SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG PRODUCT

Fortide (Budesonide + Formoterol Fumarate Dihydrate) Inhaler 200mcg + 6mcg

Strength: 200mcg + 6mcg
Pharmaceutical/Dosage Form: Metered Dose Inhaler

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each actuation delivers:
Budesonide BP… 200mcg
Formoterol Fumarate Dihydrate Ph. Eur. …. 6mcg
Also contains: CFC - Free propellant, HFA 134a

3. PHARMACEUTICAL FORM

Appearance : Aluminum canister with metering valve containing pressurized liquid, fitted over a red color actuator along with a light brown color cap.
Content Appearance: Upon spraying on black sheet white smear will appear.

4. CLINICAL PARTICULARS

4.1 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.

4.2 Posology and method of 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 dosage 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 following inhaled administration of Fortide (Budesonide + Formoterol Fumarate Dihydrate) can occur within 15 minutes of beginning treatment, although maximum benefit may not be achieved for 2 weeks or longer after beginning treatment. Individual patients will experience a variable time to onset and degree of symptom relief.
If a previously effective dosage regimen 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 corticosteroid, or initiating oral corticosteroids) should be considered.
If asthma symptoms arise in the period between doses, an inhaled, short-acting ß2 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) two inhalations twice daily. If shortness of breath occurs in the period between doses, an inhaled, short-acting $ß_2$ 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 $ß_2$ agonists, special caution should be observed when using Fortide (Budesonide + Formoterol Fumarate Dihydrate) in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by $ß_2$ 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.

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

Testing 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 one puff 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.
- Replace the mouthpiece cover.
- Do not put metal canister in water.

4.3 Contraindications

Budesonide + Formoterol is contraindicated:
- In patients with known hypersensitivity to Budesonide or Formoterol or to any excipient of the product.
- In primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.

4.4 Special warnings and special precautions for use

General
Patients should be advised that this product contains small amount of ethanol. At normal doses, the amounts of ethanol are negligible and do not pose a risk to patients.

Asthma-Related Death
Long-acting $ß_2$ 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, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of 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 Episodes
Budesonide + Formoterol inhaler should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. It should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. When beginning treatment with Budesonide + Formoterol inhaler, patients who have been taking oral or inhaled, short-acting $ß_2$ 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 inhaler and Use with Other Long-Acting $ß_2$ Agonists
Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using Budesonide + Formoterol inhaler should not use additional LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma or COPD.

Local Effects of Inhaled Corticosteroids
Candida albicans infection of the mouth and pharynx may occur in subjects treated with Budesonide + Formoterol inhaler. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise the patient to rinse the mouth following inhalation.
Pneumonia or other Respiratory tract infections:
Lower respiratory tract infections, including pneumonia, have been reported in patients with chronic obstructive pulmonary disease (COPD) following the inhaled administration of corticosteroids. Monitor patients for signs and symptoms of pneumonia and other potential lungs infections.

Immunosuppression
Persons who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. More serious or even fatal course of chickenpox or measles can occur in susceptible patients.

Transferring Patients from Systemic Corticosteroid Therapy
Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to Budesonide + Formoterol inhaler.

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

Paradoxical Bronchospasm and Upper Airway Symptoms
As with other inhaled medicines, Budesonide + Formoterol inhaler can produce paradoxical bronchospasm, which may be life threatening. If paradoxical 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.

Cardiovascular and Central Nervous System Effects
Budesonide + Formoterol inhaler should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension because of ß 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
Orally 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.

Glaucoma and Cataracts
Glaucoma and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including Budesonide. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Eosinophilic Conditions and Churg-Strauss Syndrome
In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients.

Coexisting Conditions
Budesonide + Formoterol inhaler should be used with caution in patients with convulsive disorders or thyrotoxicosis, diabetes mellitus and ketoacidosis.

Hypokalemia
ß adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects.

Hyperglycemia
As for all $ß_2$ adrenoceptor agonists, additional blood glucose controls should be considered in diabetic patients.

