120x300mm

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Ultivair-M™

(Glycopyrronium + Indacaterol + Mometasone Furoate)

Highnoon

COMPOSITION
Each capsule contains:
Glycopyrronium (as Bromide) 50mcg
Indacaterol (as Acetate) 150mcg
Mometasone Furoate 160mcg

Each delivered dose contains:
Glycopyrronium (as Bromide) 46mcg
Indacaterol (as Acetate) 114mcg
Mometasone Furoate 136mcg

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

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 glycopyrrolate 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.Mometasone furoate is a synthetic corticosteroid with high affinity for glucocorticoid receptors and local anti-inflammatory properties. It is known to inhibit the release of leukotrienes from leukocytes of allergic patients. In cell culture, mometasone furoate demonstrated high potency in inhibition of synthesis and release of IL-1, IL-5, IL-6 and TNF-alpha. It is also a potent inhibitor of leukotriene production and of the production of the Th2 cytokines IL-4 and IL-5 from human CD4+ T-cells.

PHARMACOKINETICS
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 faeces; renal clearance plays a minor role in the excretion via the urine. The average terminal half-life was 45.5 to 126 hours, but a half-life of 40 to 56 hours was calculated after repeated dosing.
Glycopyrronium is poorly absorbed from the gastrointestinal tract; about 10 to 25% is absorbed after an oral dose. Glycopyrronium bromide penetrates the blood brain barrier only poorly. Glycopyrronium is excreted in the bile and urine. Mometasone furoate is poorly absorbed after inhalation, intranasal use and tropical application. It undergoes hepatic metabolism mainly by cytochrome p450 isoenzymes CYP3A4. The terminal elimination half-life is about 5 hours; metabolites are excreted mainly in the faeces and to lesser extent in the urine. Concomitant administration of orally inhaled indacaterol, glycopyrronium and mometasone furoate under steady-state conditions did not affect the pharmacokinetics of any of the active substances.

INDICATIONS
It is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta2-agonist and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.

DOSAGE AND ADMINISTRATION
This product is for inhalation use only.
The recommended dose is the inhalation of the content of one capsule once daily. The maximum recommended dose is: indacaterol 114 mcg/ glycopyrronium 46 mcg/ mometasone 136 mcg 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. No dose adjustment is required in elderly patients (65 years of age or older). No dose adjustment is required in patients with mild to moderate renal impairment. Caution should be observed in patients with severe renal impairment or end-stage renal disease requiring dialysis. No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for the use of the medicinal product in patients with severe hepatic impairment, therefore it should be used in these patients only if the expected benefit outweighs the potential risk.
The safety and efficacy of this product in paediatric patients below 18 years of age have not been established.

CONTRAINDICATIONS
- Hypersensitivity to the active substances or to any of the ingredients.

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, cataracts, cardiovascular effects, urinary tract infection, 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, immunosuppression, increase risk of infection, insomnia, pain, dental caries, asthenia, cystitis, productive cough, numbness, hypersensitivity, throat irritation, anhidrosis, bradycardia, bronchial secretion decrease, mydriasis, photophobia, muscle spasms, musculoskeletal pain, diabetes mellitus, muscle complaint, paraesthesia, skin reaction, rhinitis, sinusitis / sinus congestion, epistaxis, dysphonia, hypoesthesia, ischaemic heart disease, dysuria, dry mouth, nausea, vomiting, pyrexia, oropharyngeal candidiasis, hypercorticism, adrenal suppression, reduction in bone mineral density and growth effects.

DRUG INTERACTION
Information on the potential for interactions is based on the potential for each of the monotherapy components:
- 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.
- Beta-adrenergic blockers may weaken or antagonise the effect of beta2 -adrenergic agonists. Therefore, this medicinal product should not be given together with beta-adrenergic blockers unless there are compelling reasons for their use. Where required, cardio selective beta-adrenergic blockers should be preferred, 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 of the sympathetic effects of indacaterol.
- Concomitant hypokalaemia treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemia effect of beta2 -adrenergic agonists.
- 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.
- Like other medicinal products containing a beta2-adrenergic agonist, this medicinal product should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or medicinal products known to prolong the QT interval, as any effect of these on the QT interval may be potentiated. Medicinal products known to prolong the QT interval may increase the risk of ventricular arrhythmia.
- Inhibition of CYP3A4 and P-glycoprotein (P-gp) has no impact on the safety of therapeutic doses of this product. Inhibition of the key contributors of indacaterol clearance (CYP3A4 and P-gp) or mometasone furoate clearance (CYP3A4) raises the systemic exposure of indacaterol or mometasone furoate up to two-fold. Due to the very low plasma concentration achieved after inhaled dosing, clinically significant interactions with mometasone furoate are unlikely. However, there may be a potential for increased systemic exposure to mometasone when strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, nelfinavir, ritonavir, cobicistat) are coadministered.
- The co-administration of this medicinal product with other medicinal products containing long-acting muscarinic antagonists or long-acting beta2 -adrenergic agonists has not been studied and is not recommended as it may potentiate adverse 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.

