FORACORT Respules (Formoterol fumarate + Budesonide respirator)

### Qualitative And Quantitative Composition

FORACORT respules 0.5 mg  
Each 2 mL contains:  
Formoterol Fumarate Dihydrate IP equivalent to Formoterol Fumarate ... 20 mcg  
Budesonide IP ........ 0.5 mg  
FORACORT respules 1 mg  
Each 2 mL contains:  
Formoterol Fumarate Dihydrate IP equivalent to Formoterol Fumarate ...... 20 mcg  
Budesonide IP ........ 1 mg

### Dosage Form(S) And Strength(S)

FORACORT (formoterol fumarate and budesonide) respirator solution is available in two strengths.  
FORACORT respules 0.5 mg containing 2 mL suspension of 0.5 mg budesonide and formoterol fumarate dihydrate, IP, equivalent to 20 mcg.  
FORACORT respules 1 mg containing 2 mL suspension of 1 mg budesonide and formoterol fumarate dihydrate, IP, equivalent to 20 mcg.  
FORACORT respules are supplied as a sterile suspension for nebulisation in low-density polyethylene unit-dose vials sealed protective foil pouch. Each pouch contains one plastic strip of five single-dose ampoules. There are 20 ampoules in a pack. Each single-dose ampoule contains 2 mL of sterile liquid suspension supplied as a sterile solution for nebulisation. The suspension is meant for inhalation via a nebuliser only.

### Clinical Particulars

#### Therapeutic Indications

FORACORT respules 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. They are also indicated in the regular long-term treatment of moderate-to-severe COPD, with frequent symptoms and a history of repeated exacerbations despite regular therapy with long-acting bronchodilators.

#### Posology and Method of Administration

**Asthma**  
**Adult**  
FORACORT respules 1 mg/0.5 mg  
One respule twice a day.  

**COPD**
FORACORT Respules 1 mg
One respule twice a day.
The contents of the respules are for inhalation use only, using a standard jet nebuliser.
A total daily dose of formoterol greater than 40 mcg is not recommended. FORACORT should be administered by the inhaled route via a standard jet nebuliser connected to an air compressor.
FORACORT respules should always be stored in the protective pouch, and only removed IMMEDIATELY BEFORE USE. Contents of any partially used container should be discarded.
If the recommended maintenance treatment regimen fails to provide the usual response, medical advice should be sought immediately, as this is often a sign of destabilisation of COPD. Under these circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic options should be considered.
The drug compatibility (physical and chemical) of FORACORT respules when mixed with the contents of respules other than Cipla respules in a nebuliser have not been established.

Contraindications
Hypersensitivity to any ingredient of the formulation.

Special Warnings and Precautions for Use
FORACORT respules are to be used with a nebuliser, and only under the direction of a physician. The solution should not be injected or administered orally. Particular care is needed in patients who are being transferred from oral corticosteroids to FORACORT respules.

Precautions during Infections
Special care is needed in patients with lung tuberculosis, and fungal and viral infections. The need for, and the dose of, inhaled corticosteroids should be re-evaluated in patients with active or quiescent pulmonary tuberculosis, or fungal and viral infections in the airways. Potential worsening of infections (e.g. existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex) can occur and, hence, is to be used with caution. Chicken pox and measles, for example, can take a more serious or even a fatal course in children on immunosuppressant corticosteroids. During long-term therapy, monitoring of haematological and adrenal function is advisable.

Oral Candidiasis
Oral candidiasis may occur during the therapy with inhaled corticosteroids. This infection may require treatment with appropriate antifungal therapy and, in some patients, discontinuation of treatment may be necessary. There is an increased incidence of pneumonia in patients with chronic obstructive pulmonary disease (COPD) treated with inhaled corticosteroids, with an adjusted odds ratio of 1.7. Care should be exercised in prescribing budesonide for those patients whose respiratory disease might have a component of COPD.
In clinical trials with nebulised budesonide, localised infections with Candida albicans occurred in the mouth and pharynx in some patients. The incidence of localised infections of Candida albicans was similar between the placebo- and nebulised budesonide-treatment groups. If these infections develop, they may require treatment with appropriate local or systemic antifungal therapy and/or discontinuance of treatment with nebulised budesonide. Patients should rinse the mouth after inhalation of FORACORT respules and should be monitored periodically for signs of adverse effects on the oral cavity.

