

FORACORT Rotacaps (Formoterol fumarate dihydrate + Budesonide)

Composition

FORACORT-100 Rotacaps

Each capsule contains:

Formoterol fumarate dihydrate IP6 mcg

Budesonide IP100 mcg

Excipient.....q.s.

FORACORT-200 Rotacaps

Each capsule contains:

Formoterol fumarate dihydrate IP.....6 mcg

Budesonide IP.....200 mcg

Excipient.....q.s.

FORACORT-400 Rotacaps

Each capsule contains:

Formoterol fumarate dihydrate IP.....6 mcg

Budesonide IP.....400 mcg

Excipient.....q.s.

Dosage Form

Dry powder for inhalation

Description

FORACORT Rotacaps are a combination of budesonide, a potent glucocorticoid, and formoterol fumarate dihydrate, a selective, long-acting beta₂-agonist, which have different modes of action and show additive effects in terms of reduction of asthma exacerbations.

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 is a very potent, long-acting, beta₂ adrenoceptor-agonist with a high intrinsic activity and a rapid onset of action.

Pharmacology

Pharmacodynamics

FORACORT Rotacaps contain both budesonide and formoterol; therefore, the mechanisms of action described below for the individual components apply to **FORACORT Rotacaps**. These drugs represent two classes of medications (a synthetic corticosteroid and a long-acting, selective beta₂-adrenoceptor agonist) that have different effects on the clinical, physiological, and inflammatory indices of Chronic Obstructive Pulmonary Disease (COPD) and asthma.

Budesonide

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol.

In glucocorticoid receptor affinity studies, the 22R form of budesonide was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.

Inflammation is an important component in the pathogenesis of COPD and asthma. Corticosteroids have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non-allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in COPD and asthma.

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects over a wide range of doses of budesonide. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85-95%), and the low potency of formed metabolites.

Formoterol

Formoterol fumarate dihydrate is a long-acting, selective beta₂-adrenergic agonist with a rapid onset of action. Inhaled formoterol fumarate dihydrate acts locally in the lungs as a bronchodilator. *In vitro* studies have shown that formoterol has over 200-fold greater agonist activity at beta₂-receptors than at beta₁-receptors. The *in vitro* binding selectivity to beta₂-adrenoceptors over beta₁-adrenoceptors is higher for formoterol than for salbutamol (5 times), whereas salmeterol has a higher (3 times) beta₂-selectivity ratio than formoterol.

Although beta₂-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-receptors are the predominant receptors in the heart, there are also beta₂-receptors in the human heart, which comprise 10-50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta₂-agonists may have cardiac effects.

The pharmacological effects of beta₂-adrenoceptor agonist drugs, including formoterol, are, at least in part, attributable to the stimulation of intracellular adenylyl 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 inhibit the release of mediators of immediate hypersensitivity from the cells, especially from mast cells.

Pharmacokinetics

Budesonide

Absorption:

Orally inhaled budesonide is rapidly absorbed in the lungs and peak concentration is typically reached within 20 minutes. After oral administration of budesonide, peak plasma concentration was achieved in about 1-2 hours and the absolute systemic availability was 6-13%, due to extensive first pass metabolism. In contrast, most of the budesonide delivered to the lungs was systemically absorbed. In healthy subjects, 34% of the metered dose was deposited in the lungs (as assessed by the plasma concentration method, and using a budesonide-containing DPI) with an absolute systemic availability of 39% of the metered dose.

Following administration of formoterol/budesonide combination 160/4.5 mcg, (two or four inhalations twice daily) for 5 days in healthy subjects, plasma concentration of budesonide generally increased in proportion to dose. The accumulation index for the group that received two inhalations twice daily was 1.32 for budesonide.

Asthma Patients: In a single-dose study, higher than recommended doses of formoterol/budesonide combination (12 inhalations of formoterol/budesonide combination 160/4.5 mcg) were administered to patients with moderate asthma. Peak budesonide plasma concentration of 4.5 nmol/L occurred at 20 minutes following dosing. This study demonstrated that the total systemic exposure to budesonide from formoterol/budesonide combination was approximately 30% lower than from inhaled budesonide via a dry powder inhaler (DPI) at the same delivered dose. Following administration of formoterol/budesonide combination, the half-life of the budesonide component was 4.7 hours.

