Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bufar Easyhaler, 80 micrograms/4.5 micrograms/inhalation, inhalation powder

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose that leaves the mouthpiece) contains: budesonide
80 micrograms/inhalation and formoterol fumarate dihydrate 4.5 micrograms/inhalation.

With the Easyhaler device the delivered dose (ex-actuator) contains similar quantity of active substance as the metered dose (ex-reservoir).

Excipients with known effect: Lactose monohydrate 4000 micrograms per delivered dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder in a device metered inhaler (Easyhaler).
White to yellowish powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Bufar Easyhaler 80 micrograms/4.5 micrograms/inhalation is indicated in adults, adolescents and children aged 6 years and older.

Bufar Easyhaler 80 micrograms/4.5 micrograms/inhalation is indicated for the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting β_2 adrenoceptor agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and “as needed” inhaled short−acting β_2 adrenoceptor agonists.

or

- patients already adequately controlled on both inhaled corticosteroids and long−acting β_2 adrenoceptor agonists.

Note: Bufar Easyhaler 80 micrograms/4.5 micrograms/inhalation is not appropriate in patients with severe asthma.

4.2 Posology and method of administration

Posology

Asthma
Bufar Easyhaler is not intended for the initial management of asthma. The dosage of the components of Bufar Easyhaler 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 β_2 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 Bufar Easyhaler 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 Bufar Easyhaler there are two treatment approaches:

A. maintenance therapy: Bufar Easyhaler is taken as regular maintenance treatment with a separate rapid−acting bronchodilator as rescue.

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

A. 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.

Children (6 years and older): 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 Bufar Easyhaler 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 under 6 years: As only limited data are available, Bufar Easyhaler 80 micrograms/4.5 micrograms/inhalation is not recommended for children younger than 6 years.

B. maintenance and reliever therapy

Patients take a daily maintenance dose of Bufar Easyhaler and in addition take Bufar Easyhaler as needed in response to symptoms. Patients should be advised to always have Bufar Easyhaler available for rescue use.

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 Bufar Easyhaler 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. 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: maintenance and reliever therapy is not recommended for children.

General information
Special patient groups:
There are no special dosing requirements for elderly patients. There are no data available for use of Bufar Easyhaler 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.

Method of administration

For inhalation use

Instructions for correct use of Bufar Easyhaler:
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 in the patient information leaflet which is packed together with each Bufar Easyhaler.
- To shake and actuate the inhaler prior to each inhalation.
- 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 as this will result in a reduction in the delivered dose. Should this happen the patient is instructed to tap the mouthpiece onto a table top or the palm of a hand to empty the powder, and then to repeat the dosing procedure.
- Never to actuate the device more than once without inhalation of the powder. Should this happen the patient is instructed to tap the mouthpiece onto a table top or the palm of a hand to empty the powder, and then to repeat the dosing procedure.
- To always replace the dust cap (and, if in use, close the protective cover) after use to prevent accidental actuation of the device (which could result in either overdosing or under dosing the patient when subsequently used).
- To rinse the 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.
- To clean the mouthpiece with a dry cloth at regular intervals. Water should never be used for cleaning because the powder is sensitive to moisture.
- To replace Bufar Easyhaler when the counter reaches zero even though powder can still be observed within the inhaler.

4.3 Contraindications

Hypersensitivity to the active substances or to the excipient listed in section 6.1(lactose, which contains small amounts of milk protein).

4.4 Special warnings and 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 Bufar Easyhaler, medical attention must be sought (see section 4.2). Sudden and progressive deterioration in control of asthma is potentially life threatening and the patient should undergo urgent medical assessment. In this situation, consideration should be given to the need for increased therapy with corticosteroids, e.g. a course of oral corticosteroids, or antibiotic treatment if an infection is present.

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

using Bufar Easyhaler as maintenance therapy only).

