Formoterol Fumarate rotacaps

FORATEC ROTACAPS

COMPOSITION
FORATEC ROTACAPS
Each rotacap contains:
Formoterol Fumarate …… 12 mcg

DOSAGE FORM
Dry powder for inhalation

PHARMACOLOGY
Pharmacodynamics
Formoterol fumarate is a long-acting, selective $beta_2$-adrenergic receptor agonist ($beta_2$-agonist). Inhaled formoterol fumarate acts locally in the lungs as a bronchodilator. *In vitro* studies have shown that formoterol has more than 200-fold greater agonist activity at $beta_2$-receptors than at $beta_1$-receptors. Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 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 $beta_2$-agonists may have cardiac effects.

The pharmacological effects of $beta_2$-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3′, 5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibit the release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lungs. Formoterol also inhibits histamine-induced plasma albumin extravasation in anaesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these *in vitro* and animal findings to humans is unknown.

Pharmacokinetics
Information on the pharmacokinetics of formoterol in plasma has been obtained in healthy subjects by oral inhalation of doses higher than the recommended range and in chronic obstructive pulmonary disease (COPD) patients after oral inhalation of doses at and above the therapeutic dose. Urinary excretion of unchanged formoterol was used as an indirect measure of systemic exposure. Plasma drug disposition data parallel urinary excretion, and the elimination half-lives calculated for urine and plasma are similar.

Absorption:
Following inhalation of a single 120 mcg dose of formoterol fumarate by 12 healthy subjects, formoterol was rapidly absorbed into plasma, reaching a maximum drug concentration of 92 pg/mL within 5 minutes of dosing. In COPD patients treated for 12 weeks with formoterol fumarate 12 mcg or 24 mcg b.i.d., the mean plasma concentrations of formoterol ranged between 4.0 and 8.8 pg/mL and 8.0 and 17.3 pg/mL, respectively, at 10 minutes, 2 hours, and 6 hours post-inhalation.

Following inhalation of 12–96 mcg of formoterol fumarate by 10 healthy males, urinary excretion of both the (R,R)- and (S,S)-enantiomers of formoterol increased proportionally to the dose. Thus, absorption of formoterol following inhalation appeared linear over the dose range studied.

In a study in patients with asthma, when formoterol 12 mcg or 24 mcg twice daily was given by oral inhalation for 4 weeks or 12 weeks, the accumulation index, based on the urinary excretion of unchanged formoterol ranged from 1.63–2.08 in comparison with the first dose. For COPD patients, when formoterol 12 mcg or 24 mcg twice daily was given by oral inhalation for 12 weeks, the accumulation index, based on the urinary excretion of unchanged formoterol was 1.19–1.38. This suggests some accumulation of formoterol in plasma with multiple dosing. The excreted amounts of formoterol at steady state were close to those predicted, based on single-dose kinetics. As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol fumarate delivered is swallowed and then absorbed from the gastrointestinal tract.

Distribution:
The binding of formoterol to human plasma proteins *in vitro* was 61–64% at concentrations from 0.1–100 ng/mL. Binding to human serum albumin *in vitro* was 31–38% over a range of 5–500 ng/mL. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma, following inhalation of a single 120 mcg dose.

***Metabolism*:**
Formoterol is metabolized primarily by direct glucuronidation at either the phenolic or aliphatic hydroxyl group and O-demethylation followed by glucuronide conjugation at either phenolic hydroxyl groups. Minor pathways involve sulfate conjugation of formoterol and deformylation followed by sulfate conjugation. The most prominent pathway involves direct conjugation at the phenolic hydroxyl group. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Four cytochrome P450 isozymes (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) are involved in the O-demethylation of formoterol. Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.

***Excretion*:**
Following oral administration of 80 mcg of radiolabelled formoterol fumarate to 2 healthy subjects, 59–62% of the radioactivity was eliminated in the urine and 32–34% in the faeces over a period of 104 hours. Renal clearance of formoterol from blood in these subjects was about 150 mL/min. Following inhalation of a 12 mcg or 24 mcg dose by 16 patients with asthma, about 10% and 15–18% of the total dose was excreted in the urine as unchanged formoterol and direct conjugates of formoterol, respectively. Following inhalation of a 12 mcg or 24 mcg dose by 18 patients with COPD, the corresponding values were 7% and 6–9% of the dose, respectively.

