SUMMARY OF PRODUCT CHARACTERISTICS

1. *NAME OF DRUG PRODUCT*

FORTIDE DPI (Budesonide + Formoterol Fumarate Dihydrate) Powder For Inhalation 200mcg + 6mcg

2. *QUALITATIVE AND QUANTITATIVE COMPOSITION*

Each capsule contains:
Budesonide BP...200mcg
Formoterol Fumarate Dihydrate Ph. Eur…6mcg

3. *PHARMACEUTICAL FORM*

Hydroxypropyl methylcellulose (HPMC) capsule shell with faded purple opaque cap and transparent body containing white powder.

4. *CLINICAL PARTICULARS*

4.1 Therapeutic indications

Asthma

Fortide (Budesonide + Formoterol fumarate dihydrate) is indicated in adults and adolescents
(12 years and older) for the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β2 adrenoceptor agonist) is appropriate:

- Patients not adequately controlled with inhaled corticosteroids and “as needed” inhaled short-acting β2 adrenoceptor agonists. or
- Patients already adequately controlled on both inhaled corticosteroids and long-acting β2 adrenoceptor agonists.

Chronic Obstructive Pulmonary Disease (COPD)

Fortide (Budesonide + Formoterol fumarate dihydrate) is indicated in adults, aged 18 years and older, for the symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV1) <70% predicted normal (post bronchodilator) and an exacerbation history despite regular bronchodilator therapy.

4.2 Posology and Method of Administration

Fortide (Budesonide + Formoterol fumarate dihydrate) is not intended for the initial management of asthma. The dosage of the components of Fortide (Budesonide + Formoterol fumarate dihydrate) is individual and should be adjusted to the severity of the disease. This should be considered not only when treatment with combination products is initiated but also when the maintenance dose is adjusted. If an individual patient should require a combination of doses other than those available in the combination inhaler, appropriate doses of β2 adrenoceptor agonists and/or corticosteroids by individual inhalers should be prescribed.
Patients should be regularly reassessed so that the dosage of Fortide (Budesonide +
Formoterol fumarate dihydrate) remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. When long-term control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.
In usual practice when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include Fortide (Budesonide + Formoterol fumarate dihydrate) given once daily, when in the opinion of the prescriber, a long-acting bronchodilator in combination with an inhaled corticosteroid would be required to maintain control.
Increasing use of a separate rapid-acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy.

Asthma

For Fortide (Budesonide + Formoterol fumarate dihydrate) DPI Powder For Inhalation 200mcg + 6mcg there are two treatment approaches:

A. Fortide maintenance therapy:

Fortide (Budesonide + Formoterol fumarate dihydrate) is taken as regular maintenance treatment with a separate rapid-acting bronchodilator as rescue. Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

Adults (18 years and older): The recommended dose for adults is 1-2 inhalations twice daily. Some patients may require up to a maximum of 4 inhalations twice daily.

Adolescents (12 – 17 years): The recommended dose for adolescents is 1-2 inhalations twice daily.

B. Fortide maintenance and reliever therapy:

Fortide (Budesonide + Formoterol fumarate dihydrate) is taken as regular maintenance treatment and as needed in response to symptoms. Patients should be advised to always have Fortide (Budesonide + Formoterol fumarate dihydrate) available for rescue use.

A persistent increase in the use of Fortide (Budesonide + Formoterol fumarate dihydrate) as needed indicates a deterioration of asthma control and the patient's condition should be re-evaluated. Fortide (Budesonide + Formoterol fumarate dihydrate) maintenance and reliever therapy should especially be considered for patients with:

- Inadequate asthma control and in frequent need of reliever medication.
- Asthma exacerbations in the past requiring medical intervention.

Close monitoring for dose-related adverse effects is needed in patients who frequently take high numbers of Fortide (Budesonide + Formoterol fumarate dihydrate) as-needed inhalations.

Adults and adolescents (12 years and older): The recommended maintenance dose is

2 inhalations per day, given either as one inhalation in the morning and evening or as
2 inhalations in either the morning or evening. For some patients a maintenance dose of 2 inhalations twice daily may be appropriate. Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion. A total daily dose of more than 8 inhalations is not normally needed; however, a total daily dose of up to 12 inhalations could be used for a limited period. Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice. They should be reassessed and their maintenance therapy should be reconsidered.

COPD
Adults: The recommended dose for adults is 2 inhalations twice daily.

4.3 Contraindications:

Budesonide + Formoterol fumarate dihydrate is contraindicated in patients with known hypersensitivity to budesonide, formoterol or inhaled lactose.

