120x240mm

Ultivair™

(Glycopyrronium + Indacaterol)

Highnoon

COMPOSITION
Each capsule contains:
Glycopyrronium (as Bromide) 50mcg
Indacaterol (as Maleate) 110mcg

Each delivered dose contains:
Glycopyrronium (as Bromide) 43mcg
Indacaterol (as Maleate) 85mcg

DESCRIPTION
Glycopyrronium is a competitive antagonist at muscarinic acetylcholine receptors, it is also referred to as anticholinergic drug. Indacaterol is a selective beta 2 adrenergic agonist.

MECHANISM OF ACTION
Glycopyrronium is a long-acting muscarinic antagonist 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 receptor at the smooth muscle leading to bronchodilation. It has competitive and reversible nature of antagonism. The bronchodilation following inhalation of glycopyrronium is predominantly a site-specific effect.

Indacaterol is a Long-Acting Beta-Agonist (LABA). When inhaled, indacaterol acts locally in the lung as a bronchodilator. The pharmacological effects of beta 2 adrenoceptor agonist drugs, including indacaterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

PHARMACOKINETICS
Glycopyrronium is poorly absorbed from the gastrointestinal tract; about 10% to 25% is absorbed after an oral dose. Glycopyrronium penetrates the blood brain barrier only poorly. Glycopyrronium is excreted in the bile and urine.

Peak concentration of indacaterol occurs about 15 minutes after inhalation, and absolute bioavailability was on average 43% to 45%. Indacaterol is metabolized by cytochrome P450 isoenzymes, particularly CYP3A4. Uridine diphosphate glucuronosyltransferase 1A1 (UGT 1A1) also contributes to metabolism and indacaterol is a low affinity substrate for P-glycoprotein. When indacaterol was given orally, at least 77% was excreted in the feces; renal clearance plays a minor role in the excretion via the urine. The average terminal half-life was 45,5 hours to 126 hours, but a half-life of 40 hours to 56 hours was calculated after repeated dosing.

INDICATIONS
It is indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

However, it is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

DOSAGE AND ADMINISTRATION
This product is for inhalation use only.

The recommended dose is the inhalation of the content of one capsule once daily. It is recommended to be administered, at the same time of the day each day. If a dose is missed, the next dose should be taken as soon as possible. Patients should be instructed not to take more than one dose in a day.

CONTRAINDICATIONS
- Hypersensitivity to the active substances or to any of the ingredients.
- Use of a long-acting beta 2 adrenergic agonist (LABA), without an inhaled corticosteroid in patients with asthma. It is not indicated for the treatment of asthma.

ADVERSE EFFECTS
The reported adverse events are; serious asthma-related events – hospitalizations, intubations, death, hypersensitivity reactions including anaphylaxis, angioedema & rash, worsening of narrow angle glaucoma, cardiovascular effects, worsening of urinary retention, upper respiratory tract infection, paradoxical bronchospasm, nasopharyngitis, oropharyngeal pain, hypertension, back pain, dyspepsia, gastroenteritis, chest pain, fatigue, peripheral oedema, rash, pruritus, dizziness, bladder obstruction, urinary retention, atrial fibrillation, palpitations, tachycardia, upper and lower respiratory tract infection, pneumonia, diarrhoea, headache, gastroesophageal reflux disease, hyperglycaemia, rhinitis, increase risk of infection, insomnia, pain, dental caries, asthenia, cystitis, productive cough, numbness, hypersensitivity, throat irritation, anhidrosis, bradycardia, bronchial secretion decrease, mydriasis, photophobia, musculoskeletal pain, diabetes mellitus, muscle complaint, paraesthesia, skin reaction, rhinitis, sinusitis / sinus congestion, epistaxis, dysphonia, hypoaesthesia, ischaemic heart disease, dysuria, dry mouth, nausea, vomiting, and pyrexia.

