Tiovair-F™

(Tiotropium + Formoterol Fumarate)

Highnoon

COMPOSITION

Tiovair-F Rotacap: Each capsule contains:
Tiotropium (as Bromide Monohydrate) 18 mcg
Formoterol Fumarate (as Dihydrate) 12 mcg

DESCRIPTION

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

Formoterol fumarate dihydrate is a selective beta2 agonist, which is slightly soluble in water. Its octanol-water partition coefficient at pH 7.4 is 2.6. The Pka of Formoterol dihydrate at 25OC is 7.9 for the phenolic group and 9.2 for the amino group.

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. By binding to the muscarinic receptors in the bronchial smooth musculature, tiotropium bromide inhibits the cholinergic (bronchoconstrictive) effects of acetylcholine, released from parasympathetic nerve endings. The long duration is probably due to very slow dissociation from M3 receptor, exhibiting a significantly longer dissociation half-life than ipratropium.

Formoterol fumarate is a long acting selective beta2 adrenergic agonist (beta2 agonist) with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lungs as a bronchodilator. The long duration of formoterol fumarate action occurs because formoterol fumarate molecules initially diffuse into the plasma membrane of the lung cells and then are slowly released back outside, where they can come into contact with beta2-adrenergic receptors. The pharmacological effect of beta2 adrenoceptor agonist drugs, including formoterol fumarate are at least in part attributable to stimulation of intracellular adenyle cyclase, the enzyme that catalyze the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'- adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

PHARMACOKINETIC

After inhalation some tiotropium bromide is absorbed from the lungs, with majority deposited in the gastrointestinal tract. In healthy subjects a systemic bioavailability of about 24% is reported after dry powder inhalation, and about 33% after inhalation of the solution. Tiotropium is about 72% bound to plasma protein. It is excreted largely unchanged in the urine, although it may undergo some metabolism by non-enzymatic cleavage and by the cytochrome P 450 isoenzymes, CYP2D6 and CYP3A4. The terminal elimination half-life is between 25 and 45 hours in COPD patients and 34 to 44 hour s in asthma patients.

Formoterol is administered by dry powder inhalation. Inhaled Formoterol is rapidly absorbed and peak plasma concentration is typically reached within 5-10 minutes after dosing. It is likely that the majority of inhaled Formoterol delivered is swallowed and then absorbed from the gastrointestinal tract.

INDICATION

- Tiotropium and Formoterol combination is indicated in the maintenance treatment of chronic obstructive pulmonary disease (COPD).
- Management of asthma

DOSAGE AND ADMINISTRATION

Tiotropium and Formoterol combination is intended for use through Revolizer or Rotaflo only and are not to be swallowed, The recommended dosage is the inhalation of the contents of one dry powder inhaler capsule once daily.

Tiovair-F dry powder inhaler capsule should only be used with the Highnoon Revolizer or Rotaflo device.
The dry powder formulation within the Tiovair-F capsule is intended for oral inhalation only

CONTRAINDICATIONS

Tiotropium and Formoterol combination is contraindicated in patients with a hypersensitivity to tiotropium, formoterol, atropine or its derivatives (e.g.ipratropium and oxitropium), lactose mononydrate or any other component of the product.

WARNINGS AND PRECAUTIONS

- Since Tiovair-F dry powder inhaler capsule contains a combination of tiotropium and formoterol, the warnings and precautions for both drugs should be observed. Tiotropium and Formoterol combination should not be used for the treatment of acute episodes of bronchospasm. It should be used which caution in patients with narrow angle glaucoma, prostatic hyperplasia or bladder neck obstruction.

- Patients should be cautioned to avoid getting its contents into their eyes. This might result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temportary blurring of vision, visual halos or coloured images in association with red eyes from conjunctival and corneal congestion. In such situation, Patients should stop using this Tiotropium and Formoterol combination and consult a physician immediately.

- Tiotropium and Formoterol combination should be used with caution in patients with severe renal impairment, cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias or hypertension. Patients should be cautioned about potential adverse cardiovascular effects such as palpitations. Formoterol fumarate, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol fumarate at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown.

- Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

- Potentially serious hypokalaemia may result from beta-agonist therapy. This may be augmented by concomitant treatment with xanthine derivatives, steroids, diuretics, and by hypoxia. The serum potassium levels should therefore be monitored in such situations. As with other inhalation therapy, the potential for paradoxical bronchospasm should be considered. If it occurs, the preparation should be discontinued immediately.