Paradoxical Bronchospasm
As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. FORACORT respules should then be discontinued; treatment should be re-assessed and alternative therapy instituted if necessary. 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.

**Other Effects**

**Adrenal Suppression**

Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, and cataract and glaucoma, or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids. A range of psychological or behavioural effects, including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) have also been reported. 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 corticosteroids. 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.

Patients should be advised that FORACORT respules may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to FORACORT respules. During transfer from oral therapy to nebulised budesonide, a generally lower systemic corticosteroid 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.

The benefits of inhaled budesonide therapy would normally minimise 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. In some cases, facial skin irritation has occurred when a nebuliser with a face mask has been used. To prevent such irritation, the face should be washed after using the face mask.

**Effect on Bone Health**

Patients with major risk factors for decreased bone mineral content, such as prolonged immobilisation, family history of osteoporosis, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), should be monitored and treated with established standards of care. Close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

**Effect on Growth in Children and Adolescents**

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 micrograms (metered dose) or in adults at daily doses of 800 micrograms (metered dose) 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 FORACORT respules therapy.
Cardiovascular Effects
Formoterol fumarate, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic and/or diastolic blood pressure, and/or symptoms. If such effects occur, FORACORT respules 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, and increase pulse rate and systolic/diastolic blood pressure. The clinical significance of these findings is unknown. Therefore, FORACORT respules, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Hepatic Effects
In patients with severe hepatic dysfunction, treatment with inhaled budesonide can result in a reduced elimination rate and, hence, enhanced systemic availability. Possible systemic effects may then result and, therefore, Hypothalamus Pituitary Adrenal axis function in these patients should be monitored at regular intervals.
Concomitant treatment with ketoconazole, HIV protease inhibitors or other potent CYP3A4 inhibitors should be avoided. If this is not possible the time interval between administration of the two drugs should be as long as possible.
Reduced liver function may affect the elimination of glucocorticosteroids. The plasma clearance following an intravenous dose of budesonide, however, was similar in cirrhotic patients and in healthy subjects. After oral ingestion, systemic availability of budesonide was increased by compromised liver function due to decreased first-pass metabolism. The clinical relevance of this to treatment with nebulised budesonide is unknown as no data exist for inhaled budesonide, but increases in plasma levels and, hence, an increased risk of systemic adverse effects could be expected.

Other Precautions
If patients find the treatment ineffective or exceed the highest recommended dose of FORACORT respules, medical attention must be sought. Sudden and progressive deterioration in the 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.
Patients should be reminded to take their FORACORT respules maintenance dose as prescribed, even when asymptomatic.
The prophylactic use of FORACORT respules, e.g. before exercise, has not been studied. 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 respules. It is recommended that the dose is tapered when the treatment is discontinued and should not be stopped abruptly. Regular review of patients as treatment is stepped down is important. The lowest effective dose of FORACORT respules should be used.
As with other inhaled beta₂-adrenergic drugs, FORACORT respules should not be used more often, at higher doses than recommended, or in conjunction with other medications containing long-acting beta₂-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.
FORACORT respules are not intended for rapid relief of acute episodes of asthma where an inhaled short-acting bronchodilator is required. Patients should not be initiated on FORACORT respules 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 respules. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation with FORACORT respules. FORACORT respules 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.

Potentially serious hypokalemia may result from high doses of beta₂-agonists 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. Beta-agonist medication may produce transient hyperglycaemia in some patients. Concomitant treatment of beta₂-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 beta₂-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 beta₂-agonists, additional blood glucose controls should be considered in diabetic patients.

Immediate hypersensitivity reactions such as anaphylactic reactions, urticaria, angio-oedema, rash, and bronchospasm may occur after administration of FORACORT respules. 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 corticosteroids 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. Healthcare providers should be alert to eosinophilia, vasculitis 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.

Drug Interactions

Pharmacokinetic Interactions

The metabolic conversion of budesonide is impeded by substances metabolised by CYP450 3A4 (e.g. itraconazole, ketoconazole, ritonavir). The concomitant administration of these potent inhibitors of CYP450 3A4 may increase plasma levels of budesonide. The concomitant use of these drugs should be avoided unless the benefit outweighs the increased risk of systemic side effects. At recommended doses, cimetidine had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide. In patients using potent CYP3A4 inhibitors, FORACORT respules are not recommended.