In a repeat dose study, the highest recommended dose of formoterol/budesonide combination (160/4.5 mcg, two inhalations twice daily) was administered to patients with moderate asthma and healthy subjects for 1 week. Peak budesonide plasma concentration of 1.2 nmol/L occurred at 21 minutes in asthma patients. Peak budesonide plasma concentration was 27% lower in asthma patients compared to that in healthy subjects. However, the total systemic exposure of budesonide was comparable to that in asthma patients.

Peak steady-state plasma concentrations of budesonide administered by DPI in adults with asthma averaged 0.6 and 1.6 nmol/L at doses of 180 mcg and 360 mcg twice daily, respectively. In asthmatic patients, budesonide showed a linear increase in AUC and C_{max} with increasing dose after both single and repeated dosing of inhaled budesonide.

COPD Patients: In a single-dose study, 12 inhalations of formoterol/budesonide combination 80/4.5 mcg (total dose 960/54 mcg) were administered to patients with COPD. Mean budesonide peak plasma concentration of 3.3 nmol/L occurred at 30 minutes following dosing. Budesonide systemic exposure was comparable between budesonide/formoterol combination pMDI and coadministration of budesonide via a metered-dose inhaler and formoterol via a dry powder inhaler (budesonide 960 mcg and formoterol 54 mcg). In the same study, an open-label group of moderate asthma patients also received the same higher dose of formoterol/budesonide combination. For budesonide, COPD patients exhibited 12% greater AUC and 10% lower C_{max} compared to asthma patients.

In the 6 month pivotal clinical study, steady-state pharmacokinetic data of budesonide was obtained in a subset of COPD patients with treatment arms of formoterol/budesonide combination pMDI 160/4.5 mcg, formoterol/budesonide combination pMDI 80/4.5 mcg, budesonide 160 mcg, budesonide 160 mcg and formoterol 4.5 mcg given together, all administered as two inhalations twice daily. Budesonide systemic exposure (AUC and C_{max}) increased proportionally with doses from 80 mcg to 160 mcg and was generally similar between the 3 treatment groups receiving the same dose of budesonide (formoterol/budesonide combination pMDI 160/4.5 mcg, budesonide 160 mcg, budesonide 160 mcg and formoterol 4.5 mcg administered together).

Distribution

The volume of distribution of budesonide was approximately 3 L/kg. It was 85-90% bound to plasma proteins. Protein binding was constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended inhaled doses. Budesonide showed little or no binding to corticosteroid binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood plasma ratio of about 0.8.

Metabolism

In vitro studies with human liver homogenates have shown that budesonide was rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16- α -hydroxyprednisolone and 6- β -hydroxybudesonide. The corticosteroid activity of each of these two metabolites was less than 1% of that of the parent compound. No qualitative differences between the *in vitro* and *in vivo* metabolic patterns were detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion/Elimination

Budesonide was excreted in urine and feces in the form of metabolites. Approximately 60% of an intravenous radiolabeled dose was recovered in the urine.

No unchanged budesonide was detected in the urine. The 22R form of budesonide was preferentially cleared by the liver with systemic clearance vs. 1.0 L/min for the 22S form. The terminal half- 2 to 3 hours was the same for both epimers and was independent of dose.

Formoterol

Absorption:

For formoterol, maximal plasma concentration was similar after administration of the fixed combination.

Inhaled formoterol is rapidly absorbed; peak plasma concentrations are typically reached at the first plasma sampling time, within 5-10 minutes after dosing. As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol delivered is swallowed and then absorbed from the gastrointestinal tract.

Healthy Subjects: Following administration of formoterol/budesonide combination (160/4.5 mcg, two or four inhalations twice daily) for 5 days in healthy subjects, plasma concentration of formoterol generally increased in proportion to dose. The accumulation index for the group that received two inhalations twice daily was 1.77 for formoterol.

