsules For Oral Inhalation Only

جینٹروپ
ڈرائی پاؤڈر کیپسولز
۱۸ مائیکروگرام
(ٹائیوٹروپیئم بروماٹیڈ)

QUALITATIVE AND QUANTITATIVE COMPOSITION
Gentrop™ Dry Powder Capsules 18mcg
Each capsule contains:
Tiotropium bromide monohydrate B.P. eq. to Tiotropium…..18mcg
Innovator's Specs.

DESCRIPTION: The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol.

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: The bronchodilation is primarily a local effect (on the airways), not a systemic one. Dissociation from M2-receptors is faster than from M3, which in functional in vitro studies, elicited (kinetically controlled) receptor subtype selectivity of M3 over M2. The high potency and slow receptor dissociation found its clinical correlate in significant and long acting bronchodilation in patients with COPD.
Pharmacokinetics: Tiotropium is administered by dry powder inhalation. In common with other inhaled drugs, the majority of the delivered dose is deposited in the gastrointestinal tract and, to a lesser extent, in the lung, the intended organ.
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. It is expected from the chemical structure of the compound (quaternary ammonium compound) that tiotropium is poorly absorbed from the gastrointestinal tract. The effect of food on tiotropium's bioavailability has not been studied. Oral solutions of tiotropium have an absolute bioavailability of 2% to 3%. Maximum tiotropium plasma concentrations were observed 5 minutes after inhalation.
Distribution: Tiotropium shows a volume of distribution of 32 L/kg, indicating that the drug binds extensively to tissues. The human plasma protein binding for tiotropium is 72%. At steady state, peak tiotropium plasma levels in COPD patients were 17 to 19 pg/mL when measured 5 minutes after dry powder inhalation of an 18mcg dose and decreased in a multi compartmental manner. Steady-state trough plasma concentrations were 3 to 4 pg/mL. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Metabolism: The extent of metabolism appears to be 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 non enzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, neither of which bind to muscarinic recep-

tors. Elimination: The terminal elimination half life of tiotropium was between 5 and 6 days following inhalation.

INDICATIONS AND USAGE: Gentrop™ (Tiotropium Bromide) Capsule is indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

CONTRAINDICATIONS: Tiotropium Bromide is contraindicated in patients with a hypersensitivity to tiotropium bromide, atropine or its derivatives, e.g. ipratropium or oxitropium or any components of this product.

INTERACTIONS: There is potential for an additive interaction with concomitantly used anticholinergic medications and therefore not recommended. However, no interaction has been found with concomitantly used short acting and long acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and inhaled steroids.

USE IN SPECIFIC POPULATION: **Pregnancy:** Teratogenic effects, Category C: There are no adequate and well-controlled studies in pregnant women. Tiotropium Bromide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing Mothers: Caution should be exercised if Tiotropium Bromide is administered to a nursing woman.
Breast feeding: Use of Tiotropium Bromide is not recommended during breast feeding. **Pediatric Use:** Tiotropium Bromide is approved for use in the maintenance treatment of bronchospasm associated with COPD and for the reduction of COPD exacerbations. COPD does not normally occur in children. The safety and effectiveness of Tiotropium Bromide in pediatric patients have not been established.
Geriatric Use: Geriatric patients can use tiotropium bromide at the recommended dose. Renal impairment: Patients with moderate to severe renal impairment (creatinine clearance of ≤ 50mL/min) treated with Tiotropium Bromide should be monitored closely for anticholinergic side effects.

PRECAUTIONS: **Not for Acute Use:** Tiotropium Bromide is intended as a once-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm (i.e., rescue therapy). Immediate Hypersensitivity Reactions: angioedema (including swelling of the lips, tongue, or throat), itching, or rash may occur after administration of Tiotropium Bromide. If such a reaction occurs, therapy with Tiotropium Bromide 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 should be closely monitored for similar hypersensitivity reactions to Tiotropium Bromide. In addition, Tiotropium Bromide should be used with caution in patients with severe hypersensitivity to milk proteins. Paradoxical Bronchospasm: Inhaled medicines, including Tiotropium Bromide, may cause paradoxical bronchospasm. If this occurs, treatment with Tiotropium Bromide should be stopped and other treatments considered.
Worsening of Narrow Angle Glaucoma: Tiotropium Bromide 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 cooled 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: Tiotropium Bromide should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder neck obstruction (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.
Renal Impairment: As a predominantly renally excreted drug, patients with

moderate to severe renal impairment (creatinine clearance of ≤ 50mL/min) treated with Tiotropium Bromide should be monitored closely for anticholinergic side effects.

ADVERSE REACTIONS: **Common or very common:** Immediate hypersensitive reactions, paradoxical bronchospasm, worsening of narrow angel glaucoma. Worsening of dizziness, worsening of urinary retention, epistaxis, oropharyngeal candidiasis, pruritus, taste disturbance, dry mouth, sinus infection, sore throat, non specific chest pain, urinary tract infection, indigestion, runny nose, constipation, increased heart rate, blurred vision. Rare: Gingivitis, glossitis, insomnia, intestinal obstruction, paralytic ileus, sinusitis, stomatitis. Frequency not known: Dehydration, joint swelling

DOSAGE AND ADMINISTRATION: For oral inhalation only. Do not swallow Gentrop™ capsules, as the intended effects on the lungs will not be obtained. The contents of the Gentrop™ capsules should only be used with inhalation device. The recommended dose of Tiotropium Bromide is one capsule, once daily with inhalation device. Do not take more than one dose in 24 hours. No dosage adjustment is required for geriatric, hepatically-impaired, or renally impaired patients. However, patients with moderate to severe renal impairment given tiotropium bromide should be monitored closely for anticholinergic effects

METHOD OF ADMINISTRATION:
Kindly follow the instructions of use with inhalation device.
Overdosage: High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once daily inhalation of 141 mcg of tiotropium.

DOSAGE: As directed by the physician.

INSTRUCTIONS: Store at 25°C, excursions permitted to 15°C-30°C. Protect from sunlight and moisture. Keep all medicines out of the reach of children. Do not swallow Gentrop™ capsules. For Oral Inhalation only.

PRESENTATION: Gentrop™ (Tiotropium Bromide) Dry Powder Capsules for oral inhalation are available in Alu-Alu blister pack of 3x10's with leaflet.

علامات/طریقہ استعمال:
جینٹروپ کیپسولز سی،او، پی،ڈی، برونکائٹس اور ایمفائیسیما کے علاج کے لئے تجویز کردہ ہے۔
جینٹروپ کیپسول اورل انہیلیشن کیلئے ہے، نگلنے سے گریز کریں۔

مضر اثرات:
خارش، نکسیر، منہ کا خشک ہونا، گلے کی سوزش، منہ کا ذائقہ خراب ہونا، قبض، بدہضمی، دھندلا پن، سینے میں درد، جوڑوں کی سوزش وغیرہ

احتیاطی تدابیر:
علاج سے پہلے حساس مریضوں کی تشخیص ضروری ہے۔ حاملہ خواتین، موتیا اور گردے کے مریض احتیاط سے استعمال کریں۔

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: ۲۵ ڈگری سینٹی گریڈ پر رکھیں، محفوظ رکھنے کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے۔
سورج کی روشنی اور نمی سے محفوظ رکھیں۔ تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

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