

Summary of Product Characteristics

FORMOCORT EASYCAP 6/100 mcg

(Formoterol Fumarate 6 micrograms / Budesonide 100 micrograms Inhalation Powder, Hard Capsule)

1 Name of the medicinal product

Formocort Easycap 6/100 mcg – Formoterol Fumarate 6 micrograms and Budesonide 100 micrograms Inhalation Powder, Hard Capsule

2 Qualitative and quantitative composition

Each hard capsule contains formoterol fumarate 6 micrograms (as formoterol fumarate dihydrate BP) and budesonide BP 100 micrograms as active substances.

Excipient(s) with known effect

Each capsule contains lactose monohydrate. Lactose contains small amounts of milk proteins.

For the full list of excipients, see section 6.1.

3 Pharmaceutical form

Inhalation powder, hard capsule.

Size “3” capsules with a yellow transparent cap imprinted “Healthcare” and a natural transparent body imprinted with the manufacturer’s logo, filled with a white to off-white granular powder.

4 Clinical particulars

4.1 Therapeutic indications

Formocort Easycap 6/100 mcg is indicated in 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.

Formocort Easycap 6/100 mcg is not intended for the initial management of asthma, and should not be used in patients whose asthma can be adequately managed by an inhaled corticosteroid together with occasional use of an inhaled short-acting β_2 -adrenoceptor agonist. Once asthma control is achieved and maintained, the patient should be assessed at regular intervals with a view to stepping down therapy.

Formocort Easycap 6/100 mcg may be used as maintenance therapy (with a separate rapid-acting bronchodilator as rescue medication), or as maintenance and reliever therapy in adults and adolescents 12 years of age and older (see section 4.2).

4.2 Posology and method of administration

Route of administration: for inhalation use.

Posology

Two treatment approaches may be used. In maintenance therapy, Formocort Easycap is taken as regular maintenance treatment with a separate rapid-acting bronchodilator as rescue medication.

In maintenance and reliever therapy, Formocort Easycap is taken as regular maintenance treatment and additionally as needed in response to symptoms.

A. Maintenance therapy

Patients should be advised to have a 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 (6–11 years): 2 inhalations twice daily. The maximum recommended daily maintenance dose in this age group is 4 inhalations.

Once control of asthma is achieved, titration to the lowest effective dose should be considered, which may include once-daily dosing where appropriate. Increasing use of a separate rapid-acting bronchodilator indicates worsening asthma and warrants reassessment of therapy.

B. Maintenance and reliever therapy

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

Recommended doses for adults and adolescents (12 years and older):

- The recommended maintenance dose is 2 inhalations daily, given either as one inhalation in the morning and one in the evening, or as 2 inhalations once daily. 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 may 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 may be used for a limited period under medical supervision. Patients requiring more than 8 inhalations daily should be reassessed, as this may indicate deteriorating asthma control. Close monitoring is required in patients using high numbers of as-needed inhalations.

Maintenance and reliever therapy is not recommended in children below 12 years of age, owing to limited clinical data in this age group.

The reliever inhalations should be taken in response to symptoms and are not intended for regular prophylactic use, for example before exercise. Where there is a frequent need for bronchodilation without a corresponding need for an increased dose of inhaled corticosteroid, an alternative reliever should be used.

General recommendations

Treatment should be individualised according to disease severity, and patients reassessed at regular intervals to ensure that the dose remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. When it is appropriate to titrate down to a lower strength than is available for Formocort Easycap, a change to an alternative fixed-dose combination of budesonide and formoterol fumarate containing a lower dose of the inhaled corticosteroid is required.

Special populations

No special dose adjustment is required in elderly patients. There are no data available for use in patients with hepatic or renal impairment. As budesonide and formoterol are primarily eliminated via hepatic metabolism, increased exposure may be expected in patients with severe hepatic impairment.

Paediatric population

Formocort Easycap 6/100 mcg is not recommended for use in children under 6 years of age.

Method of administration

The device is inspiratory flow-driven; the active substances are delivered to the lungs when the patient inhales through the mouthpiece. The capsule must be inserted into the inhaler device and must not be swallowed (see section 6.6).

Patients should be instructed:

- to read the patient information leaflet carefully;
- to inhale forcefully and deeply through the mouthpiece;
- never to exhale through the device;
- to replace the cap after use;
- to rinse the mouth with water after inhalation to reduce the risk of oropharyngeal candidiasis.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, including lactose, which contains small amounts of milk proteins.

4.4 Special warnings and precautions for use

Dosing advice

Patients should be reassessed regularly by their prescriber so that the dose of Formocort Easycap remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose; regular review of patients as treatment is stepped down is important.

Patients should be advised to have their rescue inhaler available at all times, either Formocort Easycap (for patients using it as maintenance and reliever therapy) or a separate rapid-acting bronchodilator (for patients using it as maintenance therapy only). Patients should be reminded to take their maintenance dose as prescribed, even when asymptomatic.