Asthma patients: In a single-dose study, higher than recommended doses of formoterol/budesonide combination (12 inhalations of formoterol/budesonide combination 160/4.5 mcg) were administered to patients with moderate asthma. Peak plasma concentration for formoterol of 136 pmol/L occurred at 10 minutes following dosing. Approximately 8% of the delivered dose of formoterol was recovered in the urine as unchanged drug.

In a repeat dose study, the highest recommended dose of formoterol/budesonide combination (160/4.5 mcg, two inhalations twice daily) was administered to patients with moderate asthma and healthy subjects for 1 week. Peak formoterol plasma concentration of 28 pmol/L occurred at 10 minutes in asthma patients. Peak formoterol plasma concentration was about 42% lower in asthma patients compared to that in healthy subjects. However, the total systemic exposure of formoterol was comparable to that in asthma patients.

COPD patients: Following single-dose administration of 12 inhalations of formoterol/budesonide combination 80/4.5 mcg, mean peak formoterol plasma concentration of 167 pmol/L was rapidly achieved at 15 minutes after dosing. Formoterol exposure was slightly greater (~16-18%) from formoterol/budesonide combination pMDI compared to coadministration of budesonide via a metered-dose inhaler and formoterol via a dry powder inhaler (total dose of budesonide 960 mcg and formoterol 54 mcg). In the same study, an open label group of moderate asthma patients received the same dose of formoterol/budesonide combination. COPD patients exhibited 12-15% greater AUC and C_{max} for formoterol compared to asthma patients.

In a 6 month pivotal clinical study, steady-state pharmacokinetic data of formoterol was obtained in a subset of COPD patients with treatment arms of formoterol/budesonide combination pMDI 160/4.5 mcg, formoterol/budesonide combination pMDI 80/4.5 mcg, formoterol 4.5 mcg, budesonide 160 mcg and formoterol 4.5 mcg given together, all administered as two inhalations twice daily. The systemic exposure of formoterol as evidenced by AUC, was about 30% and 16% higher from formoterol/budesonide combination pMDI compared to formoterol alone treatment arm and coadministration of individual components of budesonide and formoterol treatment arm, respectively.

Distribution

Over the concentration range of 10-500 nmol/L, plasma protein binding for the RR and SS enantiomers of formoterol was 46% and 58%, respectively. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 54 mcg dose.

Metabolism

The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6 and CYP2C have been identified as being primarily responsible for O-demethylation

Elimination:

The excretion of formoterol was studied in four healthy subjects following simultaneous administration of radiolabeled formoterol via the oral and IV routes. In that study, 62% of the radiolabeled formoterol was excreted in the urine while 24% was eliminated in the feces.

Indications

FORACORT Rotacaps are indicated in the regular treatment of asthma, where the use of a combination (long-acting, beta₂-agonist and inhaled corticosteroid) has been found to be appropriate for instance:

Patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta₂ adrenoceptor agonists.

Or

Patients already adequately controlled on both inhaled corticosteroids and long-acting beta₂ adrenoceptor agonists.

FORACORT Rotacaps are also indicated as maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema.

Dosage and Administration

Asthma

Dosage is individual and should be adjusted according to disease severity. When control has been achieved, the dose should be titrated to the lowest effective dose, which could include **FORACORT Rotacaps** used once daily.

The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Patients should be regularly reassessed by their prescriber/health care provider so that the dosage of **FORACORT Rotacaps** remains optimal.

For **FORACORT Rotacaps** there are two treatment approaches:

- A. **Maintenance Therapy:** **FORACORT Rotacaps** is taken as regular maintenance treatment with a separate rapid acting bronchodilator as rescue.
- B. **Single maintenance and reliever therapy:** **FORACORT Rotacaps** is taken as regular maintenance and as needed in response to symptoms.

A. Maintenance Therapy:

Patients should be advised to have their separate rapid acting bronchodilator available for rescue use at all times.