Patients should be reminded to take their Bufar Easyhaler maintenance dose as prescribed, even when asymptomatic. The prophylactic use of Bufar Easyhaler, e.g. before exercise, has not been studied. The reliever inhalations of Bufar Easyhaler should be taken in response to asthma symptoms but are not intended for regular prophylactic use, e.g. before exercise. For such use, a separate rapid−acting bronchodilator should be considered.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Bufar Easyhaler. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Bufar Easyhaler should be used (see section 4.2).

Patients should not be initiated on Bufar Easyhaler 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 Bufar Easyhaler. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of Bufar Easyhaler.

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 Bufar Easyhaler 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 (see section 4.8).

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) (see section 4.8).

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.

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 at higher doses is available.

If there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy, care should be taken when transferring patients to Bufar Easyhaler 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.

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.

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

During transfer from oral therapy to Bufar Easyhaler 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 (see section 4.8), the patient should be instructed to rinse their mouth out with water after inhaling the maintenance dose. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.

Concomitant treatment with itraconazole, ritonavir or other potent CYP3A inhibitors should be avoided (see section 4.5). If this is not possible the time interval between administration of the interacting drugs should be as long as possible. In patients using potent CYP3A inhibitors, maintenance and reliever therapy approach is not recommended.

Bufar Easyhaler 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 β_2 adrenoceptor agonists. Concomitant treatment of β_2 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 β_2 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 β_2 adrenoceptor agonists, additional blood glucose controls should be considered in diabetic patients.

Bufar Easyhaler contains approx. 4 mg of lactose per inhalation. This amount does not normally cause problems in lactose intolerant people. The excipient lactose contains small amounts of milk proteins, which may cause allergic reactions.

Paediatric populations

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.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Potent inhibitors of CYP3A (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone, cobicistat 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 (see section 4.4). In patients using potent CYP3A inhibitors, 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 increases 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).

Co-treatment with cobicistat-containing products is expected to increase the risk of systemic side−effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Pharmacodynamic interactions
Beta−adrenergic blockers can weaken or inhibit the effect of formoterol. Bufar Easyhaler 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 β_2−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 (see section 4.4).

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

Paediatric populations
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
For Bufar Easyhaler or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Data from an embryo-fetal 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 (see section 5.3).

Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies glucocorticosteroids have been shown to induce malformations (see section 5.3). This is not likely to be relevant for humans given recommended doses.

Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the teratogenic dose range.

During pregnancy, Bufar Easyhaler 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.

Breast-feeding
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 Bufar Easyhaler 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.

Fertility
There is no data available on the potential effect of budesonide on fertility. Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure (see section 5.3).

4.7 Effects on ability to drive and use machines

Bufar Easyhaler has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Since Bufar Easyhaler 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 β_2 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).

Table 1

SOC	**Frequency**	**Adverse Drug Reaction**
Infections and infestations	Common	Candida infections in the oropharynx
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, 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. Bufar Easyhaler should be discontinued immediately, the patient should be assessed and an alternative therapy instituted if necessary (see section 4.4).

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 β_2 agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Paediatric populations
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail:medsafety@hpra.ie.

4.9 Overdose

An overdose of formoterol would likely lead to effects that are typical for β_2 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 Bufar Easyhaler 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

Pharmacotherapeutic group: Drugs for obstructive airway diseases: Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics.

ATC−code: R03AK07

Mechanisms of action and Pharmacodynamic effects
Bufar Easyhaler contains formoterol and budesonide, which have different modes of action and show additive effects in terms of reduction of asthma 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.

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. 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 β_2 adrenoceptor adrenergic 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-dependant, with an onset of effect within 1−3 minutes. The duration of effect is at least 12 hours after a single dose.

Clinical efficacy and safety

Clinical efficacy for budesonide/formoterol maintenance therapy
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 β_2 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 beta2-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.

Clinical efficacy for budesonide/formoterol maintenance and reliever therapy

A total of 12076 asthma patients were included in 5 double−blind efficacy and safety studies (4447 were randomised to budesonide/formoterol maintenance and reliever therapy) for 6 or 12 months. Patients were required to be symptomatic despite use of inhaled glucocorticosteroids.