4.5 Interaction with other medicinal products and other forms of Interactions

- Potent inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors) are likely to markedly increase plasma levels of Budesonide and concomitant use should be avoided. If this is not possible the time interval between administration of the inhibitor and Budesonide should be as long as possible.
- ß blockers (including eye drops) may not only block the pulmonary effect of ß agonists, such as Formoterol but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with ß blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of ß adrenergic blocking agents in patients with asthma. In this setting, cardioselective ß blockers could be considered, although they should be administered with caution.
- Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines and tricyclic antidepressants can prolong the QTC -interval and increase the risk of ventricular arrhythmias.
- L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards $ß_2$- sympathomimetics.
- Budesonide + Formoterol inhaler should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within two weeks of discontinuation of such agents, because the action of Formoterol on the vascular system may be potentiated by these agents.
- There is an elevated risk of arrhythmias in patients receiving concomitant anesthesia with halogenated hydrocarbons.
- Concomitant use of other ß adrenergic drugs or anticholinergic drugs can have a potentially additive bronchodilating effect.
- Hypokalemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.
- 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 ß agonists, especially when the recommended dose of the ß agonist is exceeded. Caution is advised in the coadministration of Budesonide + Formoterol inhaler with non-potassium sparing diuretics.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
There are no adequate and well controlled studies of Budesonide + Formoterol inhaler 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 Formoterol passes into human breast milk. Administration of Budesonide + Formoterol inhaler 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.

4.7 Effects on ability to drive and use machines

Budesonide + Formoterol inhaler has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

Uncommon:
Aggression, psychomotor 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, hypokalemia, cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles and bronchospasm.

Very Rare:
Cushing's syndrome, adrenal suppression, growth retardation, decrease in bone mineral density, hyperglycemia, depression, behavioural changes, taste disturbances, cataract, glaucoma, angina pectoris, prolongation of QTC-interval and variations in blood pressure.

4.9 Overdosage

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

An overdose of Formoterol would likely lead to effects that are typical for $ß_2$ adrenoceptor agonists: tremor, headache, palpitations. Symptoms reported from isolated cases are tachycardia, hyperglycemia, hypokalemia, prolonged QTC-interval, arrhythmia, nausea and vomiting. Supportive and symptomatic treatment may be indicated.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Budesonide
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 effect of glucocorticosteroids is unknown.

Formoterol
Formoterol is a selective $ß_2$ adrenoceptor agonist which when inhaled results in rapid and long-acting 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.

5.2 Pharmacokinetic properties

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 6%-13% due to extensive first pass metabolism. In contrast, most of the Budesonide delivered to the lungs was systemically absorbed. In healthy subjects, 34% of the metered dose was deposited in the lung with an absolute systemic availability of 39% of the metered dose.
Inhaled Formoterol is rapidly absorbed; peak plasma concentrations are typically reached at the first plasma sampling time, within 5-10 minutes after dosing. As with many drug products for oral inhalation, it is likely that the majority of the inhaled Formoterol delivered is swallowed and then absorbed from the gastrointestinal tract.

Distribution and Metabolism
Plasma protein binding is approximately 90% for Budesonide and 50% for Formoterol. Volume of distribution is about 3L/kg for Budesonide and 4L/kg for Formoterol. Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6-beta-hydroxy-budesonide and 16-alfa-hydroxyprednisolone, is less than 1% of that of Budesonide. Formoterol is inactivated via conjugation reactions (active O-demethylated and deformylated metabolites are formed, but they are seen mainly 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 elimination. After inhalation, 8% to 13% of the delivered dose of Formoterol is excreted unmetabolized in the urine. Formoterol has a high systemic clearance (approximately 1.4 l/min) and the terminal elimination half-life averages 17 hours.

5.3 Preclinical safety data
The toxicity observed in animal studies with budesonide and formoterol, given in combination or separately, were effects associated with exaggerated pharmacological activity.

In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant in humans at the recommended doses. Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure and implantation losses as well as decreased early postnatal survival and birth weight at considerably higher systemic exposures than those reached during clinical use. However, these animal experimental results do not seem to be relevant in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Ethanol Absolute
- Sorbitan Trioleate
- Propellant HFA 134a

6.2 Incompatibilities

None

6.3 Shelf-life

2 Years
The expiration date refers to the product correctly stored in the required conditions.

6.4 Special precautions for storage

- Do not store above 30°C.
- Protect from direct sunlight, heat and frost.
- Keep all medicines out of reach of children.
- The canister should not be broken, punctured or burnt even when apparently empty.

6.5 Nature and contents of container

Fortide (Budesonide + Formoterol Fumarate Dihydrate) 200mcg + 6mcg is available in one pack of aluminum canister with metering valve containing pressurized inhalation suspension, fitted over a red color actuator along with a light brown color cap packed in printed unit carton along with patient information leaflet PIL & insert card.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

Getz Pharma (Private) Limited
29-30/27, Korangi Industrial Area Karachi 74900, Pakistan
Tel: (92-21) 111-111-511
Fax: (92-21) 5057592

8. DRUG PRODUCT MANUFACTURER

Getz Pharma (Private) Limited
29-30/27, Korangi Industrial Area Karachi 74900, Pakistan
Tel: (92-21) 111-111-511
Fax: (92-21) 5057592

9. NAFDAC REGISTRATION NUMBER

B4-9410