Pharmacodynamic Interactions

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 digitalis glycosides. Beta-adrenergic blockers can weaken or inhibit the effect of formoterol. FORACORT respules should, therefore, not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons. In such cases, cardioselective beta-blockers could be considered, although they should be administered with caution.

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.

Caution is advised in the co-administration of beta-agonists with non-potassium-sparing diuretics (such as loop or thiazide diuretics) as these may acutely worsen the electrocardiogram (ECG) changes and/or hypokalaemia.

Concomitant treatment with xanthine derivatives or steroids may potentiate any hypokalaemic effect. There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

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

FORACORT respules should not be used with an ultrasonic nebuliser as it is not appropriate for nebulising suspensions.

Use in Special Populations

Pregnancy
There are no adequate data from the use of formoterol and budesonide in pregnant women. Administration of FORACORT respules in pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus. 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 breastfeeding child are anticipated. It is not known whether formoterol passes into human breast milk. Administration of FORACORT respules 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.

Geriatric Patients
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 respules in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta₂-agonists.

Patients with Renal/Hepatic/Impairment
The pharmacokinetics of FORACORT respules has not been studied in elderly and paediatric patient populations and in subjects with renal impairment. There are no data regarding the specific use of the FORACORT respules in patients with hepatic impairment. But since formoterol and budesonide are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver impairment.

Effects on Ability to Drive and Use Machines

FORACORT respules have no or negligible influence on the ability to drive and use machines.

Undesirable Effects

Since FORACORT respules contain 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 major adverse effects of inhaled beta₂-agonists occur as a result of excessive activation of the systemic beta-adrenergic receptors. The most common adverse effects in adults include skeletal muscle tremor, palpitations and cramps, insomnia,
tachycardia, decreases in plasma potassium, and increases in plasma glucose. These tend to be mild and usually disappear within a few days of treatment. Adverse reactions to formoterol fumarate are expected to be similar in nature to other beta₂-adrenergic receptor agonists, including angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, muscle cramps, palpitations, nausea, dizziness, fatigue, malaise, insomnia, hypokalaemia, hyperglycaemia, and metabolic acidosis.

The common side effects observed in clinical trials with budesonide inhalation suspension and occurring at the incidence of 3% as compared with placebo were respiratory infection, rhinitis, coughing, otitis media, viral infection, moniliasis, gastroenteritis, vomiting, diarrhoea, abdominal pain, ear infection, epistaxis and conjunctivitis and rash.

The common side effects observed in 12-week clinical trial with formoterol inhalation solution in COPD patients and occurring at the incidence of 2% as compared with placebo were diarrhoea, nausea, nasopharyngitis, dry mouth, vomiting, dizziness, insomnia. Patients treated with formoterol fumarate inhalation solution 20 mcg twice daily in the 52-week open-label trial did not experience an increase in specific clinically significant adverse events above the number expected based on the medical condition and age of the patients.

Tolerance to the effects of inhaled beta-agonists can occur with regularly-scheduled, chronic use. Following are some common, uncommon and rare adverse events that occurred in the groups receiving formoterol/budesonide inhaler and formoterol and budesonide nebulising preparations.

**Cardiac Disorders**
Palpitations, tachycardia, cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles, angina pectoris.

**Endocrine Disorders**
Signs or symptoms of systemic glucocorticosteroid effects, e.g. adrenal suppression, growth retardation, decrease in bone mineral density, cataract and glaucoma, hypocorticism and hypercorticism.

**Gastrointestinal Disorders**
Gastroenteritis, abdominal pain, oral mucosal irritation, difficulty in swallowing, nausea, diarrhoea, vomiting

**Resistance Mechanism Disorder**
Otitis media, viral infection, moniliasis

**Immune System Disorders**
Immediate and delayed hypersensitivity reactions, e.g. exanthema, urticaria, pruritus, dermatitis, angio-oedema (presenting as face, lip, tongue, eye, pharyngeal, or mouth oedema) and anaphylactic reaction, eye infection, herpes simplex, external ear infection, infection, bronchospasm, rash

**Hearing and Vestibular Disorder**
Ear infection

**Infections and Infestations**
*Candida* infections in the oropharynx, sinusitis, pharyngitis, bronchitis

**Metabolic and Nutrition Disorders**
Hypokalaemia, hyperglycaemia, anorexia.

**Musculoskeletal, Connective Tissue and Bone Disorders**
Muscle cramps, myalgia, avascular necrosis of the femoral head, osteoporosis, growth suppression, growth retardation, decrease in bone density.