Recommended Dosage

Adults (18 Years and Older)

FORACORT-100 Rotacaps 1-2 rotacaps, twice daily

Maximum dose is 4 rotacaps, twice daily

FORACORT-200 Rotacaps 1-2 rotacaps, twice daily

Maximum dose is 4 rotacaps, twice daily

FORACORT-400 Rotacaps 1 rotacap, twice daily

Maximum dose is 2 rotacaps, twice daily

Adolescents (12-17 Years)

FORACORT-100 Rotacaps 1-2 rotacaps, twice daily

FORACORT-200 Rotacaps 1-2 rotacaps, twice daily

FORACORT-400 Rotacaps

1 rotacap, twice daily

Children (6-11 Years)

FORACORT-100 Rotacaps

2 rotacaps, twice daily

In usual practice when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include **FORACORT Rotacaps** given once daily, when in the opinion of the prescriber, a long-acting bronchodilator would be required to maintain control.

Increasing use of a separate rapid acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy.

B. Single Maintenance and Reliever Therapy (For FORACORT 100 and 200 Rotacaps only -)

Patients take a daily maintenance dose of **FORACORT Rotacaps** and in combination take **FORACORT Rotacaps** as needed in response to symptoms. Patients should be advised to always have **FORACORT Rotacaps** available for rescue use.

FORACORT Rotacaps maintenance and reliever therapy should especially be considered for patients with:

- Inadequate asthma control and in frequent need of reliever medication
- Asthma exacerbations in the past requiring medical intervention

Close monitoring for dose-related adverse effects is needed in patients who frequently take high numbers of **FORACORT Rotacaps** as-needed inhalations.

Adults (18 years and older):

The recommended maintenance dosage is 2 rotacaps per day as maintenance therapy (either one rotacap twice daily, or two rotacaps in either the morning or the evening),

Patients should take 1 additional rotacap as needed in response to symptoms. If symptoms persist after a few minutes, an additional rotacap should be taken. Not more than 6 rotacaps should be taken on any single occasion.

A total daily dose of more than 8 rotacaps is not normally needed; however, a total daily dose of up to 12 rotacaps could be used for a limited period. Patients using more than 8 rotacaps daily should be strongly recommended to seek medical advice. They should be reassessed and their maintenance therapy should be reconsidered.

Single inhaler as maintenance and reliever therapy is not recommended in children and adolescents.

FORACORT-400 Rotacaps should not be used for single maintenance and reliever therapy.

COPD (Chronic Obstructive Pulmonary Disease)

FORACORT-200 Rotacaps

2 rotacaps, twice daily

FORACORT Rotacaps should only be used for inhalation through **Cipla Rotahaler/ Revolizer**.

Contraindications

FORACORT Rotacaps are contraindicated in patients with a history of hypersensitivity to any of the components of the drug product.

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
- Relief from acute bronchospasm

Warnings and Precautions

General

If patients find the treatment ineffective, or exceed the highest recommended dose of **FORACORT Rotacaps**, medical attention must be sought. Sudden and progressive deterioration in control of asthma is potentially life threatening and the patient should undergo urgent medical assessment. In this situation consideration should be given to the need for increased therapy with corticosteroids e.g. a course of oral corticosteroids, or antibiotic treatment if an infection is present.

Patients should be advised to have their rescue inhaler available at all times, either **FORACORT Rotacaps** (for patients using **FORACORT Rotacaps** as maintenance and reliever therapy) or a separate rapid-acting bronchodilator (for patients using **FORACORT Rotacaps** as maintenance therapy only).

Patients should be reminded to take their **FORACORT Rotacaps** maintenance dose as prescribed, even when asymptomatic. The prophylactic use of **FORACORT Rotacaps**, e.g. before exercise, has not been studied. The reliever inhalations of **FORACORT Rotacaps** should be taken in response to asthma symptoms but are not intended for regular prophylactic use, e.g. before exercise. For such use, a separate rapid-acting bronchodilator should be considered.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of **FORACORT Rotacaps**. Regular review of patients as treatment is stepped down is important. The lowest effective dose of **FORACORT Rotacaps** should be used.

Patients should not be initiated on **FORACORT Rotacaps** during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Patients should be regularly reassessed by their health care provider, so that the dosage of formoterol/budesonide combination remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. When control of symptoms is maintained with

the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

Increasing use of a separate rapid-acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy.

In usual practice when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include formoterol/budesonide combination given once daily, when in the opinion of the prescriber, a long-acting bronchodilator would be required to maintain control.

