Tioget™

[T i o t r o p i u m]

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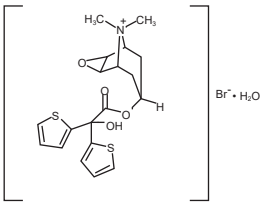
18mcg Dry Powder Inhaler (DPI) Capsules

DESCRIPTION

Tioget Dry Powder Inhaler Capsules contains tiotropium, a synthetic, non-chiral, quaternary ammonium compound. Chemically, tiotropium bromide monohydrate is (1α, 2β, 4β, 5α, 7β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane bromide monohydrate. The molecular formula of tiotropium bromide monohydrate is $C_{19}H_{22}NO_4S_2Br{\bullet}H_2O$ and the structural formula is:



Tiotropium Bromide Monohydrate

QUALITATIVE & QUANTITATIVE COMPOSITION

Tioget (Tiotropium) Dry Powder Inhaler Capsules are available for administration as:

Tioget Dry Powder Inhaler Capsules 18mcg
Each capsule contains:
Tiotropium bromide monohydrate equivalent to Tiotropium…18mcg

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, M_1 to M_5. In the airways, it exhibits pharmacological effects through inhibition of M_3-receptors at the smooth muscle leading to bronchodilation. The effect was dose dependent and lasted longer than 24h. The long duration is probably due to the very slow dissociation from the M_3 receptor. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

Pharmacokinetics

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. Maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation. Food is not expected to influence the absorption of tiotropium.

At steady state, peak tiotropium plasma levels in COPD patients were 12.9 pg/ml and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.71pg/ml.

Distribution

Tiotropium has a plasma protein binding of 72% and shows a volume of distribution of 32L/kg. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung.

Metabolism

The extent of biotransformation is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. The ester tiotropium bromide is non-enzymatically cleaved to the alcohol (N-methylscopine) and acid compound (dithienylglycolic acid) that are inactive on muscarinic receptors.

Excretion

The effective half-life of tiotropium ranges between 27-45 h in COPD patients. Total clearance was 880 ml/min after an intravenous dose in young healthy volunteers. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%). After dry powder inhalation by COPD patients to steady-state, urinary excretion is 7% (1.3µg) of the unchanged drug over 24 hours, the remainder being mainly non-absorbed drug in gut that is eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic once daily inhalation by COPD patients, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

Special Population

Renal Impairment

Following 4-week, once daily dosing in patients with COPD, mild renal impairment resulted in 6-23% higher $AUC_{0\text{-}6,ss}$ and 6-17% higher $C_{max,ss}$ values; moderate renal impairment resulted in 54-57% higher $AUC_{0\text{-}6,ss}$ and 15-31% higher $C_{max,ss}$ values compared to COPD patients with normal renal function. However, $AUC_{0\text{-}4}$ and C_{max} were 94% and 52% higher, respectively, in patients with severe renal impairment following intravenous infusion of tiotropium bromide.

THERAPEUTIC INDICATIONS

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

DOSAGE AND ADMINISTRATION

For oral inhalation only. Do not swallow Tioget (Tiotropium) Dry Powder Inhaler Capsules, as the intended effects on the lungs will not be obtained. The contents of the Tioget (Tiotropium) Dry Powder Inhaler Capsules should only be used with the Respomatic (DPI device).

The recommended dose is inhalation of the powder contents of one Tioget (Tiotropium) Dry Powder Inhaler Capsule, once-daily, with the Respomatic (DPI device) at the same time of the day. Do not take more than one dose in 24 hours.

Read the instructions for the use of Respomatic (DPI Device) before you start to use Tioget (Tiotropium) Dry Powder Inhaler Capsules. Do not store Tioget (Tiotropium) Dry Powder Inhaler Capsules in the Respomatic (DPI device). Discard the Respomatic (DPI device) 06 months after first use.

Special Population

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given Tioget (Tiotropium) Dry Powder Inhaler Capsules should be monitored closely for anticholinergic effects.

ADVERSE REACTIONS

The following adverse reactions have been reported during therapy with tiotropium:

Common: Dry mouth.

Uncommon: Dizziness, headache, taste disorders, vision blurred, atrial fibrillation, pharyngitis, dysphonia, cough, gastro-oesophageal reflux disease, constipation, oropharyngeal candidiasis, rash, dysuria and urinary retention.

Rare: Insomnia, glaucoma, intraocular pressure increased, supraventricular tachycardia, tachycardia, palpitations, bronchospasm, epistaxis, laryngitis, sinusitis, intestinal obstruction, including ileus paralytic, gingivitis, glossitis, dysphagia, stomatitis, nausea, urticaria, pruritus, hypersensitivity (including immediate reactions), angioedema and urinary tract infection.

Not Known: Dehydration, dental caries, anaphylactic reaction, skin infection, skin ulcer, dry skin and joint swelling.

CONTRAINDICATIONS

Tiotropium is contraindicated in patients with hypersensitivity to the active substance or to any excipient or to atropine and its derivatives, e.g. ipratropium or oxitropium.

PRECAUTIONS

Not for Acute Use

Tiotropium 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 tiotropium. If such a reaction occurs, therapy with tiotropium 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 tiotropium. In addition, tiotropium should be used with caution in patients with severe hypersensitivity to milk proteins.

Paradoxical Bronchospasm

Inhaled medicines, including tiotropium, may cause paradoxical bronchospasm. If this occurs, it should be treated immediately with an inhaled short acting beta$_2$-agonist such as salbutamol. Treatment with tiotropium should be stopped and other treatments considered.

Worsening of Narrow-Angle Glaucoma

Tiotropium 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
Tiotropium 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.

Renal Impairment
As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of <60mL/min) treated with tiotropium should be monitored closely for anticholinergic side effects.

Cardiac arrhythmia
Tiotropium should be used with caution in patients with recent myocardial infarction < 6 months; any unstable or life threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year; hospitalization of heart failure (NYHA Class III or IV) within the past year.

Lactose Intolerance
This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Pregnancy
There is a very limited amount of data from the use of tiotropium in pregnant women. As a precautionary measure, it is preferable to avoid the use of tiotropium during pregnancy.

Nursing Mothers
It is unknown whether tiotropium is excreted in human breast milk. Tiotropium is a long-acting compound. A decision on whether to continue / discontinue breast-feeding or to continue/discontinue therapy with tiotropium should be made taking into account the benefit of breast-feeding to the child and the benefit of tiotropium therapy to the woman.

DRUG INTERACTIONS
Sympathomimetics, Methylxanthines, Steroids
Tiotropium has been used concomitantly with short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and inhaled steroids without increases in adverse reactions.

Anticholinergics
There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of tiotropium with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

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 282mcg tiotropium in healthy volunteers.
Treatment of overdosage consists of discontinuation of tiotropium together with institution of appropriate symptomatic and/or supportive therapy.
Acute intoxication by inadvertent oral ingestion of tiotropium capsules is unlikely due to low oral bioavailability.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Tioget (Tiotropium) Dry Powder Inhaler Capsules 18mcg are available in pack of 30's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz pharma (PVT) LIMITED
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