Fortide
(Budesonide + Formoterol fumarate dihydrate)
CFC Free Inhaler
200mcg + 6mcg

DESCRIPTION
Fortide contains Budesonide + Formoterol fumarate dihydrate. Budesonide is a synthetic corticosteroid. Chemically, it is \( (\text{C}_{21}\text{H}_{26}\text{O}_{2}) \). Molar mass 352.42 dalton; cycle 16:1 alpha with butylpyridine. Its molecular formula is \( \text{C}_{21}\text{H}_{26}\text{O}_{2} \) and the structural formula is:

\[
\text{Budesonide}
\]

Formoterol fumarate dihydrate is a long-acting selective \( \beta_2 \) adrenoceptor agonist. Chemically, it is \( (\text{C}_{14}\text{H}_{17}\text{O}_{4} \text{N}) \). Molar mass 305.30 dalton; \( \beta_2 \)-adenosine dihydrogen phosphate (\( \text{C}_{21}\text{H}_{26}\text{O}_{14}\text{N} \)). Its molecular formula is \( \text{C}_{21}\text{H}_{26}\text{O}_{14}\text{N} \) and the structural formula is:

\[
\text{Formoterol fumarate dihydrate}
\]

QUALITATIVE & QUANTITATIVE COMPOSITION
Fortide (Budesonide + Formoterol fumarate dihydrate) is available for administration as:

Fortide Inhaler 200mcg + 6mcg
Each metered dose contains:
Budesonide BP… 200mcg
Formoterol fumarate dihydrate Ph. Eur. … 6mcg

CLINICAL PHARMACOLOGY
Mechanism of Action
Budesonide is a glucocorticosteroid which when inhaled has a dose-dependent anti-inflammatory action in the Airways, resulting in reduced symptoms and fewer exacerbations. Inhaled Budesonide has less severe adverse effects than systemic corticosteroids. The exact mechanism responsible for the anti-inflammatory action of glucocorticosteroids is unknown.

Formoterol is a selective \( \beta_2 \) adrenoceptor agonist which when inhaled results in rapid bronchodilatation (relaxation of bronchial smooth muscle in patients with reversible airways obstruction). The bronchodilating effect is dose dependent, with an onset of effect within 1-3 minutes. The duration of effect is at least 12 hours after a single dose.

Pharmacokinetics
Absorption
Orally inhaled Budesonide is rapidly absorbed in the lungs and peak concentration is typically reached within 20 minutes. After oral administration of budesonide peak plasma concentration was achieved in about 1 to 2 hours and the absolute systemic availability was determined to be about 90%. Formoterol is rapidly absorbed through the lungs and peak plasma concentration is typically reached within 5-10 minutes after dosing. A large number of drug products for oral inhalation, it is likely that the majority of the inhaled Formoterol delivered is swallowed and then absorbed from the gastrointestinal tract.

Distribution and Metabolism
Plasma protein binding is approximately 90% for Budesonide and 50% for Formoterol. Volume of distribution is about 34.3L for Budesonide and 4.4L for Formoterol. Budesonide undergoes an extensive degree (approximately 90%) of bioconversion on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6beta-hydroxy-budesonide and 16alpha-hydroxy-budesonide, is less than 1% of that of Budesonide. Formoterol is inactivated via conjugation reactions (active 10-desmethyl) and dehydroxylated metabolites are formed, but they are seen more as inactivated conjugates).

Excretion
Budesonide is eliminated via metabolism mainly catalyzed by the enzyme CYP3A4. The metabolites of Budesonide are eliminated in urine as such or in conjugated form. Budesonide has a high systemic clearance (approximately 1.2 l/min). The major part of dose of Formoterol is transformed by liver metabolism followed by renal excretion. After inhalation, 8% - 15% of the delivered dose of Formoterol is recovered in the urine. Its half-life is approximately 1.4 l/min and the terminal elimination half-life averages 17 hours.

THERAPEUTIC INDICATIONS
Fortide (Budesonide + Formoterol fumarate dihydrate) is indicated for:

Treatment of Asthma
Fortide (Budesonide + Formoterol fumarate dihydrate) is indicated for the treatment of asthma in patients 12 years of age and older.

Maintenance Treatment of Chronic Obstructive Pulmonary Disease (COPD)
Fortide (Budesonide + Formoterol fumarate dihydrate) is indicated for the twice daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

DOSE AND ADMINISTRATION
Fortide (Budesonide + Formoterol fumarate dihydrate) should be administered twice daily every day by the orally inhaled route only. After inhalation, the patient should rinse the mouth with water without swallowing.

Asthma
Adult and Adolescent Patients 12 Years of Age and Older:
For patients 12 years of age and older, the dose is 2 inhalations twice daily (morning and evening, approximately 12 hours apart).

The recommended starting dosages for Fortide (Budesonide + Formoterol fumarate dihydrate) for patients 12 years of age and older are based upon patients’ asthma severity. The maximum recommended dosage is Fortide (Budesonide + Formoterol fumarate dihydrate) 200mcg + 6mcg twice daily.