It is recommended that the dose is tapered when the treatment is discontinued and should not be stopped abruptly.

Serious asthma-related adverse events and exacerbations may occur during treatment with **FORACORT Rotacaps**. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation with **FORACORT Rotacaps**.

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. **FORACORT Rotacaps** should then be discontinued; treatment should be re-assessed and alternative therapy instituted if necessary. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway.

Serious Asthma-Related Events - Hospitalizations, Intubations and Death

Use of long-acting beta -adrenergic agonist (LABA) as monotherapy (without inhaled corticosteroids [ICS]) for asthma is associated with an increased risk of asthma related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared to ICS alone.

Deterioration of Disease and Acute Episodes

Formoterol/budesonide combination should not be initiated in patients during rapidly deteriorating or potentially life threatening episodes of asthma or COPD. The fixed dose combination of budesonide and formoterol fumarate dihydrate has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of formoterol/budesonide combination in this setting is not appropriate.

Increasing use of inhaled, short-acting beta -agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of formoterol/budesonide combination with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids.

Patients should not use more than 2 inhalations twice daily (morning and evening) of formoterol/budesonide combination. Formoterol/budesonide combination should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta -agonist, not formoterol/budesonide combination, should be used to relieve acute symptoms such as shortness of breath.

When beginning treatment with formoterol/budesonide combination, patients who have been taking oral or inhaled, short-acting beta -agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

Excessive Use of Formoterol/Budesonide Combination and Use with Other Long-Acting Beta-Agonists

As with other inhaled drugs containing beta -adrenergic agents, formoterol/budesonide combination 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 formoterol/budesonide combination should not use an additional LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma or COPD.

Local Effects

In clinical studies, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with formoterol/budesonide combination. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with formoterol/budesonide combination continues, but at times therapy with formoterol/budesonide combination 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.

Pneumonia and Other Lower Respiratory Tract Infections

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.

Immunosuppression

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. 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, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated (see the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension. 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.

Transferring Patients from Systemic Corticosteroid Therapy

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 adrenocortical (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 formoterol/budesonide combination may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

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. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, a severe asthma attack, or a severe COPD exacerbation.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to formoterol/budesonide combination. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with formoterol/budesonide combination. Lung function (mean forced expiratory volume in 1 second [FEV] 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.

Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or formoterol/budesonide combination may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Hypercorticism and Adrenal Suppression

Budesonide, a component of formoterol/budesonide combination, 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 formoterol/budesonide combination 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 formoterol/budesonide combination 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 formoterol/budesonide combination should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medications, formoterol/ budesonide combination can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with formoterol/ budesonide combination, it should be treated immediately with an inhaled, short-acting bronchodilator, formoterol/ budesonide combination should be discontinued immediately, and alternative therapy should be instituted.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of formoterol/ budesonide combination, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

Cardiovascular and Central Nervous System Effects

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, formoterol/budesonide combination, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischemic heart disease, tachyarrhythmias or severe heart failure.

Formoterol, a component of formoterol/budesonide combination, 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 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.

Effects on Bone Density

Potential effects on bone should be considered, particularly in patients on high doses for prolonged periods that have co-existing risk factors for osteoporosis. Long-term studies with inhaled budesonide in children at mean daily doses of 400 mcg (metered dose) or in adults at daily doses of 800 mcg (metered dose) have not shown any significant effects on bone mineral density. No information regarding the effect of formoterol/budesonide at higher doses is available.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving formoterol/budesonide combination routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including formoterol/budesonide combination, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms.

Visual Disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Glaucoma and Cataracts

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, a component of formoterol/ budesonide combination. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Eosinophilic Conditions and Churg-Strauss Syndrome

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.

Coexisting Conditions

Formoterol/budesonide combination, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis, pheochromocytoma, diabetes mellitus, and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta -adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

The need for, and dose of inhaled corticosteroids should be re-evaluated in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.

Hypokalemia and Hyperglycemia

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. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with formoterol/budesonide combination at recommended doses.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition consideration should be given to referring the patient to a pediatric respiratory specialist.

Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide will ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment.