WARNINGS AND PRECAUTIONS
- This medicinal product (indacaterol, glycopyrronium and mometasone) should not be used to treat acute asthma symptoms, including acute episodes of bronchospasm, for which a short-acting bronchodilator is required. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician. Patients should not stop treatment without physician supervision since symptoms may recur after discontinuation. It is recommended that treatment with this medicinal product (indacaterol, glycopyrronium and mometasone) should not be stopped abruptly. If patients find the treatment ineffective, they should continue treatment but must seek medical attention. Increasing use of reliever bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the therapy. Sudden and progressive deterioration in the symptoms of asthma is potentially life-threatening and the patient should undergo urgent medical assessment.
- 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 (Indacaterol, Glycopyrronium and Mometasone) should be discontinued immediately, and alternative therapy instituted. This combination (Indacaterol, Glycopyrronium and Mometasone) should be used with caution in patients with severe hypersensitivity to milk proteins.
- As with other inhalation therapy, administration of this medicinal product may result in paradoxical bronchospasm, which can be life-threatening. If this occurs, treatment should be discontinued immediately, and alternative therapy instituted.
- This combination (indacaterol, glycopyrronium and mometasone) 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.
- This combination (indacaterol, glycopyrronium and mometasone) 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.
- 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 (Indacaterol, Glycopyrronium and Mometasone) should not use another medicine containing a LABA for any reason.
- Like other medicinal products containing beta 2-adrenergic agonists, this combination (indacaterol, glycopyrronium and mometasone) 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 (Indacaterol, Glycopyrronium and Mometasone) 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.
- This medicinal product (indacaterol, glycopyrronium and mometasone) should be used with caution in patients with coexisting conditions like cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta 2-adrenergic agonists.
- Doses of the related beta 2-agonist salbutamol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.
- 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.
- It is known to develop. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while remaining on treatment with Mometasone or its combination therapy, but at times therapy with it may need to be interrupted. After administration, advise patients to rinse the mouth with water and spit out contents without swallowing.
- Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or who are not properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin may be indicated. If chickenpox develops, treatment with antiviral agents may be considered. Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.
- Hypothalamic-pituitary-adrenal suppression/adrenal insufficiency. Particular care is needed for patients who are transferred from systemically active corticosteroids because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although mometasone may improve control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does not provide the mineralocorticoid activity necessary for coping with these emergencies. During periods of stress or severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to mometasone containing combination. Lung function (FEV1 or PEFR), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.
- Transfer of patients from systemic corticosteroid therapy to mometasone or its combination may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.
- During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.
- This combination (indacaterol, glycopyrronium and mometasone) will cause less suppression of HPA function than therapeutically similar oral doses of prednisone. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing it. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly when this combination is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of this combination (indacaterol, glycopyrronium and mometasone) should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma.
- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids, including mometasone. The clinical significance of small changes in BMD with regard to long-term outcomes is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids) should be monitored and treated with established standards of care.
- Orally inhaled corticosteroids, including Mometasone or its combination may cause a reduction in growth velocity when administered to paediatric patients. Monitor the growth of paediatric patients receiving it routinely (e.g., via stadiometry).

USE IN SPECIAL POPULATION
Pregnancy.
There are no adequate and well-controlled studies with this combination (Indacaterol, Glycopyrronium and Mometasone) in pregnant women. Women should be advised to contact their healthcare provider if they become pregnant while taking this combination (Indacaterol, Glycopyrronium and Mometasone). 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 (Indacaterol, Glycopyrronium and Mometasone) and their metabolites are excreted in human milk, have effects on a breast-fed infant, or its effects on milk production.
Excretion of indacaterol, glycopyrronium and their metabolites in the milk of lactating rats is known. Other inhaled corticosteroids similar to mometasone furoate are transferred into human milk. The use of this combination (Indacaterol, Glycopyrronium and Mometasone) 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
No adjustment of this combination (Indacaterol, Glycopyrronium and Mometasone) dosage in geriatric patients is warranted. It can be used at the recommended dosage in elderly patients 65 years of age and older.

Renal impairment
Based on the pharmacokinetic characteristics of its monotherapy components, this combination (Indacaterol, Glycopyrronium and Mometasone) 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 m^2) or end-stage renal disease requiring dialysis, use it only if the expected benefit outweighs the potential risk since the systemic exposure to glycopyrrolate may be increased in this population.

Hepatic impairment
This combination (Indacaterol, Glycopyrronium and Mometasone) 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 (Indacaterol, Glycopyrronium and Mometasone) in paediatric patients (below 18 years of age) have not been established. This combination is not indicated for use in paediatric patients.

OVERDOSAGE
General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose. An overdose will likely produce signs, symptoms or adverse effects associated with the pharmacological actions of the individual components (e.g. tachycardia, tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalaemia, hyperglycaemia, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), constipation or difficulties in voiding, suppression of hypothalamic pituitary adrenal axis function). Use of cardio selective beta blockers may be considered for treating beta2-adrenergic effects, but only under the supervision of a physician and with extreme caution, since the use of beta 2-adrenergic blockers may provoke bronchospasm. In serious cases, patients should be hospitalised.

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

الٹی وائیر-ایم ™

(گلائیکوپائیرونیم + انڈاکیٹیرال + موومیٹاسون فیوروئیٹ)

خوراک وہدایات:

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 کے لئے نہیں ہے۔

صرف روٹافلو یا ریوولائزر کے ذریعے استعمال کریں۔

Manufactured by
HIGHNOON LABORATORIES LTD
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www.highnoon-labs.com

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