- Patients with moderate to severe renal impairment treated with Tiotropium; their (creatinine clearance 50m/L or less) should be monitored closely as tiotropium is mainly excreted by the kidneys.

- 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 bromide inhalation powder.

ADVERSE EFFECTS

The type and severity of adverse effects associated with each of the compounds may be expected.

Formoterol
Tremors, palpitations and headache have been reported but tend to be transient and reduce with regular therapy.

Cardiac arrhythmias, muscle cramps and hypersensitivity reactions including rash, oedema and angioedema may occur in some patients.

Tiotropium
The reported adverse events are; systemic anticholinergic effects include dry month, dry throat, increased heart rate, blurred vision, glaucoma, urinary difficulty, urinary retention, constipation, upper airway irritant phenomena, an increased incidence of dry mouth and constipation.
The additional reported adverse events are; diarrhoea, hypertension, tonsillitis, abdominal pain, insomnia, angioedema, dehydration, arthralgia, muscle spasms, pain in extremity, chest pain, hepatic function abnormal, liver function test abnormal, atrial fibrillation, tachycardia, glossitis, stomatitis, urticarial, pharyngitis, cough, sinusitis, rhinitis, palpitations, oropharyngeal candidiasis, dizziness, headache, taste disorders, epistaxis, dysphonia, pruritus, rash, dysphagia, gingivitis, nausea, intestinal obstruction including ileus paralytic, joint swelling, dysuria, laryngitis, angioedema, dry skin, skin infection, increase risk of stroke, subacute cutaneous erythematosus, photosensitive lichenoid, acute porphyria, and skin ulcer.

DRUG INTERACTIONS

- Concomitant administration of other oral beta-adrenergic stimulants, catecholamines or other substances with a similar type of action must be avoided owing to the risk of potentiated cardiovascular effects.

- Concomitant treatment with xanthine derivatives, steroids or diuretics may potentiate a possible hypokalaemic effect of beta-agonists. Hypokalaemia may increase susceptibility to cardiac arrhythmias in patients treated with digitalis.

- Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), monoamine oxidase inhibitors and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias. In addition, L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta-sympathomimetics. Beta-adrenergic blockers (including eye drops) can weaken or inhibit the effect of formoterol. There is an elevated risk of arrhythmias in patients receiving concomitant anesthesia with halogenated hydrocarbons. The co-administration of Tiotropium and Formoterol combination with other anticholinergic containing drugs has not been studied and is therefore not recommended.

- Ppatients with moderate to severe renal impairment (creatinine clearance of <50ml/min) treated with Tiotropium and Formoterol combination should be monitored closely due to its excretion by the kidneys.

- Tiotropium Bromide has been used concomitantly with short-acting and long-acting sympathomimetic (beta-agonists) bronchodilator, methylxanthines, oral and inhaled steroids, antihistamine, mucolytic, leukotriene modifiers, cromones, and anti-IgF treatment without increase in adverse reactions.

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

USE IN SPECIFIC POPULATIONS

Pregnancy
Use of Tiotropium and Formoterol combination during pregnancy should be considered if the expected benefit to the mother is greater than the risk to the fetus.

Lactation
Since it is not known whether the active substances pass into the breast milk, Tiotropium and Formoterol combination is not recommended for use during lactation.

Paediatric Use
Safety and effectiveness of tiotropium bromide inhalation in paediatric patients has not been established and therefore Tiotropium and Formoterol combination should not be used in patients under 18 years of age.

OVERDOSAGE

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.
An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for beta2agonists: seizures, angina, hypertension, hypotension, tachycardia, prolonged QT interval, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol fumarate. Treatment of formoterol fumarate overdosage consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardio selective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol

DOSAGE AND INSTRUCTIONS

To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

ROTACAPS ARE INTENDED FOR USE THROUGH ROTAFLO OR REVOLIZER ONLY AND ARE NOT TO BE SWALLOWED.

PRESENTATION

Tiovair-F Rotacaps: Alu. Alu. Blister Pack of 3 x10's.

ٹائیوواِئیر۔ایف™

(ٹائیوٹروپیئم+فورموٹیرول فیوماریٹ)

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
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