**Nervous System Disorders**
Headache, tremor, dizziness, taste disturbances, hyperkinesia.

**Psychiatric Disorders**
Agitation, restlessness, nervousness, sleep disturbances, depression, behavioural disturbances (mainly in children), psychosis, anxiety, irritability, aggressive reactions, psychomotor hyperactivity, emotional liability.  

**Respiratory, Thoracic and Mediastinal Disorders**  
Respiratory infection, rhinitis, throat irritation, dry mouth, coughing, hoarseness, bronchospasm, nasopharyngitis, chest pain, dysphonia, stridor  

**Skin and Subcutaneous Tissue Disorders**  
Bruises, facial skin irritation, urticaria, rash, dermatitis, pruritus, purpura  

**Vascular Disorders**  
Variations in blood pressure  

**Blood and Lymphatic System Disorders**  
Cervical lymphadenopathy  

**Ear and Labyrinth Disorders**  
Ear ache  

**General Disorders and Administration Site Conditions**  
Fatigue, flu-like disorder, fever, pain  

**Injury, Procedural Complication**  
Fracture  

There is an increased risk of pneumonia in patients with newly diagnosed COPD starting treatment with inhaled corticosteroids. However, results from the seven pooled clinical trials, published as meta-analysis did not demonstrate an increased risk of pneumonia in patients randomised with budesonide compared to non-ICS treatments.  

Facial skin irritation has occurred in some cases when a nebuliser with a face mask has been used. To prevent irritation, the facial skin should be washed with water after use of the face mask.  

Treatment with beta$_2$-agonists may result in an increase in the blood levels of insulin, free fatty acids, glycerol and ketone bodies. If case of 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 Programme of India (PvPI) by calling on 1800 180 3024 or you can report to Cipla Ltd on 1800 267 7779. By reporting adverse events, you can help provide more information on the safety of this product.  

**Overdose**  

An overdose of formoterol would likely lead to effects that are typical for beta$_2$-adrenergic agonists: angina, hypertension or hypotension, tremor, headache, palpitations, muscle cramps, dry mouth, nausea, dizziness, fatigue, malaise, insomnia, tachycardia, with rate up to 200 beats/min, hyperglycaemia, hypokalaemia, prolonged QTc interval, angina, hypertension or hypotension, arrhythmia, metabolic acidosis and vomiting. Supportive and symptomatic treatment may be indicated. A dose of 90 micrograms administered during 3 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 continually in excessive doses, systemic glucocorticosteroid effects, such as hypercorticism and adrenal suppression, may appear.  

If FORACORT respules therapy has to be withdrawn due to overdose of the formoterol component of the drug, provision of appropriate inhaled corticosteroid therapy must be considered. In case of over dosage, appropriate symptomatic and/or supportive therapy should be instituted. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of
FORACORT respules. Cardiac monitoring is recommended in cases of overdosage.

## Pharmacological Properties

### Mechanism of Action

FORACORT respules are a combination of budesonide, a potent glucocorticoid, and formoterol fumarate, a selective, long-acting beta\textsubscript{2}-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. The precise mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Anti-inflammatory effects (including T-cells, eosinophilic cells and mast cells) such as inhibition of the release of inflammatory mediators and inhibition of cytokine-mediated immune response, are probably important. The strength of budesonide, measured as affinity for glucocorticoid receptors, is approximately 15 times stronger than that of prednisolone. 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.

Formoterol fumarate is a potent, long-acting, beta\textsubscript{2}-adrenoceptor-agonist with a high intrinsic activity and a rapid onset of action. The pharmacologic effects of beta\textsubscript{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 inhibition of release of mediators of immediate hypersensitivity from the 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 anaesthetised 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 with COPD is unknown.

### Pharmacodynamic Properties

FORACORT respules contain an aqueous suspension of budesonide and formoterol fumarate, both of which have different effects on the clinical, physiological and inflammatory indices of 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 1,000-fold higher topical anti-inflammatory potency than cortisol.

Inflammation is an important component in the pathogenesis of 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 asthma.

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Studies in asthmatic patients have shown a favourable 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.