Long-term studies with inhaled budesonide in children at mean daily doses of 400 mcg (metered dose) or in adults at daily doses of 800 mcg (metered dose) have not shown any significant effects on bone mineral density. No information regarding the effect of formoterol/budesonide at higher doses is available.

If there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy, care should be taken when transferring patients to formoterol/budesonide combination therapy.

The benefits of inhaled budesonide therapy would normally minimize the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Patients, who have required high dose emergency corticosteroid therapy in the past or prolonged treatment with high doses of inhaled corticosteroids, may also be at risk. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

As for all beta₂-agonists, additional blood glucose controls should be considered in diabetic patients.

Drug Interactions

Pharmacokinetic Interactions

Potent Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of formoterol/ budesonide combination 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. In patients using potent CYP3A4 inhibitors, a budesonide/formoterol fumarate fixed-dose combination is not recommended.

The potent CYP3A4 inhibitor ketoconazole, 200 mg once daily, increased plasma levels of concomitantly orally administered budesonide (single dose of 3 mg) on average six-fold. When ketoconazole was administered 12 hours after budesonide the concentration was on average increased only three-fold showing that separation of the administration times can reduce the increase in plasma levels. Limited data about this interaction for high-dose inhaled budesonide indicates that marked increases in plasma levels (on average four fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 µg).

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit

outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Pharmacodynamic Interactions

Beta-adrenergic blockers can weaken or inhibit the effect of formoterol. **FORACORT Rotacaps** should therefore not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons.

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 beta₂-sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors including medicinal products with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions.

There is an elevated risk of arrhythmias in patients receiving concomitant anesthesia with halogenated hydrocarbons.

Concomitant use of other beta-adrenergic drugs and anticholinergic medicinal products can have a potentially additive bronchodilating effect.

Hypokalemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides. Hypokalemia may also be potentiated by concomitant treatment with xanthine derivatives and corticosteroids. The ECG changes and/or hypokalemia 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 in the coadministration of formoterol/budesonide combination with non-potassium sparing diuretics.

Budesonide and formoterol have not been observed to interact with any other drugs used in the treatment of asthma.

Renal Impairment

There are no data regarding the specific use of the budesonide/formoterol combination in patients with renal impairment.

Hepatic Impairment

Formal pharmacokinetic studies using budesonide/formoterol combination have not been conducted in patients with hepatic impairment. However, since both budesonide and formoterol fumarate dihydrate are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of budesonide and formoterol fumarate dihydrate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Pregnancy

For formoterol/budesonide combination or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Data from an embryo-fetal

development study in the rat, showed no evidence of any additional effect from the combination.

There are no adequate data from use of formoterol in pregnant women. In animal studies formoterol has caused adverse effects in reproduction studies at very high systemic exposure levels.

Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies glucocorticosteroids have been shown to induce malformations. This is not likely to be relevant for humans given recommended doses.

Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behavior at exposures below the teratogenic dose range.

During pregnancy, **FORACORT Rotacaps** 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.

Labor or Delivery

There are no well-controlled human studies that have investigated the effects of formoterol/budesonide during labor and delivery. Because of the potential for beta-agonist interference with uterine contractility, use of formoterol/budesonide during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Lactation

Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the suckling child are anticipated. It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of **FORACORT Rotacaps** to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Fertility

There is no data available on the potential effect of budesonide on fertility. Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure.

Pediatric Use

Safety and effectiveness of formoterol/budesonide combination in asthma patients 12 years of age and older have been established in studies up to 12 months. The safety and effectiveness of formoterol/budesonide combination in asthma patients less than 6 years of age have not been established.

The growth of pediatric patients receiving orally inhaled corticosteroids, including **FORACORT Rotacaps**, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including **FORACORT Rotacaps**, each patient should be titrated to the lowest strength that

effectively controls his/her asthma.

Geriatric Use

No overall differences in safety were observed between these patients and younger patients. As with other products containing beta₂-agonists, special caution should be observed when using **FORACORT Rotacaps** in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta₂-agonists. Based on available data for formoterol and budesonide or its active components, no adjustment of dosage for formoterol/budesonide combination in geriatric patients is warranted.

Effects on Ability to Drive and Use Machines

Formoterol/budesonide combination has no or negligible influence on the ability to drive and use machines.

