BUSONIDE®

(BUDESONIDE+FORMOTEROL FUMARATE DIHYDRATE)

بیوسونائیڈ

COMPOSITION
Busonide 200/6mcg
Each capsule contains:
Budesonide Ph. Eur.....200mcg
Formoterol fumarate dihydrate Ph. Eur.....6mcg
Busonide 400/12mcg
Each capsule contains:
Budesonide Ph. Eur.....400mcg
Formoterol fumarate dihydrate Ph. Eur.....12mcg
(As per Innovator's Specs.)

DESCRIPTION
Busonide 200/6mcg and Busonide 400/12mcg each contain micronized budesonide and micronized formoterol fumarate dihydrate for oral inhalation only.
Budesonide is a corticosteroid 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.
Formoterol fumarate dihydrate is a selective beta-2 agonist designated chemically as (R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1methylethyl]amino]ethyl]phenyl] formamide, (E)-2-butendioate(2:1), dihydrate. The empirical formula of formoterol is $C_{42}H_{56}N_4O_{14}$ and its molecular weight is 840.9.
Each delivered dose (the dose that leaves the mouthpiece) from Busonide 200/6mcg contains: budesonide 160 micrograms/inhalation and formoterol fumarate dihydrate 4.5 micrograms/inhalation.
Each metered dose in Busonide 200/6mcg contains: budesonide 200 micrograms/inhalation and formoterol fumarate dihydrate 6 micrograms/inhalation.
Each delivered dose (the dose that leaves the mouthpiece) from Busonide 400/12mcg contains: budesonide 320 micrograms/inhalation and formoterol fumarate dihydrate 9 micrograms/inhalation.
Each metered dose in Busonide 400/12mcg contains: budesonide 400 micrograms/inhalation and formoterol fumarate dihydrate 12 micrograms/inhalation.

CLINICAL PHARMACOLOGY
Mechanism of Action
Busonide contains both budesonide and formoterol; therefore, the mechanisms of action described below for the individual components apply to Busonide. These drugs represent two classes of medications (a synthetic corticosteroid and a long-acting selective beta-2 adrenoceptor agonist) that have different effects on clinical, physiological, and inflammatory indices of COPD and 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 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.
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.
Inflammation is an important component in the pathogenesis of COPD and 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 COPD and asthma.
Studies in asthmatic patients have shown a favorable 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.

Formoterol
Formoterol fumarate is a long-acting selective beta-2 adrenergic agonist (beta-2 agonist) with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. In vitro studies have shown that formoterol has more than 200-fold greater agonist activity at beta-2 receptors than at beta-1receptors. The in vitro binding selectivity to beta-2 over beta-1 adrenoceptors is higher for formoterol than for albuterol (5 times), whereas salmeterol has a higher (3 times) beta-2 selectivity ratio than formoterol.
Although beta-2 receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta-1 receptors are the predominant receptors in the heart, there are also beta-2 receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta-2 agonists may have cardiac effects.
The pharmacologic effects of beta-2 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.
In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these in vitro and animal findings to humans is unknown.

Pharmacodynamics

Clinical efficacy and safety
Asthma
Clinical studies in adults have shown that the addition of formoterol to budesonide improved asthma symptoms and lung function, and reduced exacerbations. In two 12-week studies, the effect on lung function of budesonide/formoterol was equal to that of the free combination of budesonide and formoterol, and exceeded that of budesonide alone. All treatment arms used a short-acting β2 adrenoceptor agonist as needed. There was no sign of attenuation of the anti-asthmatic effect over time.

Two 12-week paediatric studies have been performed in which 265 children aged 6-11 years were treated with a maintenance dose of budesonide/formoterol (2 inhalations of 80 micrograms /4.5 micrograms/inhalation twice daily), and a short-acting β2-adrenoceptor agonist as needed. In both studies, lung function was improved and the treatment was well tolerated compared to the corresponding dose of budesonide alone.

COPD
In two 12-month studies, the effect on lung function and the rate of exacerbation (defined as courses of oral steroids and/or course of antibiotics and/or hospitalisations) in patients with moderate to severe COPD was evaluated. The inclusion criteria for both studies was pre-bronchodilator FEV1 <50% predicted normal. Median post-bronchodilator FEV1 at inclusion in the trials was 42% predicted normal.
The mean number of exacerbations per year (as defined above) was significantly reduced with budesonide/formoterol as compared with treatment with formoterol alone or placebo (mean rate 1.4 compared with 1.8-1.9 in the placebo/formoterol group). The mean number of days on oral corticosteroids/patient during the 12 months was slightly reduced in the budesonide/formoterol group (7-8 days/patient/year compared with 11-12 and 9-12 days in the placebo and formoterol groups, respectively). For changes in lung-function parameters, such as FEV1, budesonide/-formoterol was not superior to treatment with formoterol alone.