**Influence on Plasma Cortisol Concentration**

Inhaled corticosteroid products, may impact the HPA axis, especially in susceptible individuals and in patients given high doses for prolonged periods. In younger children, it may affect growth

**Formoterol Fumarate**

Formoterol fumarate is a potent, long-acting, beta₂-adrenoceptor-agonist with a high intrinsic activity and a rapid onset of action. 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 beta₂-receptors than at beta₁-receptors. 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 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 beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Linear pharmacokinetic/pharmacodynamic (PK/PD) relationships between urinary formoterol excretion and decreases in serum potassium, increases in plasma glucose, and increases in heart rate were generally observed with another inhalation formulation of formoterol fumarate and, hence, would be expected with the formoterol component of the respules also.

**Pharmacokinetic Properties**

Budesonide is primarily cleared by the liver. In asthmatic children, 4 to 6 years of age, the terminal half-life of budesonide after nebulisation is 2.3 hours and the systemic clearance is 0.5 L/min, which is approximately 50% greater than in healthy adults after adjustment for differences in weight. Also, after a single dose of 1 mg budesonide, a peak plasma concentration of 2.6 nmol/L was obtained approximately 20 minutes after nebulisation. Moreover, the exposure (AUC) of budesonide, following administration of a single 1 mg dose of budesonide by nebulisation, is comparable with healthy adults given a single 2 mg dose by nebulisation.

Information on the pharmacokinetics of formoterol (dry powder and/or inhalation solution) in plasma and/or urine is available in healthy subjects as well as patients with COPD 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**

**Budesonide**

In asthmatic children, 4 to 6 years of age, the total absolute bioavailability (i.e. lungs plus oral) following administration of budesonide respules via a jet nebuliser was approximately 6% of the labelled dose. The peak plasma concentration of budesonide occurred 10–30 minutes after the start of nebulisation.

**Formoterol Fumarate**

Pharmacokinetic properties of formoterol fumarate were evaluated in 12 COPD patients following inhalation
of single doses of formoterol inhalation solution containing 10, 20 and 244 mcg of formoterol fumarate (calculated on an anhydrous basis) and 12 mcg formoterol fumarate dry powder, through 36 hours after single-dose administration. Formoterol fumarate concentrations in plasma following the 10 and 20 mcg doses of formoterol inhalation solution and the 12 mcg dose of formoterol fumarate dry powder were undetectable or only detected sporadically at very low concentrations. Following a single 244 mcg dose of formoterol inhalation solution (approximately 12 times the recommended clinical dose), formoterol fumarate concentrations were readily measurable in plasma, exhibiting rapid absorption into plasma, and reaching a maximum drug concentration of 72 pg/mL within approximately 12 minutes of dosing. The mean amount of formoterol excreted unchanged in 24-hour urine following single oral inhalation doses of 10, 20 and 244 mcg formoterol inhalation solution were found to be 109.7 ng, 349.6 ng and 3317.5 ng, respectively. These findings indicate a near dose-proportional increase in systemic exposure within the dose range tested. When 12 mcg of a dry powder formulation of formoterol fumarate was given twice daily to COPD patients by oral inhalation for 12 weeks, the accumulation index, based on the urinary excretion of unchanged formoterol, was 1.19 to 1.38. This suggests some accumulation of formoterol in plasma with multiple dosing. Although multiple-dose pharmacokinetic data is unavailable from formoterol inhalation solution, assumption of linear pharmacokinetics allows a reasonable prediction of minimal accumulation based on single-dose pharmacokinetics. 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**

**Budesonide**

In asthmatic children, 4 to 6 years of age, the volume of distribution of budesonide at the steady state was 3 L/kg, approximately the same as in healthy adults. Budesonide is 85–90% bound to plasma proteins, the degree of binding being constant over the concentration range (1 to 100 nmol/L) achieved with, and exceeding, recommended 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.

**Formoterol Fumarate**

The binding of formoterol to human plasma proteins in vitro ranged from 61% to 64% at concentrations from 0.1 to 100 ng/mL. Binding to human serum albumin in vitro was 31% to 38% over a range of 5 to 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 244 mcg dose of formoterol inhalation solution.

**Metabolism**

**Budesonide**

*In vitro* studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolised in the liver. Two major metabolites, formed via the cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4)-catalysed biotransformation, have been isolated and identified as 16-alpha-hydroxybudesonide and 6-beta-hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No qualitative difference between the *in vitro* and *in vivo* metabolic patterns has been detected. Negligible metabolic inactivation was observed in the human lungs and in serum preparations.