Improvement in asthma control is usually achieved within 1-10 minutes of beginning treatment, although maximum benefit may not be achieved for 2-3 weeks or longer after beginning treatment.

Individual patients may experience a variable time to onset and degree of symptom relief.

If a previously effective dosage regimens of Fortide (Budesonide + Formoterol fumarate dihydrate) fails to provide adequate control of asthma, the therapeutic regimen should be re-evaluated and additional therapeutic options (e.g., adding additional inhaled corticosteroids, or initiating oral corticosteroids) should be considered.

If asthma symptoms arise in the period between doses, an inhaled, short-acting \( \beta_2 \) agonist should be taken for immediate relief.

Chronic Obstructive Pulmonary Disease (COPD):
For patients with COPD the recommended dose is Fortide (Budesonide + Formoterol fumarate dihydrate), 2 inhalations twice daily. If shortness of breath occurs in the period between doses, an inhaled, short-acting \( \beta_2 \) agonist should be taken for immediate relief.

Special Population:
Pediatric Use
There is no relevant use of Fortide (Budesonide + Formoterol fumarate dihydrate) in children 11 years of age and under or in adolescents 12 to 17 years of age in the symptomatic treatment of COPD.

Geriatric Use
As with other products containing \( \beta_2 \) agonists, special caution should be observed when using Fortide (Budesonide + Formoterol fumarate dihydrate) in geriatric patients who have concurrent cardiovascular disease that could be adversely affected by \( \beta_2 \) agonists. No adjustment of dosage of Fortide (Budesonide + Formoterol fumarate dihydrate) in geriatric patients is warranted.

Hepatic Impairment
Since both Budesonide and Formoterol are predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of Budesonide and Formoterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Instructions for Use
Patients should be instructed on the correct inhalation technique.

Tapping the Inhaler:
Before using for the first time or if your inhaler has not been used for a week or more, remove the mouthpiece cover by gently squeezing the sides of the cover. Shake the inhaler well, and release the dose into the air to make sure that it works.

Cleaning:
Your inhaler should be cleaned at least once a week:
- Remove the mouthpiece cover.
- Do not remove the canister from the plastic casing.
- Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth, tissue or cotton bud.

Do not put metal casing in water.

ADVERSE REACTIONS
Common
Candida infections in the oropharynx, headache, tremor, palpitations, mild irritation in the throat, coughing and hoarseness.

Uncommon
Aggravation, psychosis, hyperactivity, anxiety, sleep disorders, dizziness, tachycardia, nausea, bruises and muscle cramps.

Rare
- Immediate and delayed hypersensitivity reactions, e.g., exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction, hypokalaemia, cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, electrocardiograms and bronchosplasm.
- Very Rare
Cushing syndrome, adrenal suppression, growth retardation, decrease in bone mineral density, hyperglycemia, depression, behavioral changes, taste disturbances, cataract, Cushing’s syndrome, adrenal suppression, growth retardation, decrease in bone mineral density.
- Very Rare
- In patients with known hypersensitivity to Budesonide or Formoterol or to any excipient used in this product.
- In patients with concurrent cardiovascular disease that could be adversely affected by \( \beta_2 \) agonists.
- In patients with chronic obstructive pulmonary disease (COPD) who are at increased risk of exacerbation of asthma.
- In patients with severe asthma, who are at increased risk of exacerbation of asthma.
- In patients with severe chronic obstructive pulmonary disease (COPD) and/or severe bronchial asthma.
- In patients with COPD with a history of smoking.

CONTRAINDICATIONS
Budesonide + Formoterol is contraindicated:
- In patients with known hypersensitivity to Budesonide or Formoterol or to any excipient used in this product.
- In patients with concurrent cardiovascular disease that could be adversely affected by \( \beta_2 \) agonists.
- In patients with severe asthma, who are at increased risk of exacerbation of asthma.
- In patients with severe chronic obstructive pulmonary disease (COPD) and/or severe bronchial asthma.
- In patients with COPD with a history of smoking.

PRECAUTIONS
Asthma-Related Death
Long-acting \( \beta_2 \) adrenergic agonists (LABA), such as Formoterol, increase the risk of asthma-related death. When treating patients with asthma, Budesonide + Formoterol should only be used for patients not adequately controlled on a long term asthma control medication. FORTIDE (Budesonide + Formoterol fumarate dihydrate) is contraindicated for the initial treatment of patients with asthma. If the need for treatment arises during treatment with both an inhaled corticosteroid and a LABA, once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue Budesonide + Formoterol inhaler) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such
as an inhaled corticosteroid. Do not use Budesonide + Formoterol inhaler for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

**Deterioration of Disease and Acute Exacerbations**

Budesonide + Formoterol inhaler should not be used in patients during rapidly deteriorating or potentially life-threatening episodes of asthma and COPD as it should be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute exacerbations of bronchospasm. When beginning treatment with Budesonide + Formoterol inhaler, patients who have been taking oral or inhaled, short-acting β2 agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

**Excessive Use of Budesonide + Formoterol**

It is possible that systemic corticosteroidal effects and local effects have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using Budesonide + Formoterol inhaler should not take oral inhaled or nasal corticosteroids, cromolyn sodium, antihistamines; systemic corticosteroids, or other β2 agonists in excess of the recommended dose over 28 days. Excessive use of oral corticosteroids can be acutely worsened by β2 agonists, especially when the recommended dose of the β2 agonist is exceeded. Caution is advised in the coadministration of Budesonide + Formoterol inhaler with inhaled long-acting β2 agonists.

