FORACORT Rotacaps (Formoterol fumarate dihydrate + Budesonide)

**Composition**

FORACORT-100 Rotacaps
Each capsule contains:
Formoterol fumarate dihydrate IP ....... 6 mcg
Budesonide IP .......... 100 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, 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 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 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 inhibit the release of mediators of immediate hypersensitivity from the cells, especially from mast cells.

Pharmacokinetics

Budesonide

Absorption:

For budesonide, AUC was slightly higher; rate of absorption more rapid and maximal plasma concentration higher after administration of the fixed combination. Inhaled budesonide is rapidly absorbed and the maximum plasma concentration is reached within 30 minutes after inhalation. In studies, mean lung deposition of budesonide after inhalation via DPI ranged from 32% to 44% of the delivered dose. The systemic bioavailability is approximately 49% of the delivered dose. In children 6-16 years the lung deposition fall in the same range as in adults for the same given dose, the resulting plasma concentrations were not determined.

Distribution and metabolism:

Plasma protein binding is approximately 90% for budesonide. Volume of distribution is about 3 L/kg for budesonide. Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6-beta-
-hydroxy-budesonide and 16-alpha-hydroxy-prednisolone, is less than 1% of that of budesonide. There are no indications of any metabolic interactions or any displacement reactions between formoterol and budesonide.

**Elimination:**
Budesonide is eliminated via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites of budesonide are eliminated in urine as such or in conjugated form. Only negligible amounts of unchanged budesonide have been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 L/min) and the plasma elimination half-life after i.v. dosing averages 4 hours.

**Formoterol**

**Absorption:**
For formoterol, maximal plasma concentration was similar after administration of the fixed combination. Inhaled formoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation. In studies the mean lung deposition of formoterol after inhalation via DPI ranged from 28% to 49% of the delivered dose. The systemic bioavailability is about 61% of the delivered dose.

**Distribution and Metabolism:**
Plasma protein binding is approximately 50% for formoterol. Volume of distribution is about 4 L/kg for formoterol. Formoterol is inactivated via conjugation reactions (active O-demethylated and deformylated metabolites are formed, but they are seen mainly as inactivated conjugates). There are no indications of any metabolic interactions or any displacement reactions between formoterol and budesonide.

**Elimination:**
The major part of a dose of formoterol is transformed by liver metabolism followed by renal elimination. After inhalation, 8% to 13% of the delivered dose of formoterol is excreted unmetabolised in the urine. Formoterol has a high systemic clearance (approximately 1.4 L/min) and the terminal elimination half-life averages 17 hours. The pharmacokinetics of formoterol in children have not been studied.

The pharmacokinetics of budesonide and formoterol in patients with renal failure are unknown. The exposure of budesonide and formoterol may be increased in patients with liver disease.

**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. It is also indicated in the symptomatic treatment of severe Chronic Obstructive Pulmonary Disease (COPD), with a history of repeated exacerbations despite regular therapy with long-acting bronchodilators.

**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.

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 of 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.

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.

**Warnings And Precautions**

It is recommended that the dose is tapered when the treatment is discontinued and should not be stopped abruptly. 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. Patients using FORACORT Inhaler should not use additional long-acting beta2 agonists such as salmeterol, formoterol fumarate, arformoterol tartrate for any reason including prevention of exercise-induced bronchospasm or treatment of asthma or COPD.

Immediate hypersensitivity reactions may occur in patients using this combination inhaler as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm. 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. 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.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing’s syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in
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 paediatric 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. Recovery may take a considerable amount of time after cessation of oral steroid therapy and hence oral steroid-dependent patients transferred to inhaled budesonide may remain at risk from impaired adrenal function for some considerable time. In such circumstances HPA axis function should be monitored regularly. Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Therefore additional systemic corticosteroid cover should be considered during periods of stress such as severe infections or elective surgery. Rapid reduction in the dose of steroids can induce acute adrenal crisis. Symptoms and signs which might be seen in acute adrenal crisis may be somewhat vague but may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, seizures, hypotension and hypoglycaemia. Treatment with supplementary systemic steroids or inhaled budesonide should not be stopped abruptly. During transfer from oral therapy to formoterol/budesonide combination therapy, a generally lower systemic steroid action will be experienced which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema and muscle and joint pain. Specific treatment should be initiated for these conditions. A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary.