**Formoterol Fumarate**

Formoterol fumarate is metabolised primarily by direct glucuronidation at either the phenolic 2- or aliphatic-hydroxyl group, and O-demethylation followed by glucuronide conjugation at either phenolic 2- or the aliphatic-hydroxyl groups. Minor pathways involve sulphate conjugation of formoterol and deformylation followed by sulphate conjugation. The most prominent pathway involves direct conjugation at the phenolic 2-
The second major pathway involves O-demethylation followed by conjugation at the phenolic 2- or aliphatic-hydroxyl. In vitro studies showed that multiple drug-metabolising enzymes catalyse glucuronidation (UGT1A1, 1A8, 1A9, 2B7 and 2B15 were the most predominant enzymes) and O-demethylation (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) of formoterol. Formoterol fumarate did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. It has not been adequately explored as to whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects.

**Excretion**

**Budesonide**

Budesonide is excreted in the urine and the faeces in the form of metabolites. In adults, approximately 60% of an intravenous radiolabelled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

In asthmatic children, 4 to 6 years of age, the terminal half-life of budesonide after nebulisation is 2.3 hours and the systemic clearance is 0.5 L/min, which is approximately 50% greater than in healthy adults after adjustment for differences in weight. Also, after a single dose of 1 mg budesonide, a peak plasma concentration of 2.6 nmol/L was obtained approximately 20 minutes after nebulisation. Moreover, the exposure (AUC) of budesonide, following administration of a single 1 mg dose of budesonide by nebulisation, is comparable to healthy adults given a single 2 mg dose by nebulisation.

**Formoterol Fumarate**

Following administration, via a nebuliser, of single 10, 20 and 244 mcg formoterol inhalation solution doses (calculated on an anhydrous basis) in 12 COPD patients, on average, about 1.1–1.7% of the dose was excreted in the urine as unchanged formoterol as compared with about 3.4% excreted unchanged following inhalation administration of 12 mcg of formoterol fumarate dry powder. Renal clearance of formoterol following inhalation administration of formoterol inhalation solution in these subjects was about 157 mL/min. Based on plasma concentrations measured following the 244 mcg dose, the mean terminal elimination half-life was determined to be 7 hours.

**Non-Clinical Properties**

**Animal Toxicology or Pharmacology**

**Budesonide**

Preclinical data revealed no special hazard for humans in the therapeutic dose range based on studies of chronic toxicity, genotoxicity and carcinogenicity.

Glucocorticoids, including budesonide, have produced teratogenic effects in animals, including cleft palate and skeletal abnormalities. Similar effects are considered unlikely to occur in humans at the recommended dose levels.

**Formoterol Fumarate**

Carcinogenesis, mutagenesis, impairment of fertility

The carcinogenic potential of formoterol fumarate has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15,000 mcg/kg and above in the drinking water study and at 20,000 mcg/kg in the dietary study (AUC exposure approximately 2,300 times human exposure at the maximum recommended daily inhalation dose), but not at dietary doses up to 5,000 mcg/kg (AUC exposure approximately 570 times human exposure at the maximum recommended daily inhalation dose). In the dietary study, the incidence of benign ovarian theca-cell tumours was increased at doses of 500 mcg/kg (AUC exposure was approximately 57 times human...
exposure at the maximum recommended daily inhalation dose) and above. This finding was not observed in the drinking water study, nor was it seen in mice.

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69,000 mcg/kg (AUC exposure approximately 1000 times human exposure at the maximum recommended daily inhalation dose) and above in the drinking water study, but not at doses up to 50,000 mcg/kg (AUC exposure approximately 750 times human exposure at the maximum recommended daily inhalation dose) in the dietary study. The incidence of hepatocarcinomas was increased in the dietary study at doses of 20,000 and 50,000 mcg/kg in females (AUC exposures approximately 300 and 750 times human exposure at the maximum recommended daily inhalation dose, respectively) and 50,000 mcg/kg in males, but not at doses up to 5,000 mcg/kg (AUC exposure approximately 75 times human exposure at the maximum recommended daily inhalation dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2,000 mcg/kg (AUC exposure was approximately 30 times human exposure at the maximum recommended daily inhalation dose) and above. Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs. Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats. Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3,000 mcg/kg (approximately 730 times the maximum recommended daily inhalation powder dose in humans on a mcg/m2 basis).

### Description

FORACORT respules are a combination of formoterol fumarate dihydrate and budesonide.