Based on plasma concentrations measured following inhalation of a single 120 mcg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. From urinary excretion rates measured in these subjects, the mean terminal elimination half-lives for the (R,R)- and (S,S)-enantiomers were determined to be 13.9 and 12.3 hours, respectively. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively, following single inhaled doses between 12 mcg and 120 mcg in healthy volunteers, and single and repeated doses of 12 mcg and 24 mcg in patients with asthma. Thus, the relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing.

Special Populations:

Geriatric:
The pharmacokinetics of formoterol has not been studied in the elderly population.

Paediatric:
Limited data on the pharmacokinetics of formoterol are available in pediatric patients. In a study of children with asthma who were 5 to 12 years of age, when formoterol fumarate 12 or 24 mcg was given twice daily by oral inhalation for 12 weeks, the accumulation index ranged from 1.18 to 1.84 based on urinary excretion of unchanged formoterol. Hence, the accumulation in children did not exceed that in adults, where the accumulation index ranged from 1.63 to 2.08. Approximately 6% and 6.5% to 9% of the dose was recovered in the urine of the children as unchanged and conjugated formoterol, respectively.

Gender:
After correction for body weight, formoterol pharmacokinetics did not differ significantly between males and females.

Renal Impairment:
The pharmacokinetics of formoterol has not been studied in subjects with renal impairment.

Hepatic Impairment:
The pharmacokinetics of formoterol has not been studied in subjects with hepatic impairment.

INDICATIONS

Asthma

FORATEC is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma.

Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, **FORATEC ROTACAPS** should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, including **FORATEC ROTACAPS**. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting, beta$_2$-agonists or for patients whose asthma can be successfully managed by inhaled corticosteroids or other controller medications along with occasional use of inhaled, short-acting beta2-agonists.

FORATEC ROTACAPS is also indicated for the acute prevention of exercise-induced bronchospasm (EIB) in adults and children 5 years of age and older, when administered on an occasional, as-needed basis.

Chronic Obstructive Pulmonary Disease

FORATEC ROTACAPS is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with Chronic Obstructive Pulmonary Disease including chronic bronchitis and emphysema.

DOSAGE AND ADMINISTRATION

Adults

Asthma:
1 rotacap, once or twice daily in the morning and/or night.
Maximum daily dose is 48 mcg daily.

Exercise-induced Asthma:
1 rotacap, 15 minutes before exercise.

COPD:
1 rotacap, once or twice daily.

Children (over 5 years)

Asthma:
1 rotacap, once or twice daily in the morning and/or night.

Maximum daily dose is 24 mcg daily.

Exercise-induced Asthma:
1 rotacap, 15 minutes before exercise.

FORATEC ROTACAPS should be inhaled only with the **Cipla Rotahaler / Revolizer** device.
FORATEC ROTACAPS must not be swallowed.

CONTRAINDICATIONS
FORATEC ROTACAPS are contraindicated in patients with a history of hypersensitivity to formoterol or any other component of the drug product.

WARNINGS AND PRECAUTIONS
Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, **FORATEC ROTACAPS** should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, including **FORATEC ROTACAPS**.

A 28-week, placebo-controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death may represent a class effect of the long-acting beta$_2$-adrenergic agonists, including formoterol. No study adequate to determine whether the rate of asthma-related death is increased with formoterol has been conducted.

Clinical studies with **FORATEC ROTACAPS** suggested a higher incidence of serious asthma exacerbations in patients who received **FORATEC ROTACAPS** than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

- The studies described above enrolled patients with asthma. No studies have been conducted that were adequate to determine whether the rate of death in patients with COPD is increased by long-acting beta$_2$-adrenergic agonists.

- **FORATEC ROTACAPS** should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition. The use of **FORATEC ROTACAPS** in this setting is inappropriate.

- **FORATEC ROTACAPS** should not be used in conjunction with an inhaled, long-acting beta$_2$-agonist. **FORATEC ROTACAPS** should not be used with other medications containing long-acting beta$_2$-agonists.

- **FORATEC ROTACAPS** is not a substitute for inhaled or oral corticosteroids. Corticosteroids should not be stopped or reduced at the time **FORATEC ROTACAPS** is initiated.

- When beginning treatment with **FORATEC ROTACAPS**, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute asthma symptoms.