4.4 Special warnings and special precautions for use

- It is recommended that the dose is tapered when the treatment is discontinued and should not be stopped abruptly.
- If patients find the treatment ineffective or exceed the highest recommended dose of Budesonide + Formoterol fumarate dihydrate, medical attention must be sought. Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy. Sudden and progressive deterioration in control of asthma or COPD is potentially life threatening and the patient should undergo urgent medical assessment.
- Patients should be advised to have their rescue inhaler available at all times.

- Patients should be reminded to take their Budesonide + Formoterol fumarate dehydrate maintenance dose as prescribed, even when asymptomatic.
- The reliever inhalations of Budesonide + Formoterol fumarate dihydrate should be taken in response to asthma symptoms but are not intended for regular prophylactic use, e.g before exercise.
- Patients should not be initiated on Budesonide + Formoterol fumarate dihydrate 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 Budesonide + Formoterol fumarate dihydrate. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation with Budesonide + Formoterol fumarate dihydrate.
- As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath, after dosing. If the patient experiences paradoxical bronchospasm Budesonide + Formoterol fumarate dihydrate should be discontinued immediately, the patient should be assessed and an alternative therapy instituted, if necessary.
- Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. It is important therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.
- Potential effects on bone density should be considered particularly in patients on high doses for prolonged periods that have co-existing risk factors for osteoporosis.
- 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 Budesonide + Formoterol fumarate dihydrate therapy.
- 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. Recovery may take a considerable amount of time after cessation of oral steroid therapy and hence oral steroid-dependent

patients transferred to inhaled budesonide may remain at risk from impaired adrenal function for some considerable time. In such circumstances HPA-axis function should be monitored regularly.

- The prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Therefore, additional systemic corticosteroid cover should be considered during periods of stress such as severe infections or elective surgery. Rapid reduction in the dose of steroids can induce acute adrenal crisis.
- Treatment with supplementary systemic steroids or inhaled budesonide should not be stopped abruptly.
- During transfer from oral therapy to Budesonide + Formoterol fumarate dehydrate DPI, a generally lower systemic steroid action will be experienced which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema and muscle and joint pain. Specific treatment should be initiated for these conditions. A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary.
- To minimise the risk of oropharyngeal candida infection, the patient should be instructed to rinse their mouth out with water after inhaling the maintenance dose.
- Budesonide + Formoterol fumarate dihydrate should be administered with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure.
- Caution should be observed when treating patients with prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval.
- The need for and dose of inhaled corticosteroids should be re-evaluated in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.

- Potentially serious hypokalaemia may result from high doses of β2 adrenoceptor agonists. 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 is increased. It is recommended that serum potassium levels are monitored during these circumstances.
- As for all β2 adrenoceptor agonists, additional blood glucose controls should be considered in diabetic patients. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes, which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR), which have been reported after use of systemic and topical corticosteroids.
- It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained, if possible. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed.
- An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.
- Corticosteroids may mask some signs of infection and new infections may appear. A decreased resistance to localized infection has been observed during corticosteroid therapy.
- In patients with increased susceptibility to sympathomimetic amines (eg inadequately controlled hyperthyroidism), formoterol should be used with caution.

- In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions, with some patients presenting with

clinical features of vasculitis consistent with Churg-Strauss syndrome. Physicians should be alerted to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications and/or neuropathy presenting in the patients.

- This medicine contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsosption should not take this medicine

4.5 Interaction with other medicaments

- Potent inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors) are likely to increase plasma levels of budesonide and concomitant use should be avoided. If this is not possible the time interval between administration of the inhibitor and budesonide should be as long as possible. In patients using potent CYP3A4 inhibitors, Budesonide + Formoterol fumarate dihydrate maintenance and reliever therapy is not recommended.
- β-adrenergic blockers can weaken or inhibit the effect of formoterol. Budesonide + Formoterol fumarate dihydrate sould therefore not be given together with β-adrenergic blockers (including eye drops) unless there are compelling reasons. Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine) 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 β2 sympathomimetics.
- Concomitant treatment with monoamine oxidase inhibitors, including agents with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions.
- There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.
- Concomitant use of other β-adrenergic drugs or anticholinergic drugs can have a potentially additive bronchodilating effect.

- Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.
- Hypokalaemia may result from β2-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids and diuretics.