Undesirable Effects

Since **FORACORT Rotacaps** contains both budesonide and formoterol, the same pattern of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side-effects of beta₂-agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment.

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment.

Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

The common undesirable effects seen in $\geq 3\%$ in clinical trials with asthmatic patients 12 years and older are: nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting and oral candidiasis.

The common undesirable effects with an incidence of 3% or more in clinical trials with duration of 12 weeks in adult COPD patients are: nasopharyngitis, oral candidiasis, bronchitis, sinusitis, viral upper respiratory tract infections.

Other adverse reactions, which have been associated with budesonide or formoterol are as follows frequencies are defined as: very common [$\geq 1/10$], common [$\geq 1/100 < 1/10$], uncommon ($\geq 1/1,000, < 1/100$), rare ($\geq 1/10,000, < 1/1,000$), very rare [$< 1/10,000$] and not known [cannot be estimated from the available data]:

Infections and Infestations (common): Candida infections in the oropharynx, pneumonia (in COPD patients)

Immune system disorders (Rare): Immediate and delayed hypersensitivity reactions, e.g. exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction.

Endocrine disorders: (very rare): Cushing

(Rare): adrenal suppression, growth retardation, decrease in bone mineral density

Metabolic and nutrition disorders: Hypokalemia, hyperglycemia.

Psychiatric disorders: (uncommon); Aggression, psychomotor hyperactivity, anxiety, sleep disorders (Very rare); Depression, behavioral changes (predominantly in children)

Nervous system disorders: Headache, tremors (common), dizziness (uncommon), taste disturbances (very rare).

Cardiac disorders: (Common); Palpitations

(Uncommon); Tachycardia

(Rare); Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles (Very rare); Angina pectoris. Prolongation of QTc-interval

Eye Disorders: Cataract and glaucoma (very rare), Vision, blurred (uncommon)

Cardiac disorders: Palpitations (common), Tachycardia (uncommon), Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles (rare), Angina pectoris. Prolongation of QTc-interval (very rare)

Vascular Disorders (very rare): Variations in blood pressure

Respiratory, thoracic and mediastinal disorders: Mild irritation in the throat, coughing, hoarseness (common), Bronchospasm (rare), Paradoxical bronchospasm (very rare)

Gastrointestinal Disorders (Uncommon): Nausea

Skin and subcutaneous tissue disorders: Bruises.

Musculoskeletal and Connective Tissue Disorders: (Uncommon); Muscle cramps

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of formoterol/budesonide combination.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with formoterol/budesonide combination.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations

Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients

Eye disorders: cataract, glaucoma, increased intraocular pressure

Gastrointestinal disorders: oropharyngeal candidiasis, nausea

Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus

Metabolic and nutrition disorders: hyperglycemia, hypokalemia

Musculoskeletal, connective tissue, and bone disorders: muscle cramps

Nervous system disorders: tremor, dizziness

Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness

Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation

Skin and subcutaneous tissue disorders: skin bruising

Vascular disorders: hypotension, hypertension

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.

By reporting side-effects, you can help provide more information on the safety of this product.

Overdosage

An overdose of formoterol would likely lead to effects that are typical for beta₂-adrenergic agonists: tremor, headache, palpitations. Symptoms reported from isolated cases are tachycardia, hyperglycemia, hypokalemia, prolonged QTc-interval, arrhythmia, nausea and vomiting. Supportive and symptomatic treatment may be indicated. A dose of 90 mcg administered during three hours in patients with acute bronchial obstruction raised no safety concerns.

Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses, systemic glucocorticosteroid effects, such as hypercorticism and adrenal suppression, may appear.

If **FORACORT Rotacaps** therapy has to be withdrawn due to overdose of the formoterol component of the drug, provision of appropriate inhaled corticosteroid therapy must be considered.

Storage and Handling Instructions

Store below 30 °C

Do not freeze.

Packaging Information

FORACORT-100 Rotacaps

FORACORT-200 Rotacaps

FORACORT-400 Rotacaps

Each sales pack contains 30 rotacaps

Last Updated: *November 2018*

Last Reviewed: *December 2018*