Pharmacokinetics
Absorption
The fixed-dose combination of budesonide and formoterol, and the corresponding monoproducts have been shown to be bioequivalent with regard to systemic exposure of budesonide and formoterol, respectively. In spite of this, a small increase in cortisol suppression was seen after administration of the fixed-dose combination compared to the monoproducts. The difference is considered not to have an impact on clinical safety.

There was no evidence of pharmacokinetic interactions between budesonide and formoterol.

Pharmacokinetic parameters for the respective substances were comparable after the administration of budesonide and formoterol as monoproducts or as the fixed-dose combination. For budesonide, AUC was slightly higher, rate of absorption more rapid and maximal plasma concentration higher after administration of the fixed combination. For formoterol, maximal plasma concentration was similar after administration of the fixed combination. Inhaled budesonide is rapidly absorbed and the maximum plasma concentration is reached within 30 minutes after inhalation. In studies, 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. In studies the 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 and biotransformation
Plasma protein binding is approximately 50% for formoterol and 90% for budesonide. Volume of distribution is about 4 l/kg for formoterol and 3 l/kg for budesonide. Formoterol is inactivated via conjugation reactions (active O-demethylated and deformylated metabolites are formed, but they are seen mainly as inactivated conjugates). 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. There are no indications of any metabolic interactions or any displacement reactions between formoterol and budesonide.

Elimination
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.
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 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.

Pharmacokinetics in special populations
There are no special dosing requirements for elderly patients. There are no data available for use of Busonide in patients with hepatic or renal impairment. As budesonide and formoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis.

INDICATIONS
Asthma
Busonide 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)
Busonide 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.

DOSAGE AND ADMINISTRATION
Asthma
Busonide is not intended for the initial management of asthma. The dosage of the components of Busonide 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.

The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Patients should be regularly reassessed by their prescriber/health care provider so that the dosage of Busonide remains optimal. 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.

For Busonide there are two treatment approaches:

A. Busonide maintenance therapy:
Busonide is taken as regular maintenance treatment with a separate rapid-acting bronchodilator as rescue.

B. Busonide maintenance and reliever therapy:
Busonide is taken as regular maintenance treatment and as needed in response to symptoms.

A. Busonide maintenance therapy
Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

Recommended doses:
Adults (18 years and older): 1-2 inhalations twice daily. Some patients may require up to a maximum of 4 inhalations twice daily.

Adolescents (12 – 17 years): 1-2 inhalations twice daily.
In usual practice when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include Busonide 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.
Children (6 years and older): A lower strength (100 micrograms/6 micrograms/inhalation) is available for children 6-11 years.
Children under 6 years: As only limited data are available, Busonide is not recommended for children younger than 6 years.

B. Busonide maintenance and reliever therapy
Patients take a daily maintenance dose of Busonide and in addition take Busonide as needed in response to symptoms. Patients should be advised to always have Busonide available for rescue use.
For patients taking Busonide as reliever, preventative use of Busonide for allergen-or exercise-induced bronchoconstriction should be discussed between physician and patient; the recommended use should take into consideration the frequency of need. In case of frequent need of bronchodilation without corresponding need for an increased dose of inhaled corticosteroids, an alternative reliever should be used.

Busonide 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 Busonide as-needed inhalations.

Recommended doses:
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.

Children under 12 years: Busonide maintenance and reliever therapy is not recommended for children.

COPD
Recommended doses:
Adults: 2 inhalations twice daily

Method of administration
Instructions for correct use of Busonide:
The inhaler is inspiratory flow-driven, which means that when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

Note: It is important to instruct the patient
• to carefully read the instructions for use given at the end of this patient information leaflet.
• to breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs.
• never to breathe out through the mouthpiece.
• to replace the cover of the AirCare inhaler device after use.
• to rinse their mouth out with water after inhaling the maintenance dose to minimise the risk of oropharyngeal thrush. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.
The patient may not taste or feel any medication when using AirCare inhaler device due to the small amount of drug dispensed.

Using the AirCare device:
Busonide capsules should only be used with AirCare device. Do not ingest Busonide capsules. Detailed instructions for use are given at the end of this patient information leaflet.

CONTRAINDICATIONS
The use of Busonide is contraindicated in the following conditions:
• Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.

• Hypersensitivity to any of the ingredients in Busonide.

WARNING AND PRECAUTIONS
Dosing advice
Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Busonide. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Busonide should be used.