**Transferring Patients from Systemic Corticosteroid Therapy**

Hypercorticism and Adrenal Suppression

- It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear.
- Adrenal suppression may appear with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue Budesonide + Formoterol inhaler.

**Parotidal Bronchospasm and Upper Airway Symptoms**

As with all inhaled medicines, Budesonide + Formoterol inhaler can produce parotidal bronchospasm, which may be life threatening. If parotidal bronchospasm occurs discontinue Budesonide + Formoterol inhaler and institute alternative therapy.

**Immediate Hypersensitivity Reactions**

Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm) may occur after administration of Budesonide + Formoterol inhaler. Patients should be observed for signs of anaphylaxis. If such an event occurs, discontinue Budesonide + Formoterol inhaler.

**Cardiovascular and Central Nervous System Effects**

Budesonide + Formoterol inhaler should be used with caution in patients with cardiovascular disease, especially coronary insufficiency, cardiac arrhythmias, and hypertension because of its adrenergic stimulation.

**Reduction in Bone Mineral Density**

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients should be assessed for bone mineral density initially and periodically thereafter.

**Effect on Growth**

Only inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving Budesonide + Formoterol inhaler routinely.

**Glucoma and Cataracts**

Glucoma and cataracts have been reported in patients with asthma and COPD following the use of inhaled corticosteroids. Patients should be assessed for signs of glucoma and STUDY IN CASES, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients.

**Cushingoid Conditions**

Budesonide + Formoterol inhaler should be used with caution in patients with connective tissue disorders and allergy. Some patients, possibly through intracarital shaping, which has the potential to produce adverse cardiovascular effects.

**Hypokalemia**

- For all β2 adrenergic agonists, additional blood glucose controls should be considered in diabetic patients.

**Pregnancy**

There are no adequate and well-controlled studies of Budesonide + Formoterol in pregnant women. Budesonide + Formoterol inhaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mother**

Budesonide is secreted in breast milk. It is not known whether Budesonide + Formoterol in pregnant women. Budesonide + Formoterol inhaler should be used during pregnancy only if the potential benefit justifies the potential risk to the mother.

**DRUG INTERACTIONS**

- Potent inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, voriconazole, terfenadine, astemizole, and non-selective beta-blockers) are metabolic inhibitors of Budesonide + Formoterol inhaler. Therefore, patients with asthma should not normally be treated with β2 agonists. However, under certain circumstances, there may be acceptable alternatives to discontinuing one of these drugs. Therefore, β2 agonists should be used with caution in patients treated with key inhibitors. In these patients, cardioselective β2 blockers could be considered, although they should be administered with caution.
- Concomitant treatment with quinidine, diisopropramide, procarbaminate, phosphodiesterase-1, and tricyclic antidepressants can prolong the QTc interval and increase the risk of ventricular arrhythmias.
- Drug interactions with a known increase in QTc interval, such as class Ia and class III antiarrhythmics, may occur.
- The QTc interval should be monitored in patients treated with Budesonide + Formoterol inhaler. Clinically significant cardiovascular effects and fatalities have been reported in association with the use of Budesonide + Formoterol inhaler.

**Overdosage**

Acute overdose with Budesonide, even in excessive doses, is not expected to be a life-threatening event. When used chronically in excessive doses, systemic glucocorticoid effects, such as hypercorticism and adrenal suppression, may appear.

An overdose of Budesonide would likely lead to effects that are typical for β2 adrenergic agonist: tremor, headache, palpitations. Symptoms reported from isolated cases are hypertension, tachycardia, hyperglycemia, hypokalemia, prolonged QTc interval, arrhythmias, nausea and vomiting. Supportive and symptomatic treatment may be indicated.

If Budesonide + Formoterol therapy has to be withdrawn due to overdose of the Budesonide component of the drug, provision of appropriate inhaled corticosteroid therapy must be considered.

**STORAGE**

Store below 30°C. Protect from direct sunlight. Heat and frost. Shake well before use.

As with all inhaled medicinal products in pressure-sustained canisters, the therapeutic effect of this medicinal product may decrease when the canister is cold. The canister should not be broken, punctured or burnt, even when apparently empty. The expiration date refers to the product correctly stored at the required conditions.

**HOW SUPPLIED**

Budesonide + Formoterol inhaler: Budesonide 200 microg + Formoterol fumarate dihydrate Inhaler 200 mg + 6mg is available in pack of 1’s. Each canister provides 120 inhalations.

**Keep out of reach of children.**

To be prescribed on a registered medical practitioner only.

Please read the contents carefully before use. This package insert is continually updated from time to time.

Manufactured by: GETZ PHARMA LIMITED

L-200008873