It is recommended that the dose is tapered when treatment is discontinued; treatment should not be stopped abruptly. Complete withdrawal of inhaled corticosteroids should not be considered unless temporarily required to confirm a diagnosis of asthma.

The prophylactic use of Formocort Easycap, for example before exercise, has not been studied.

Deterioration of disease

Serious asthma-related adverse reactions and exacerbations may occur during treatment. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation. If patients find the treatment ineffective, or exceed the highest recommended dose, medical attention must be sought. Sudden and progressive deterioration in asthma control is potentially life threatening and the patient should undergo urgent medical assessment; consideration should be given to the need for increased corticosteroid therapy, for example a course of oral corticosteroids, or antibiotic treatment if an infection is present.

Patients should not be initiated on Formocort Easycap during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

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).

Visual disturbance

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, referral to an ophthalmologist should be considered 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.

Effects on bone density

Potential effects on bone density should be considered, particularly in patients on high doses for prolonged periods who have coexisting risk factors for osteoporosis. Long-term studies with inhaled budesonide 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 a budesonide/formoterol fumarate dihydrate fixed-dose combination at higher doses is available.

Adrenal function

Treatment with supplementary systemic steroids or inhaled budesonide should not be stopped abruptly. Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may result in clinically significant adrenal suppression. Additional systemic corticosteroid cover should therefore 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 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

Paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath after dosing. If the patient experiences paradoxical bronchospasm, Formocort Easycap should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straight away.

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 budesonide/formoterol fixed-dose combination 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 time after cessation of oral steroid therapy, and oral steroid-dependent patients transferred to inhaled budesonide may therefore remain at risk of impaired adrenal function for some considerable time. In such circumstances, hypothalamic-pituitary-adrenal (HPA) axis function should be monitored regularly.

During transfer from oral therapy, 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 generally insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting occur; in these cases a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary.

Oral infections

To minimise the risk of oropharyngeal candida infection, the patient should be instructed to rinse the mouth out with water after inhaling the dose. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.

Excipients

Formocort Easycap contains lactose monohydrate. 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.

Interaction with other medicinal products

Concomitant treatment with itraconazole, ritonavir or other potent CYP3A4 inhibitors should be avoided. If this is not possible, the time interval between administration of the interacting medicinal products should be as long as possible. In patients using potent CYP3A4 inhibitors, maintenance and reliever therapy with a budesonide/formoterol fixed-dose combination is not recommended (see section 4.5).

Caution with special diseases

Formocort Easycap 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, and fungal and viral infections of the airways. Additional blood glucose controls should be considered in diabetic patients.

β 2-adrenoceptor agonists

Potentially serious hypokalaemia may result from high doses of β 2-adrenoceptor agonists. Concomitant treatment of β 2-adrenoceptor agonists with medicinal products which can induce hypokalaemia or potentiate a hypokalaemic effect, for example xanthine derivatives, steroids and diuretics, may add to a possible hypokalaemic effect. Treatment with β 2-adrenoceptor agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma where the associated risk may be augmented by hypoxia, and in other conditions where the likelihood of hypokalaemia is increased. It is recommended that serum potassium levels are monitored in these circumstances.

Paediatric population

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 corticosteroid therapy and the possible risks of

growth suppression must be carefully weighed, and consideration 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, generally within the first year of treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Potent inhibitors of CYP3A4 (for example 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, maintenance and reliever therapy with a budesonide/formoterol fixed-dose combination 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 on this interaction for high-dose inhaled budesonide indicate that a 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 1,000 micrograms).

Co-treatment with CYP3A inhibitors, including 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. Formocort Easycap 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, levodopa, levothyroxine, oxytocin and alcohol can impair cardiac tolerance towards β 2-sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors, including medicinal products 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 or anticholinergic medicinal products can have a potentially additive bronchodilating effect. Hypokalaemia may increase the disposition towards arrhythmias in patients treated with digitalis glycosides.

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

For the fixed-dose combination of budesonide and formoterol fumarate dihydrate, 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 the use of formoterol in pregnant women; in animal studies formoterol has caused adverse reactions in reproduction studies at very high systemic exposure levels.

Data on approximately 2,000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies, glucocorticosteroids have been shown to induce malformations, but 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 of 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, Formocort Easycap 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 Formocort Easycap 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 are 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.

4.7 Effects on ability to drive and use machines

Formocort Easycap has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Since Formocort Easycap contains both budesonide and formoterol, the same pattern of adverse reactions 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 adverse reactions are pharmacologically predictable effects of β_2 -adrenoceptor agonist therapy, such as tremor and palpitations; these tend to be mild and usually disappear within a few days of treatment.

Tabulated list of adverse reactions

Adverse reactions which have been associated with budesonide or formoterol are listed below by System Organ Class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reaction
<i>Infections and infestations</i>	Common	Candida infections in the oropharynx
	Common	Pneumonia

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

Description of selected adverse reactions

Candida infection in the oropharynx is due to active substance deposition. Advising the patient to rinse the mouth out with water after each dose will minimise the risk. Oropharyngeal candida infection usually responds to topical antifungal 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.

