# Combivair®

(Budesonide + Formoterol Fumarate)

Highnoon

**COMPOSITION**

**Combivair 100 Rotacap:** Each capsule contains:
Budesonide 100mcg
Formoterol Fumarate (as dihydrate) 6mcg
**Combivair 200 Rotacap:** Each capsule contains:
Budesonide 200mcg
Formoterol Fumarate (as dihydrate) 6mcg
**Combivair 400 Rotacap:** Each capsule contains:
Budesonide 400mcg
Formoterol Fumarate (as dihydrate) 6mcg
**Combivair Forte Rotacap:** Each capsule contains:
Budesonide 400mcg
Formoterol Fumarate (as dihydrate) 12mcg

**DESCRIPTION**

Combivair Rotacaps is a combination of budesonide, a potent glucocorticoid and formoterol fumarate, a selective long-acting beta2-agonist. Budesonide is a potent glucocorticoid that binds with high affinity to the glucocorticoid receptor. It has a high ratio of topical to systemic activity. Formoterol fumarate is a very potent long-acting beta2-agonist with a high intrinsic activity and a rapid onset of action.

**MECHANISM OF ACTION**

Combivair contains both budesonide and formoterol fumarate; therefore, the mechanisms of action described below for the individual components apply to it. These drugs represent two classes of medications (a synthetic corticosteroid and a long-acting selective beta$_2$-adrenoceptor agonist) that have different effects on clinical, physiological, and inflammatory indices of COPD and asthma. Budesonide is an anti-inflammatory corticosteroids that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. It has demonstrated a reduction in the number and activation of inflammatory cells in the epithelium and sub-mucosa after regular Inhaled corticosteroids, together with healing of damaged epithelium. Inflammation is an important component in the pathogenesis of COPD and asthma. Budesonide potentially inhibit the formation of cytokines (e.g. IL-1, IL3, IL4, IL5, IL9, IL-13, TNF and granulocyte-macrophages colony-stimulating factor, GM-CSF) that are secreted in asthma by T-lymphocytes, macrophages and mast cells. Budesonide also decreases eosinophils survival by inducing apoptosis. Budesonide inhibit the expression of multiple inflammatory genes in airway epithelial cells, probably the most important action of Budesonide in suppressing asthmatic inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in COPD and asthma. Formoterol fumarate is a long acting selective beta$_2$ adrenergic agonist (beta$_2$ agonist) with a rapid onset of action. Inhaled formoterol fumarate fumarate acts locally in the lungs as a bronchodilator. The long duration of formoterol fumarate action occurs because formoterol fumarate molecules initially diffuses into the plasma membrane of the lung cells and then are slowly released back outside, where they can come into contact with beta$_2$ adrenergic receptors. The pharmacological effect of beta$_2$ 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**

Orally inhaled Budesonide is rapidly absorbed in the lungs and peak concentration is typically reached within 20 minutes and peak plasma concentration is achieved in about 1-2 hours. The pharmacokinetics of Budesonide is important in relation to the systemic effects. The fraction of drug that is inhaled into the lungs acts locally on the airway mucosa but may be absorbed from the airway and alveolar surface. Thus a portion of inhaled dose reaches the systemic circulation. Furthermore, the fraction of inhaled drug that is deposited in the oropharynx is swallowed and absorbed from the gut. The absorbed fraction may be metabolized in the liver (first pass metabolism) before reaching the system circulation. Budesonide has a lower oral bioavailability. The volume of distribution of Budesonide was approximately 3L/kg. It is 80 to 90% bound to the plasma proteins. Budesonide is rapidly and extensively metabolized by liver isoenzymes. The Budesonide was excreted in the urine and faeces in the form of metabolites. Inhaled formoterol fumarate 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 fumarate delivered is swallowed and then absorbed from the gastrointestinal tract.

**INDICATIONS**

It is indicated in:

- Asthma in adults, and adolescents aged 12 - 17 years, for the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting β2 adrenoceptor agonist) is appropriate:
  - o patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 adrenoceptor agonists, Or
  - o patients already adequately controlled on both inhaled corticosteroids and long acting β2 adrenoceptor agonists.
- COPD in adults, aged 18 years and older, for the symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV1) <70% predicted normal (post bronchodilator) and an exacerbation history despite regular bronchodilator therapy.
- It is not indicated for the relief of acute bronchospasm.

**DOSAGE AND ADMINISTRATION**

Capsules are intended for use through Revolizer or Rotaflo only and are not to be swallowed. Dosage is individual and adjusted according to disease severity. When control has been achieved, the dose should be titrated to the lowest effective dose, which could include Combivair Rotacap given once daily.

- In Asthma, it is not intended for its initial management. The dosage of the components of Combivair is individual and should be adjusted to the severity of the disease. This should be considered not only when treatment with combination products is initiated but also when the maintenance dose is adjusted. If an individual patient should require a combination of doses other than those available in the combination inhaler, appropriate doses of β2 adrenoceptor agonists and/or corticosteroids by individual inhalers should be prescribed.

| Age Group | Combivair 200 | Combivair 400 | Combivair forte |
|---|---|---|---|
| Adults (18 years and older) | 1-2 inhalation twice daily, maximum dose is 4 inhalations twice daily | 1 inhalation twice daily, maximum dose is 2 inhalations twice daily | 1 inhalation twice daily, maximum dose is 2 inhalations twice daily |
| Adolescent (12-17 years) | 1-2 inhalation twice daily | 1 inhalation twice daily | 1 inhalation twice daily |
| Children (6-11 years) | 1 inhalation twice daily | 1 inhalation twice daily | - |

- For Chronic obstructive pulmonary disease, or COPD in adults 2 inhalations twice daily is recommended for Combivair and 1 inhalation twice daily for Combivair Forte.