DRUG INTERACTION
- Beta-adrenergic receptor antagonists (beta-blockers) and this combination (Glycopyrronium and Indacaterol) may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardio selective beta-blockers could be considered, although they should be administered with caution.
- If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of indacaterol.
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalaemia effect of beta 2 adrenergic agonists, such as indacaterol.
- Electrocardiographic (ECG) changes and/or hypokalaemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as indacaterol.
- Indacaterol as with other beta 2 agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may have an increased risk of ventricular arrhythmias.
- Drug interaction studies with indacaterol which were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e., ketoconazole, erythromycin, verapamil, and ritonavir) suggest that systemic clearance of indacaterol is influenced by modulation of both P-gp and CYP3A4 activities and that the 2-fold area under the curve (AUC) increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition.
- Concurrent administration of short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators (including indacaterol), methylxanthines, oral and inhaled steroids showed no increase in adverse drug reactions.
- Cimetidine, an inhibitor of organic cation transport which is thought to contribute to the renal excretion of glycopyrronium, increased total exposure (AUC) to glycopyrronium by 22% and decreased renal clearance by 23%. Based on the magnitude of these changes, no clinically relevant drug interaction is expected when glycopyrronium is co-administered with cimetidine or other inhibitors of organic cation transport.
- There is a potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid its coadministration with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic effects.

WARNINGS AND PRECAUTIONS

Serious asthma related events
The safety and efficacy of this combination (Glycopyrronium and Indacaterol) in patients with asthma have not been established. This combination (Glycopyrronium and Indacaterol) is not indicated for the treatment of asthma. Use of LABA as monotherapy [without inhaled corticosteroids (ICS)] for asthma is associated with an increased risk of asthma-related death.

Deterioration of Disease and Acute Episodes
This combination (Glycopyrronium and Indacaterol) should not be initiated in patients with acutely deteriorating or potentially life-threatening episodes of COPD. This combination (Glycopyrronium and Indacaterol) has not been studied in patients with acutely deteriorating COPD. The initiation of this combination (Glycopyrronium and Indacaterol) in this setting is not appropriate.

It should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. This combination (Glycopyrronium and Indacaterol) has not been studied in the relief of acute symptoms, and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta 2 agonist.

Before initiation of this combination (Glycopyrronium and Indacaterol), patients who have been taking oral or inhaled, short-acting beta 2-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing this combination (Glycopyrronium and Indacaterol), the healthcare provider should also prescribe an inhaled, short-acting beta 2 agonist and instruct the patient on how it should be used. Increasing inhaled beta 2 agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If this combination (Glycopyrronium and Indacaterol), no longer controls the symptoms of bronchoconstriction; the patient's inhaled, short-acting beta 2 agonist becomes less effective; or the patient needs more inhalation of short-acting beta 2 agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of his combination (Glycopyrronium and Indacaterol), beyond the recommended dose is not appropriate in this situation.

120x240mm

Avoid excessive use of Ultivair and avoid use with other long-acting beta 2 adrenergic agonists
As with other inhaled drugs containing beta 2 adrenergics, it should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.
Patients using this combination (Glycopyrronium and Indacaterol) should not use another medicine containing a LABA for any reason.

Hypersensitivity
Immediate hypersensitivity including anaphylaxis reactions have been reported. If signs suggesting allergic reactions occur, in particular angioedema (including difficulties in breathing or swallowing, swelling of the tongue, lips, and face), urticaria or skin rash, this combination (Glycopyrronium and Indacaterol) should be discontinued immediately, and alternative therapy instituted. This combination (Glycopyrronium and Indacaterol) should be used with caution in patients with severe hypersensitivity to milk proteins.

Paradoxical bronchospasm
As with other inhaled medicines, this combination (Glycopyrronium and Indacaterol) can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs following dosing, it should be treated immediately with an inhaled, short-acting bronchodilator; this combination (Glycopyrronium and Indacaterol) should be discontinued immediately, and alternative therapy instituted.

Worsening of narrow angle glaucoma
This combination (Glycopyrronium and Indacaterol) 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 coloured images in association with red eyes from conjunctival congestion and corneal oedema). Instruct patients to contact their doctor immediately should any of these signs or symptoms develop.