To minimize the risk of oropharyngeal Candida infection, the patient should be instructed to rinse their mouth out with water after inhaling the maintenance dose. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations. 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. 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. Concomitant treatment with itraconazole, ritonavir or other potent CYP3A4 inhibitors should be avoided. If this is not possible the time interval between administrations of the interacting drugs should be as long as possible. In patients using potent CYP3A4 inhibitors, formoterol/budesonide maintenance and reliever therapy is not recommended.
Formoterol/budesonide should be administered with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

Caution should be observed when treating patients with prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval.

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.

Potentially serious hypokalaemia may result from high doses of beta<sub>2</sub>-agonists. Concomitant treatment of beta<sub>2</sub>-agonists with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine-derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the beta<sub>2</sub>-agonist. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalaemia adverse effects is increased. It is recommended that serum potassium levels are monitored during these circumstances.

As for all beta<sub>2</sub>-agonists, additional blood glucose controls should be considered in diabetic patients.

**Drug Interactions**

Pharmacokinetic interactions:
Potent inhibitors of CYP3A4 (eg, ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors) are likely to markedly increase plasma levels of budesonide and concomitant use should be avoided. If this is not possible the time interval between administration of the inhibitor and budesonide should be as long as possible. In patients using potent CYP3A4 inhibitors, formoterol/budesonide maintenance and reliever therapy 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 increase 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).

Formoterol/budesonide combination 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, a component of FORACORT Rotacaps, on the vascular system may be potentiated by these agents. In clinical trials with formoterol/budesonide combination, a limited number of COPD and asthma patients received tricyclic antidepressants, and, therefore, no clinically meaningful conclusions on adverse events can be made.

Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of FORACORT Rotacaps but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers.

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 FORACORT Rotacaps with non-potassium-sparing diuretics.

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 agents with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions.

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons. Concomitant use of other beta-adrenergic drugs can have a potentially additive effect. Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitals glycosides.

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. Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

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 behaviour 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.

### 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. 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.

### Paediatric Use

The growth of paediatric 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 of FORACORT Rotacaps in geriatric patients is warranted.

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. In a 3-year clinical trial with budesonide in COPD, skin bruises and pneumonia occurred at a frequencies of 10% and 6%, respectively, compared with 4% and 3% in the placebo group (p<0.001 and p<0.01, respectively).

The common undesirable effects seen in >/= 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 seen in >/= 3% in clinical trials with adult COPD patients are: nasopharyngitis, oral candidiasis, bronchitis, sinusitis, viral upper respiratory tract infections.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with formoterol/budesonide combination compared with placebo (7.9% vs. 5.1%, respectively).

There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, haematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

Following are some common, uncommon and rare adverse events that occurred in the groups receiving formoterol/budesonide were derived from clinical trial data:

Cardiac disorders: Palpitations, tachycardia, cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extra systoles, angina pectoris, prolongation of QTc-interval

Endocrine disorders: Signs or symptoms of systemic glucocorticosteroid effects e.g. adrenal suppression, growth retardation, decrease in bone mineral density, cataract and glaucoma, Cushing's syndrome.

Gastrointestinal disorders: Nausea, oropharyngeal candidiasis.

Eye disorders: Cataract, glaucoma, increased intraocular pressure

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

Metabolic and nutrition disorders: Hypokalemia, hyperglycemia.

Musculoskeletal, connective tissue and bone disorders: Muscle cramps.

Nervous system disorders: Headache, tremors, dizziness, tastes disturbances.
Psychiatric disorders: Aggression, psychomotor hyperactivity, anxiety, sleep disorders, agitation, restlessness, nervousness, sleep disturbances, depression, behavioural disturbances (mainly in children).

Respiratory, thoracic and mediastinal disorders: Mild irritation in the throat, coughing, hoarseness, bronchospasm, dysphonia, pneumonia or lower respiratory tract infections in patients with COPD.

Skin and subcutaneous tissue disorders: Bruises.

Vascular disorders: Variations in blood pressure.

Candida infection in the oropharynx is due to drug deposition. Advising the patient to rinse the mouth out with water after each dose will minimise the risk. Oropharyngeal Candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroid.

As with other inhalation therapy, paradoxical bronchospasm may occur very rarely, affecting less than 1 in 10,000 people, with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. FORACORT Rotacaps should be discontinued immediately, the patient should be assessed and an alternative therapy instituted if necessary.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's Syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. Increased susceptibility to infections and impairment of the ability to adapt to stress may also occur. Effects are probably dependent on dose, exposure time, concomitant and previous steroid exposure and individual sensitivity.

Treatment with beta₂-agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

**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, hyperglycaemia, hypokalaemia, 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.

**Packaging Information**

FORACORT-100 Rotacaps
FORACORT-200 Rotacaps
FORACORT-400 Rotacaps
Each sales pack contains 30 rotacaps

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