Budesonide/formoterol maintenance and reliever therapy provided statistically significant and clinically meaningful reductions in severe exacerbations for all comparisons in all 5 studies. This included a comparison with budesonide/formoterol at a higher maintenance dose with terbutaline as reliever (study 735) and budesonide/formoterol at the same maintenance dose with either formoterol or terbutaline as reliever (study 734) (Table 2). In Study 735, lung function, symptom control, and reliever use were similar in all treatment groups. In Study 734, symptoms and reliever use were reduced and lung function improved, compared with both comparator treatments. In the 5 studies combined, patients receiving budesonide/formoterol maintenance and reliever therapy used, on average, no reliever inhalations on 57% of treatment days. There was no sign of development of tolerance over time.

Table 2 Overview of severe exacerbations in clinical studies

Study No. Duration	Treatment groups	n	Severe exacerbations[a]	
			Events	Events/ patient−year
Study 735 6 months	**Budesonide/formoterol 160/4.5 µg bd + as needed**	**1103**	**125**	**0.23**[b]
	Budesonide/formoterol 320/9 µg bd + terbutaline 0.4 mg as needed	1099	173	0.32
	Salmeterol/fluticasone 2 x 25/125 µg bd + terbutaline 0.4 mg as needed	1119	208	0.38
Study 734 12 months	**Budesonide/formoterol 160/4.5 µg bd + as needed**	**1107**	**194**	**0.19**[b]
	Budesonide/formoterol 160/4.5 µg bd + formoterol 4.5 µg as needed	1137	296	0.29
	Budesonide/formoterol 160/4.5 µg bd + terbutaline 0.4 mg as needed	1138	377	0.37

a Hospitalisation/emergency room treatment or treatment with oral steroids

b Reduction in exacerbation rate is statistically significant (P−value <0.01) for both comparisons

Comparable efficacy and safety in adolescents and adults was demonstrated in 6 double-blind studies, comprising the 5 studies mentioned above and an additional study using a higher maintenance dose of 160/4.5 micrograms, two inhalations twice daily. These assessments were based on a total of 14385 asthma patients of whom 1847 were adolescents. The number of adolescent patients taking more than 8 inhalations on at least one day as part of budesonide/formoterol maintenance and reliever therapy was limited, and such use was infrequent.

In 2 other studies with patients seeking medical attention due to acute asthma symptoms, budesonide/formoterol provided rapid and effective relief of bronchoconstriction similar to salbutamol and formoterol.

5.2 Pharmacokinetic properties

Absorption

Bufar Easyhaler and Symbicort Turbuhaler fixed−dose combination of budesonide and formoterol have been shown to be bioequivalent with regard to total systemic exposure and exposure via the lungs.
Symbicort Turbuhaler 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 children and patients with renal failure are unknown. The exposure of budesonide and formoterol may be increased in patients with liver disease.

Linearity/non-linearity

Systemic exposure for both budesonide and formoterol correlates in a linear fashion to administered dose.

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

Lactose monohydrate (which contains milk proteins).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

As packaged for sale: 2 years.
After first opening the laminate bag: 4 months. Do not store above 25°C and protect from moisture.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

The multidose powder inhaler consists of seven plastic parts and a stainless steel spring. The plastic materials of the inhaler are: polybutylene terepthalate, low density polyethylene, polycarbonate, styrene butadiene, polypropylene. The inhaler is sealed in a laminate bag and packed with or without a protective cover (polypropylene and thermoplastic elastomer) in a cardboard box.

Packages:
Bufar Easyhaler 80 micrograms/4.5 micrograms/inhalation, inhalation powder:
60 doses
60 doses + protective cover
120 doses
120 doses + protective cover
180 doses (3 x 60 doses)
360 doses (3 x 120 doses)

Not all packs may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8 MARKETING AUTHORISATION NUMBER

PA1327/018/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th March 2016

10 DATE OF REVISION OF THE TEXT

June 2018