FORATEC ROTACAPS should not be used to treat acute symptoms of asthma. **FORATEC ROTACAPS** has not been studied in the relief of acute asthma symptoms and extra doses should not be used for that purpose. When prescribing **FORATEC ROTACAPS**, the physician should also provide the patient with an inhaled, short-acting beta$_2$-agonist for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of **FORATEC ROTACAPS**. Patients should also be cautioned that increasing inhaled beta$_2$-agonist use is a signal of deteriorating asthma.

Formoterol fumarate, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and/or diastolic blood pressure, pulse rate and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with formoterol. Doses of the related beta$_2$-agonist salbutamol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intra-cellular 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 infrequent during clinical studies with long-term administration of **FORATEC ROTACAPS** at the recommended dose. **FORATEC ROTACAPS** contains lactose, which contains trace levels of milk proteins. Allergic reactions to products containing milk proteins may occur in patients with severe milk protein allergy.

Paradoxical Bronchospasm

As with other inhaled beta$_2$-agonists, formoterol can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, **FORATEC ROTACAPS** should be discontinued immediately and alternative therapy instituted.

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. It is important to watch for signs of worsening asthma, such as increasing use of inhaled, short-acting beta$_2$-adrenergic agonists or a significant decrease in peak expiratory flow (PEF) or lung function. Such findings require immediate evaluation. Patients should be advised to seek immediate attention should their condition deteriorate. Increasing the daily dosage of **FORATEC ROTACAPS** beyond the recommended dose in this situation is not appropriate. **FORATEC ROTACAPS** should not be used more frequently than twice daily (morning and evening) at the recommended dose.

Use of Anti-inflammatory Agents
For the treatment of asthma, **FORATEC ROTACAPS** should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, including **FORATEC ROTACAPS**. There are no data demonstrating that Formoterol has any clinical anti-inflammatory effect and therefore it cannot be expected to take the place of corticosteroids. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on this type of treatment even if they feel better as a result of initiating **FORATEC ROTACAPS**. Any change in corticosteroid dosage, in particular a reduction, should be made ONLY after clinical evaluation.

Cardiovascular Effects
Formoterol fumarate, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in 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. Therefore, formoterol fumarate, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Immediate Hypersensitivity Reactions
Immediate hypersensitivity reactions may occur after administration of Formoterol fumarate, as demonstrated by cases of anaphylactic reactions, urticaria, angioedema, rash, and bronchospasm.

Do Not Exceed Recommended Dose
Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected. In addition, data from clinical trials with Formoterol suggest that the use of doses higher than recommended is associated with an increased risk of serious asthma exacerbations.

Drug Interactions
If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of formoterol may be potentiated.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

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 co-administration of beta-agonist with non-potassium sparing diuretics.

Formoterol, as with other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of $beta_2$-agonists, such as formoterol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Pregnancy
Use of **FORATEC ROTACAPS** in pregnant women or nursing mothers should be considered only if the expected benefit to the woman is greater than any possible risk to the foetus or the infant.

Lactation
Since it is not known whether the active substance passes into the breast milk, **FORATEC ROTACAPS** are not recommended for use during lactation.

UNDESIRABLE EFFECTS
Overall adverse events that occur with >1%incidence: viral Infection, bronchitis, chest pain, tremors, dizziness, insomnia, tonsillitis, rash, dysphonia.

Adverse events occurring in more than 1% of patients with COPD: upper respiratory tract infection, pain back, pharyngitis, pain chest, sinusitis, fever, cramps in muscles and leg, anxiety, pruritus, increased sputum and dry mouth.

Rare reports of anaphylactic reactions, including severe hypotension and angioedema, have also been received in association with the use of Formoterol fumarate inhalation powder.

Other adverse reactions to Formoterol are similar in nature to other selective beta$_2$-adrenoceptor agonists; e.g., angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, nausea, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

Pharmacological side effects of beta$_2$-agonist treatment, such as palpitations, and headache have been reported, but tend to be transient and reduce with regular therapy.

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing and drop in peak expiratory flow rate (PEFR). This responds to a fast-acting inhaled bronchodilator. **FORATEC ROTACAPS** should be discontinued immediately, the patient assessed, and an alternative form of therapy must be instituted.

OVERDOSAGE

The expected signs and symptoms with overdosage of Formoterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms e.g., angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of Formoterol.

The preferred antidotes are other cardioselective beta$_2$-blocking agents, but these should be used with caution in patients with a history of bronchospasm.

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PACKAGING INFORMATION

FORATEC ROTACAPS Available as canisters containing 30 rotacaps

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