4.6 Uses in Pregnancy and Lactation

Pregnancy

During pregnancy, Budesonide + Formoterol fumarate dihydrate should only be used when the benefits outweigh the potential risks. Only after special consideration should Budesonide + Formoterol fumarate dihydrate be used during the first 3 months and shortly before delivery. Because β-agonists, including formoterol, may potentially interfere with uterine contractility, due to a relaxant effect on uterine smooth muscle, Budesonide + Formoterol fumarate dihydrate should be used during labour only if the potential benefit justifies the potential risk.

Nursing Mother

Budesonide is excreted in breast milk. Administration of Budesonide + Formoterol fumarate dihydrate to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

4.7 Undesirable effects

Common: Candida infections in the oropharynx, pneumonia (in COPD patients), headache, tremor, palpitations, mild irritation in the throat, coughing and hoarsenes.
Uncommon: Aggression, psychomotor hyperactivity, anxiety, sleep disorders, dizziness, vision blurred, 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, extrasystoles and bronchospasm.

Very rare: Cushing's syndrome, adrenal suppression, growth retardation, decreae in bone mineral density, hyperglycaemia, depression, behavioural changes, taste disturbances, cataract and glaucoma, angina pectoris, prolongation of QTc-interval and variations in blood pressure.).

4.8 Overdosage

Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem. However, the plasma cortisol level will decrease and number and percentage of circulating neutrophils will increase. The number and percentage of lymphocytes and eosinophils will decrease concurrently. When used chronically in excessive doses, systemic glucocorticosteroid effects, such as hypercorticism and adrenal suppression, may appear. Withdrawing Budesonide + Formoterol fumarate dihydrate or decreasing the dose of budesonide will abolish these effects, although the normalisation of the HPA-axis may be a slow process.
An overdose of formoterol may lead to effects that are typical for β2-adrenergic agonists: tremor, headache, palpitations and tachycardia. Monitoring of serum potassium concentrations may be warranted. Hypotension, metabolic acidosis, hypokalaemia and hyperglycaemia may also occur. Supportive and symptomatic treatment may be indicated. β-blockers should be used with care because of the possibility of inducing bronchospasm in sensitive individuals. A metered dose of 120mcg administered during three hours in patients with acute bronchial obstruction raised no safety concerns. If Budesonide + Formoterol fumarate dihydrate 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 Pharmacokinetic Properties

Absorption
Inhaled budesonide is rapidly absorbed and the maximum plasma concentration is reached within 30 minutes after inhalation. Mean lung

deposition of budesonide after inhalation via the powder inhaler ranged from 32% to 44% of the delivered dose. The systemic bioavailability is approximately 49% of the delivered dose. In children 6-16 years of age the lung deposition falls in the same range as in adults for the same given dose. The resulting plasma concentrations were not determined.
Inhaled formoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation. Mean lung deposition of formoterol after inhalation via the powder inhaler ranged from 28% to 49% of the delivered dose. The systemic bioavailability is about 61% of the delivered dose.

Distribution
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.

Metabolism
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-hydroxy-prednisolone, 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).

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

The major part of a dose of formoterol is transformed by liver metabolism followed by renal elimination. After inhalation, 8% to 13% of the delivered dose of formoterol is excreted unmetabolised in the urine. Formoterol has a high systemic clearance (approximately 1.4 l/min) and the terminal elimination half-life averages 17 hours.

Special Population

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

5.2 Pharmacodynamic properties

Mechanism of Action

Budesonide and Formoterol fumarate dihydrate have different modes of action and show additive effects in terms of reduction of asthma exacerbations and COPD exacerbations. The specific properties of budesonide and formoterol allow the combination to be used either as maintenance and reliever therapy or as maintenance treatment of asthma and for symptomatic treatment of patients with moderate to severe COPD.

Budesonide

Budesonide is a glucocorticosteroid which when inhaled has a dose-dependent anti-inflammatory action in the airways, resulting in reduced symptoms and fewer asthma exacerbations. Budesonide has also been shown to decrease airway reactivity to both direct and indirect challenge in hyper reactive patients.

Formoterol fumarate dihydrate

Formoterol is a selective β2 adrenoceptor agonist that 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.

5.3 Clinical 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

- Lactose Monohydrate (Lactohale 200)
- Empty Hypromellose Capsules Size # “3”

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

2 Years

The expiration dates 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.

6.5 Nature and contents of container

FORTIDE (Budesonide + Formoterol Fumarate Dihydrate) DPI Powder For Inhalation 200mcg + 6mcg are available in blister pack of 30's.

6.6 Special precautions for disposal

No special requirements.

6.7 Instructions for use/handling

- Keep out of reach of children.
- To be sold on prescription of a registered medical practitioner only.

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

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