Patients should be advised to have their rescue inhaler available at all times, either Busonide (for asthma patients using Busonide as maintenance and reliever therapy) or a separate rapid-acting bronchodilator (for all patients using Busonide as maintenance therapy only).

Patients should be reminded to take their Busonide maintenance dose as prescribed, even when asymptomatic.
It is recommended that the dose is tapered when the treatment is discontinued and should not be stopped abruptly.
Complete withdrawal of inhaled corticosteroids should not be considered unless it is temporarily required to confirm diagnosis of asthma.

Deterioration of disease
Serious asthma-related adverse events and exacerbations may occur during treatment with Busonide. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation with Busonide.
If patients find the treatment ineffective, or exceed the highest recommended dose of Busonide, medical attention must be sought. Sudden and progressive deterioration in control of asthma or COPD 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 not be initiated on Busonide during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Transfer from oral therapy
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 Busonide 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.
During transfer from oral therapy to Busonide, 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.

Caution with special diseases
Busonide 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.
Potentially serious hypokalaemia may result from high doses of β2 adrenoceptor agonists. Concomitant treatment of β2 adrenoceptor 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 β2 adrenoceptor 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 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.
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.

Systemic effects
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. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).
Potential effects on bone density should be considered particularly in patients on high doses for prolonged periods that have coexisting risk factors for osteoporosis. 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) have not shown any significant effects on bone mineral density. No information regarding the effect of Busonide at higher doses is available.
Visual disturbance may be reported with systemic and topical corticosteroid use. 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.

Adrenal function
Treatment with supplementary systemic steroids or inhaled budesonide should not be stopped abruptly.

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. Symptoms and signs which might be seen in acute adrenal crisis may be somewhat vague but may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, seizures, hypotension and hypoglycaemia.

Paradoxical bronchospasm
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 Busonide should be discontinued immediately, the patient should be assessed and an alternative therapy instituted, if necessary. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway.

COPD population
There are no clinical study data on Busonide available in COPD patients with a pre-bronchodilator FEV1 >50% predicted normal and with a post-bronchodilator FEV1 <70% predicted normal.

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in

patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.
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.
Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

ADVERSE REACTIONS
Since Busonide contains 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 most common drug related adverse reactions are pharmacologically predictable side effects of β2 adrenoceptor agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment.
Adverse reactions, which have been associated with budesonide or formoterol, are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000) and very rare (<1/10 000).

SOC	Frequency	Adverse Drug Reaction
Infections and infestations	Common	Candida infections in the oropharynx Pneumonia (in COPD patients)
Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions, e.g. exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction
Endocrine disorders	Very rare	Cushing's syndrome, adrenal suppression, growth retardation, decrease in bone mineral density
Metabolism and nutrition disorders	Rare	Hypokalaemia
	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Aggression, psychomotor hyperactivity, anxiety, sleep disorders
	Very rare	Depression, behavioural changes (predominantly in children)
Nervous system disorders	Common	Headache, tremor
	Uncommon	Dizziness
	Very rare	Taste disturbances
Eye disorders	Uncommon	Vision blurred (see also section 4.4)
	Very rare	Cataract and glaucoma
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Rare	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles
	Very rare	Angina pectoris. Prolongation of QTc-interval
Vascular disorders	Very rare	Variations in blood pressure
Respiratory, thoracic and mediastinal disorders	Common	Mild irritation in the throat, coughing, dysphonia including hoarseness
	Rare	Bronchospasm
Gastrointestinal disorders	Uncommon	Nausea
Skin and subcutaneous tissue disorders	Uncommon	Bruises
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps

Candida infection in the oropharynx is due to drug deposition. Advising the patient to rinse the mouth out with water after each maintenance dose will minimise the risk. Oropharyngeal Candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroid. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.
As with other inhalation therapy, paradoxical bronchospasm may occur very rarely, affecting less than 1 in 10,000 people, with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. Busonide should be discontinued immediately, the patient should be assessed and an alternative therapy instituted if necessary.
Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. Increased susceptibility to infections and impairment of the ability to adapt to stress may also occur. Effects are probably dependent on dose, exposure time, concomitant and previous steroid exposure and individual sensitivity.
Treatment with β2 adrenoceptor agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

DRUG INTERACTIONS
Pharmacokinetic 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. In patients using potent CYP3A4 inhibitors, Busonide maintenance and reliever therapy is not recommended.
The potent CYP3A4 inhibitor ketoconazole, 200 mg once daily, increased plasma levels of concomitantly orally administered budesonide (single dose of 3 mg) on average six-fold. When ketoconazole was administered 12 hours after budesonide the concentration was on average increased only three-fold showing that separation of the administration times can reduce the increase in plasma levels. Limited data about this interaction for high-dose inhaled budesonide indicates that marked increase in plasma levels (on average four fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 µg).