Worsening of Urinary Retention
This combination (Glycopyrronium and Indacaterol) 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.

Cardiovascular Effects
Indacaterol, like other beta 2 agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, this combination (Glycopyrronium and Indacaterol) may need to be discontinued. In addition, beta- adrenergic agonists have been reported to produce ECG changes, such as flattening of the T-wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Therefore, this combination (Glycopyrronium and Indacaterol) should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Coexisting Conditions
Like all medicines containing sympathomimetic amines, this combination (Glycopyrronium and Indacaterol) should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta 2 agonist salbutamol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Hypokalaemia and Hyperglycaemia
Beta 2 adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Inhalation of high doses of beta 2 adrenergic agonists may produce increases in plasma glucose.

In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility for cardiac arrhythmias.

USE IN SPECIAL POPULATION

Pregnancy
There are no adequate and well-controlled studies with this combination (Glycopyrronium and Indacaterol) in pregnant women. Women should be advised to contact their healthcare provider if they become pregnant while taking this combination (Glycopyrronium and Indacaterol). Indacaterol may inhibit labour due to a relaxant effect on uterine smooth muscle. Therefore, it should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus.

Lactation
It is not known whether this combination (Glycopyrronium and Indacaterol) and their metabolites are excreted in human milk. Excretion of indacaterol, glycopyrronium and their metabolites in the milk of lactating rats is known. The use of this combination (Glycopyrronium and Indacaterol) by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

Fertility
Reproduction studies and other data in animals do not indicate a concern regarding fertility in either males or females.

Elderly population
Based on available data, no adjustment of this combination (Glycopyrronium and Indacaterol) dosage in geriatric patients is warranted. It can be used at the recommended dosage in elderly patients 75 years of age and older.

Renal impairment
Based on the pharmacokinetic characteristics of its monotherapy components, this combination (Glycopyrronium and Indacaterol) can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment (estimated GFR less than 30 mL/min/1.73 m²) or end-stage renal disease requiring dialysis, use it only if the expected benefit outweighs the potential risk since the systemic exposure to glycopyrronium may be increased in this population.

Hepatic impairment
Based on the pharmacokinetic characteristics of its monotherapy components, this combination (Glycopyrronium and Indacaterol) can be used at the recommended dose in patients with mild and moderate hepatic impairment. Studies in subjects with severe hepatic impairment have not been performed.

Paediatric population
The safety and effectiveness of this combination (Glycopyrronium and Indacaterol) in paediatric patients have not been established. This combination (Glycopyrronium and Indacaterol) is not indicated for use in paediatric patients.

OVERDOSAGE
This combination contains both indacaterol and glycopyrronium; therefore, the risks associated with overdosage for the individual components applied on it. Treatment of overdosage consists of discontinuation of this combination (Glycopyrronium and Indacaterol) together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

Glycopyrronium: An overdosage of glycopyrronium may lead to anticholinergic signs and symptoms, such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances, or reddening of the eye), obstipation or difficulties in voiding.

Indacaterol: The potential signs and symptoms associated with overdosage of indacaterol are those of excessive beta-adrenergic stimulation and occurrence or exaggeration of any of the signs and symptoms, e.g., angina, hypertension or hypotension, tachycardia, with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, vomiting, drowsiness, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis, and insomnia. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of indacaterol.

In COPD patients, single doses of indacaterol 3,000 mcg were associated with moderate increases in pulse rate, systolic blood pressure, and QTc interval.

DOSAGE & 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 30ºC. Keep in a dry place. Protect from light.

ROTACAP IS INTENDED FOR USE THROUGH ROTAFLO OR REVOLIZER ONLY AND IS NOT TO BE SWALLOWED.

PRESENTATION
Ultivair Rotacaps: Alu. Alu. Blister Pack of 3 x 10's.

الٹی وائیر™

(گلائیکوپائرونیم + انڈاکیٹیرال)

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۔

روٹا کیپسول کھانے کیلئے نہیں ہے۔
صرف روٹا فلو یا ریوولائزر کے ذریعے استعمال کریں۔

Manufactured by
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