**CONTRAINDICATIONS**

- It is contraindicated in patients with a history of hypersensitivity to any of the component of the drug product.
- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.

**ADVERSE REACTIONS**

The reported adverse events are; serious asthma-related events, death, candida albicans infection, pneumonia or lower respiratory tract infections in patients with COPD, immunosuppression, hypercorticism and adrenal suppression, growth effects in paediatric patients, glaucoma, cataracts, nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting, oral Candidiasis and bronchitis.

The additional reported adverse events are; angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations, growth velocity reduction in pediatric patients, cataract, glaucoma, increased intraocular pressure, oropharyngeal candidiasis, nausea, immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus, hyperglycemia, hypokalemia, muscle cramps, tremor, dizziness behaviour disturbances, anxiety, sleep disturbances, nervousness, agitation, depression, restlessness, dysphonia, cough, throat irritation, taste disturbance, vision blurred, skin bruising, prolonged QT interval, Cushing's syndrome, hypotension and hypertension.

**WARNINGS AND PRECAUTIONS**

- Patients should be advised to have their relief medication available at all times.
- Sudden and progressive deterioration in control of asthma is potentially life threatening and consideration should be given to the need for increased therapy with corticosteroid.
- Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death.
- It should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. It has not been studied in patients with acutely deteriorating asthma or COPD. Increasing use of inhaled, short-acting beta2-agonists is a marker of deteriorating asthma. Patients should not use more than 2 inhalations twice daily (morning and evening) of it. It should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm.
- As with other inhaled drugs containing beta2-adrenergic agents, it should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABA, 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 should not use an additional LABA (e.g., salmeterol, formoterol fumarate fumarate, arformoterol fumarate tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma or COPD.
- The local effect includes development of localized infections of the mouth and pharynx, the candida albicans has occurred in patients treated with it. When such infections develop, it should be treated with appropriate local or systemic (i.e., oral, antifungal) therapy, while treatment with this is continues, but at times therapy with this may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids.
- Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox 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 been properly immunized, particular care should be taken to avoid exposure. Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.
- Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma 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. During periods of stress, a severe asthma attack or a severe COPD exacerbation, 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 this medicine. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with this medicine. Lung function (mean forced expiratory volume in 1 second [FEV1] or morning peak expiratory flow [PEF]), beta-agonist use, and asthma or COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.
- Budesonide, will often help control asthma and COPD symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of this medicine is in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with it should be observed carefully for any evidence of systemic corticosteroid effects. 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 (including adrenal crisis) may appear in a small number of patients, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of it should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.
- Caution should be exercised when its coadministration ion with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur.
- As with other inhaled medications, it can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following its administration, it should be treated immediately with an inhaled, short-acting bronchodilator. It should be discontinued immediately, and alternative therapy should be instituted.
- Immediate hypersensitivity reactions may occur after its administration, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.
- Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Therefore, like all products containing sympathomimetic amines, it should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- 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.
- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to its initiation and periodically thereafter.
- Orally inhaled corticosteroids 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). To minimize the systemic effects of orally inhaled corticosteroids, titrate each patient's dose to the lowest dosage that effectively controls symptoms.
- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.
- In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.
- Like all medications containing sympathomimetic amines, it should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta2-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.
- Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

**DRUG INTERACTIONS**

- The main route of metabolism of corticosteroids, including budesonide, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of CYP3A4 may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering its coadministration with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin).
- It should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of formoterol fumarate on the vascular system may be potentiated by these agents.
- Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol fumarate, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardio selective beta-blockers could be considered, although they should be administered with caution.
- The 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, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised when its coadministration with non-potassium-sparing diuretics.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

There is no adequate and well-controlled studies one of its individual components, formoterol fumarate, in pregnant women; however studies are available for the other component budesonide. During pregnancy, it should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used.

**Lactation**

There are no available data on the effects of budesonide or formoterol fumarate on the breastfed child or on milk production. Budesonide, like other inhaled corticosteroids, is present in human milk. There are no available data on the presence of formoterol fumarate in human milk. Its administration to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

**Pediatric Use**

The safety and effectiveness in asthma patients less than 6 years of age have not been established.

**Geriatric Use**

As with other products containing beta$_2$-agonists, special caution should be observed when using it in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta$_2$-agonists. No dosage adjustment in geriatric patients is warranted.

**Hepatic Impairment**

Both budesonide and formoterol fumarate are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of budesonide and formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

**OVERDOSAGE**

It contains both budesonide and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply.

**Budesonide**

The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur.

**Formoterol Fumarate**

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for beta$_2$ agonists: 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, hypokalaemia. 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 fumarate. Cardiac monitoring is recommended in cases of overdosage.

**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**

**Combivair 100 Rotacaps:** Alu. Alu. Blister Pack of 3 x 10's.
**Combivair 200 Rotacaps:** Alu. Alu. Blister Pack of 3 x 10's.
**Combivair 400 Rotacaps:** Alu. Alu. Blister Pack of 3 x 10's.
**Combivair Forte Rotacaps:** Alu. Alu. Blister Pack of 3 x 10's.

# کومبی وائیر®

(بیوڈیسونائیڈ + فارموٹیرول فیوماریٹ)

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