Pharmacodynamic interactions

Beta-adrenergic blockers can weaken or inhibit the effect of formoterol. Busonide should therefore not be given together with beta-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.
In addition 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 beta-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 beta-2 agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids and diuretics.
Budesonide and formoterol have not been observed to interact with any other drugs used in the treatment of asthma.

USE IN SPECIAL POPULATIONS
Pregnancy
For Busonide or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Data from an embryo-foetal development study in the rat, showed no evidence of any additional effect from the combination.
There are no adequate data from use of formoterol in pregnant women. In animal studies formoterol has caused adverse effects in reproduction studies at very high systemic exposure levels.
During pregnancy, Busonide should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used.

Breastfeeding
Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the suckling child are anticipated. It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of Busonide 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.

Paediatric
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. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

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.

Elderly
There are no special dosing requirements for elderly patients.

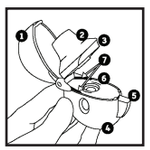
Renal & Hepatic impairment
There are no data available for use of Busonide in patients with hepatic or renal impairment. As budesonide and formoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis.

OVER DOSAGE
An overdose of formoterol would likely lead to effects that are typical for β2 adrenoceptor agonists: tremor, headache, palpitations. Symptoms reported from isolated cases are tachycardia, hyperglycaemia, hypokalaemia, prolonged QTc-interval, arrhythmia, nausea and vomiting. Supportive and symptomatic treatment may be indicated. A dose of 90 micrograms administered during three 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 chronically in excessive doses, systemic glucocorticosteroid effects, such as hypercorticism and adrenal suppression, may appear.

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

INSTRUCTION ON HOW TO USE CAPSULE

کیپسول استعمال کرنے کا طریقہ



Components of AirCare Device:
1. Dust Cap
2. Mouthpiece
3. Mouthpiece grip
4. Base
5. Piercing button
6. Capsule chamber
7. Air intake vents

ایئر کیئر ڈیوائس کے کمپونینٹ
۱ ۔ ڈسٹ کیپ
۲ ۔ ماؤتھ پیس
۳ ۔ ماؤتھ پیس کا گرپ
۴ ۔ بیس
۵ ۔ کیپسول پنچر کرنے کا بٹن
۶ ۔ کیپسول کا چیمبر
۷ ۔ ہوا کے داخل ہونے کا راستہ


1

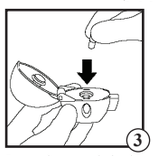
Open the dust cap by pulling it upwards and lift the mouthpiece with help of the mouthpiece grip.

ایئر کیئر ڈیوائس کے ڈسٹ کیپ کو کھولیں اور ماؤتھ پیس گرپ کی مدد سے ماؤتھ پیس کو اوپر کھینچیے۔


2

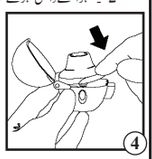
Remove the capsule from the blister right before use. Do not store the capsule in the AirCare device.

استعمال سے بلکل پہلے کیپسول بلسٹر میں سے نکالیں۔ کیپسول کو ایئر کیئر ڈیوائس میں اسٹور نہ کریں۔


3

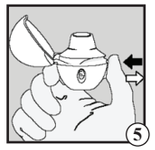
Insert the capsule in the capsule chamber of the AirCare device.

کیپسول کو ایئر کیئر ڈیوائس کے کیپسول چیمبر میں ڈالیں۔


4

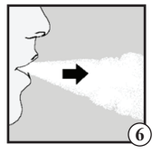
Close the mouthpiece until you hear a click, but leave the dust cap open.

جب تک کلک کی آواز نہ سُنائی دے تب تک ماؤتھ پیس کو بند کریں، لیکن ڈسٹ کیپ کو کھلا رہنے دیں۔


5

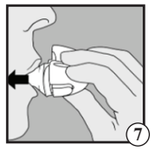
Hold the AirCare device with the mouthpiece upright. Press the piercing button once completely and release. This is how you make holes in the capsule so that you get medicine when you breathe in.

ایئر کیئر ڈیوائس کو سیدھا پکڑیں۔ کیپسول پنچر کرنے والے بٹن کو ایک دفعہ مکمل طور پر دبائیں اور چھوڑ دیں۔ اس طرح آپ کیپسول میں سوراخ کرتے ہیں تاکہ سانس لینے پر آپ کو دوا مل جائے۔


6

Breathe out completely. Do not breathe (exhale) into the mouthpiece of the AirCare device at any time.