#### Formoterol Fumarate

Formoterol fumarate dihydrate, USP, a racemate. Formoterol fumarate dihydrate is a beta₂-adrenergic bronchodilator. Its chemical name is (±)-2-hydroxy-5-amino[ethyl] formanilide fumarate dihydrate; its structural formula is as below:

![Formoterol Fumarate](image)

Formoterol fumarate dihydrate, USP has a molecular weight of 840.92 and its empirical formula is \((C_{19}H_{24}N_2O_4)_2\cdot C_4H_4O_4\cdot 2H_2O\).

#### Budesonide

Budesonide is designated chemically as (RS)-11β, 16α, 17, 21-tetrahydroxypregna-1, 4-diene-3, 20 dione cyclic 16, 17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is \(C_{25}H_{34}O_6\) and its molecular weight is 430.5. Its structural formula is as below:

![Budesonide](image)
Budesonide is a white to off-white, tasteless, odourless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is $1.6 \times 10^3$.

FORACORT respules do not require dilution prior to administration by nebulisation. Like all other nebulised treatments, the amount delivered to the lungs will depend on patient factors and the nebulisation system used and its performance.

### Pharmaceutical Particulars

#### Incompatibilities

The drug compatibility (physical and chemical) of FORACORT respules when mixed with other drugs (other than Cipla respules) in a nebuliser have not been established.

This medicinal product must not be mixed with other medicinal products.

#### Shelf-Life

As on the pack.

#### Packaging Information

FORACORT respules are supplied as a 2 mL sterile suspension for nebulisation in low-density polyethylene unit dose vials. A strip containing 5 respules are packed in a protective pouch. Four such pouches are in one pack – hence, there are 20 respules, each of 2 mL, in one pack.

#### Storage and Handling Instructions

Store in the protective foil pouch under refrigeration at 2°–8°C. Do not freeze.

Once opened, the foil pouch containing the respules can be stored at room temperature below 25°C for up to 4 weeks. If kept at room temperature for more than 4 weeks, do not use the respules and discard. Contents of a respule once opened should be used immediately. Unopened respules should be stored in the pouch.

- Protect from light and heat.
- FORACORT respirator suspension should only be administered via a standard jet nebuliser connected to an air compressor with an adequate airflow and equipped with a facemask or mouthpiece.
- Vial should always be stored in the foil pouch, and only removed IMMEDIATELY before use.
- For single use only. Contents of any partially used container should be discarded.
- Discard the container and top after use.
- Keep out of the reach of children.
● What is FORACORT respules?
FORACORT respules are a combination of formoterol fumarate a long-acting, beta₂-adrenergic agonist (LABA) and budesonide a glucocorticosteroid with potent anti-inflammatory property. FORACORT respules are to be used for inhalation only, using a conventional jet nebuliser. They should not be swallowed or administered with any other method.
LABA medicines help the muscles around the airways in your lungs to stay relaxed to prevent symptoms such as wheezing, cough, chest tightness, and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe.

● Who should use the FORACORT respules?
FORACORT respules are indicated in the regular treatment of asthma, where the use of a combination of LABA and ICS (inhaled corticosteroid) has been found to be appropriate.
It is also indicated in the regular treatment of moderate-to-severe COPD, with frequent symptoms and a history of repeated exacerbations despite regular therapy with long-acting bronchodilators.
FORACORT respules is not used to relieve sudden breathing problems and will not replace a rescue inhaler.
Do not use FORACORT respules
• to treat sudden severe symptoms of asthma or COPD; and/or
• if you are allergic to any of the ingredients in FORACORT respules.

● What should I tell my doctor before I start using FORACORT respules?
Before you use FORACORT respules, tell your healthcare provider about all of your medical conditions, including if you have any of the following:
• heart problems
• high blood pressure
• seizures
• thyroid problems
• diabetes
• liver problems
• osteoporosis
• an immune system problem
• eye problems such as increased pressure in the eye, glaucoma, or cataracts
• are allergic to any medicines
• have any type of viral, bacterial, fungal, or parasitic infection
  are exposed to chicken pox or measles
• are pregnant or plan to become pregnant; it is not known if FORACORT respules may harm your unborn baby
• are breastfeeding

Budesonide, one of the active ingredients in FORACORT respules, passes into breast milk. You and your healthcare provider should decide if you will take FORACORT respules while breastfeeding.
Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. FORACORT respules and certain other medicines may interact with each other. This may cause serious side effects. Especially tell your healthcare provider if you take antifungal or anti-HIV medicines. Know all the medicines you take. Keep a list and show it to your healthcare provider and pharmacist each time you get a new medicine.