مکمل طور پر سانس باہر نکالیں۔ کبھی بھی ایئر کیئر ڈیوائس کے ماؤتھ پیس میں پھونک نہ ماریں۔


7

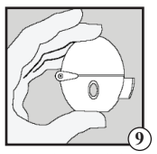
Raise the AirCare device to your mouth and close your lips tightly around the mouthpiece. Keep your head in an upright position. Breathe in slowly and deeply so that you hear or feel the capsule vibrate. Breathe in as much as you can and hold your breath as long as possible. At the same time, remove the AirCare device from your mouth. Breathe normally again. Repeat steps 6 & 7, in order to empty the capsule completely.

ایئر کیئر ڈیوائس کو اپنے منہ کی طرف اٹھائیں اور اپنے ہونٹوں سے ماؤتھ پیس کو مضبوطی سے پکڑیں۔ اپنے سر کو سیدھا رکھیں۔ آہستہ اور گہری سانس لیں یہاں تک کہ آپکو کیپسول ہلتی ہوئی محسوس ہو یا سنائی دے۔ جتنا ہو سکے سانس لیں اور اپنی سانس کو جتنی دیر ہو سکے روکے رکھیں۔ ساتھ ہی ایئر کیئر ڈیوائس کو منہ سے ہٹالیں۔ پھر حسب معمول سانس لیں۔ کیپسول کو مکمل طور پر خالی کرنے کے لیے اقدامات 6 اور 7 کو دہرائیں۔


8

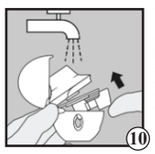
After taking your dose, open the mouthpiece. Tip out the used capsule and throw it away.

اپنی دوا لینے کے بعد، ماؤتھ پیس کو کھولیں۔ استعمال شدہ کیپسول نکال کر پھینک دیں۔


9

Close the mouthpiece and dust cap for storing your AirCare device.

ایئر کیئر ڈیوائس کو اسٹور کرنے سے پہلے ماؤتھ پیس اور ڈسٹ کیپ کو بند کر دیں۔


10

Clean the AirCare device once a month. Open the dust cap and mouthpiece. Then open the base by lifting the piercing button. Rinse the AirCare device with warm water and check if any powder buildup or capsule fragments remain. Dry the AirCare device thoroughly by tipping excess of water out on a paper towel and air-dry afterwards, leaving the dust cap, mouthpiece and base open.
Do not use detergents or a dishwasher to clean the AirCare device. It takes 24 hours to air dry, so clean it immediately after use so that it will be ready for your next dose. Do not use a hair dryer to dry the AirCare device. Do not use the AirCare device when it is wet. If needed, you may clean the outside of the mouthpiece with a clean damp cloth.

ایئر کیئر ڈیوائس کو مہینے میں ایک مرتبہ صاف کریں۔ ڈسٹ کیپ اور ماؤتھ پیس کھولیں۔ پھر پنچنگ کرنے والے بٹن کو اٹھا کر بیس کو کھولیں۔ ایئر کیئر ڈیوائس کو نیم گرم پانی سے کھنگال لیں اور چیک کر لیں کہ پاؤڈر یا کیپسول کے ذرات رہ نہ گئے ہوں۔ ایئر کیئر ڈیوائس میں موجود پانی کو ڈسپوزیبل تولیے پر نکال لیں۔ کیپ، ماؤتھ پیس اور بیس کو کھلا رکھیں اور ہوا میں خشک ہونے دیں۔ ایئر کیئر ڈیوائس کی صفائی کے لئے ڈیٹرجینٹ یا ڈش واشر کا استعمال نہ کریں۔ ایئر کیئر ڈیوائس 24 گھنٹے میں ہوا میں خشک ہوتا ہے، اس لیے اسے استعمال کے فوراً بعد صاف کریں تاکہ یہ آپ کی اگلی خوراک کے لیے تیار ہو۔ ایئر کیئر ڈیوائس کو خشک کرنے کے لیے ہیئر ڈرائر کا استعمال نہ کریں۔ ایئر کیئر ڈیوائس گیلا ہونے کی صورت میں استعمال نہ کریں۔ ماؤتھ پیس کا بیرونی حصہ گیلے کپڑے سے صاف کیا جا سکتا ہے۔

PRESENTATION
Busonide 200/6mcg: Pack of 30 capsules.
Busonide 400/12mcg: Pack of 30 capsules.

INSTRUCTIONS:
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
Capsules are intended for use through Aircare only and are not to be swallowed.

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