● How should I use FORACORT respules?
Talk to your doctor or pharmacist if you have any questions.  
Take FORACORT respules exactly as prescribed by your doctor. Do not change your dose or how often you use FORACORT respules without talking to your doctor. Inhale the contents of FORACORT respules by using mouthpiece and into your lungs by using a machine called a nebuliser. 
Frequency of use: Do not increase the dose or use this inhalation solution more frequently than recommended without consulting your physician. If you find that treatment with FORACORT respules becomes less effective or symptoms become worse, or you need to use the product more frequently than usual, they should seek medical attention immediately.  

What are the possible side effects of FORACORT respules after inhalation? 
FORACORT respules may cause serious side effects, including the following:
- chest pain
- palpitation
- increased blood pressure
- a fast and irregular heartbeat
- headache
- tremor
- nervousness

Other side effects also include the following:
- Fungal infection in your mouth or throat (thrush): Rinse your mouth with water without swallowing after using FORACORT respules to help reduce your chance of getting thrush.  
- Pneumonia and other lower respiratory tract infections: People with COPD have a higher chance of getting pneumonia and other lung infections. Inhaled corticosteroids may increase the chance of getting pneumonia. Decreases in blood potassium levels (hypokalaemia).  
- Increases in blood sugar levels (hyperglycaemia).  
- Adrenal insufficiency is a condition in which the adrenal glands do not make enough steroid hormones. This can happen when you stop taking oral corticosteroid medicines and start inhaled corticosteroid medicine.  
- Lower bone mineral density: This can happen in people who have a high chance for low bone mineral density (osteoporosis). Your healthcare provider should check you for this during treatment with FORACORT respules.  
- Eye problems, including glaucoma and cataracts: You should have regular eye exams while using FORACORT respules.  
- Swelling of your blood vessels: This can happen in people with asthma.  

Consult your healthcare provider if you notice any of these symptoms:
- increase in mucus (sputum) production or change in mucus colour
- fever
- chills
- increased cough
- increased breathing problems
- body aches
- feeling tired
- nausea
- vomiting
- a feeling of pins and needles or flu-like symptoms
numbness of your arms or legs
pain and swelling of the sinuses
rash
hives
swelling of the face, mouth, and tongue
breathing problems

Call your healthcare provider or get emergency medical care if you get any symptoms of a serious allergic reaction.

Respiratory effects: Increased wheezing right after taking FORACORT respules. Always have a rescue inhaler with you to treat sudden wheezing.

Other most common side effects of FORACORT respules include the following:

In people with asthma:
- throat irritation
- headache
- upper respiratory tract infection
- throat pain
- inflammation of mucous membranes of the sinuses (sinusitis)
- flu
- nasal congestion
- back pain
- vomiting
- stomach discomfort
- thrush in the mouth and throat

Rinse your mouth with water without swallowing after use to help prevent thrush

In people with COPD:
- throat irritation
- thrush in the mouth and throat; rinse your mouth with water without swallowing after use to help prevent thrush
- infection and inflammation of the mucous membranes of the bronchial tubes (bronchitis)
- inflammation of mucous membranes in the sinuses (sinusitis)
- upper respiratory tract infection

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all the possible side effects of FORACORT respules.

If case of 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 Programme of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 18002677779.

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

● How should I store FORACORT respules?

Store FORACORT respules under refrigeration at 2°–8°C. Do not freeze. Protect from light.

Do not use after the expiration date stamped on the container. Open the foil pouch just prior to administration. Once the foil pouch is opened, use the contents of the vial immediately. Keep the unused vials in the foil pouch or carton refrigerated.

Safely discard FORACORT respules that are out-of-date or are no longer needed.

Keep FORACORT respules and all medicines out of the reach of children.

General advice about FORACORT respules
Medicines are sometimes prescribed for conditions that are not mentioned in the patient information leaflet. Do not use FORACORT respules for a condition for which it was not prescribed. Do not give FORACORT respules to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarises the most important information about FORACORT respules. If you would like more information, talk to your doctor.

**Details Of The Manufacturer**

Cipla Ltd, Kumrek, Rangpo, Sikkim 737132, India.

**Details Of Permission Or License Number With Date**

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**FORACORT Respules**

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