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 straight away; Formocort Easycap should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for long periods, although 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 -adrenoceptor agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

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 to the National Regulatory Authority.

4.9 Overdose

An overdose of formoterol would likely lead to effects that are typical for β 2-adrenoceptor agonists: tremor, headache and 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 over three hours in patients with acute bronchial obstruction raised no safety concerns.

Acute overdose 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 Formocort Easycap therapy has to be withdrawn owing to overdose of the formoterol component, 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, excluding anticholinergics.

ATC code: R03AK07

Mechanism of action and pharmacodynamic effects

Formocort Easycap 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 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 reactions than systemic corticosteroids. The exact mechanism responsible for the anti-inflammatory effect of glucocorticosteroids is unknown.

Formoterol is a selective β 2-adrenoceptor agonist which, when inhaled, results in rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose-dependent, with an onset of effect within 1–3 minutes. The duration of effect is at least 12 hours after a single dose.

Clinical efficacy and safety – 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.

Clinical efficacy and safety – maintenance and reliever therapy

A total of 12,076 asthma patients were included in 5 double-blind clinical studies, of whom 4,447 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). 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.

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 budesonide/formoterol 160/4.5 micrograms, two inhalations twice daily. These assessments were based on a total of 14,385 asthma patients, of whom 1,847 were adolescents. The number of adolescent patients taking more than 8 inhalations on at least one day as part of maintenance and reliever therapy was limited, and such use was infrequent.

In 2 further 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.

Peak inspiratory flow rate through the device

A randomised, open-label, placebo study was performed in children and adolescents with asthma (aged 6–17 years), adults with asthma (aged 18–45 years), adults with chronic obstructive pulmonary disease (aged over 50 years) and healthy volunteers (aged 18–45 years), to evaluate the peak inspiratory flow rate (PIFR) and other related inhalation parameters following inhalation from the Formocort Easycap device (containing placebo) compared with inhalation from an already marketed multi-dose dry powder inhaler device (containing placebo). The impact of enhanced training in dry powder inhaler technique on inhalation speed and volume was also assessed.

The data indicated that, regardless of age and underlying disease severity, children, adolescents and adults with asthma, as well as patients with COPD, were able to achieve inspiratory flow rates through the Formocort Easycap device that were similar to those generated through the marketed multi-dose dry powder inhaler device. The mean PIFR achieved by patients with asthma or COPD was over 60 l/min, a flow rate at which both devices studied are known to deliver comparable amounts of drug to the lungs. Very few patients had PIFR values below 40 l/min, and where PIFR values were less than 40 l/min there appeared to be no clustering by age or disease severity.

5.2 Pharmacokinetic properties

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 with 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, the rate of absorption more rapid and the maximal plasma concentration higher after administration of the fixed combination. For formoterol, the 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 a powder inhaler ranged from 32% to 44% of the delivered dose, and the systemic bioavailability is approximately 49% of the delivered dose. In children 6–16 years of age, lung deposition falls in the same range as in adults for the same given dose. 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 a powder inhaler ranged from 28% to 49% of the delivered dose, and 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. The 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 deformedylated 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-hydroxybudesonide and 16-alpha-hydroxyprednisolone, 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 intravenous dosing averages 4 hours.

Special populations

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

Product pharmacokinetic profile

In pharmacokinetic studies with and without charcoal blockade, Formocort Easycap was evaluated by comparison with an alternative authorised fixed-dose combination inhaled product containing the same active substances, budesonide and formoterol, and has been shown to be equivalent in both systemic exposure (safety) and pulmonary deposition (efficacy).

Linearity

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

5.3 Preclinical safety data

The toxicity observed in animal studies with budesonide and formoterol, given in combination or separately, comprised effects associated with exaggerated pharmacological activity.

In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate and skeletal malformations). However, these experimental animal results do not appear to be relevant to humans at the recommended doses. Animal reproduction

studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure, as well as implantation losses and decreased early postnatal survival and birth weight at considerably higher systemic exposures than those reached during clinical use. These experimental animal results do not appear to be relevant to humans.

Neither budesonide nor formoterol was genotoxic in a range of in vitro and in vivo tests. Carcinogenicity studies in rodents with budesonide and with formoterol produced findings, including benign uterine leiomyomas in rats with formoterol, that are considered to be a class effect of β_2 -adrenoceptor agonists in rodents and of no relevance to humans at therapeutic exposures.

6 Pharmaceutical particulars

6.1 List of excipients

- Alpha-lactose monohydrate (Lactohale LH 200)
- Alpha-lactose monohydrate (Lactohale LH 300)
- Magnesium stearate
- Hard gelatin capsule shell, size “3”

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C in a dry place. Avoid storage in direct sunlight or heat. Keep out of the sight and reach of children.

6.5 Nature and contents of container

Alu-Alu blisters (aluminium lid foil with a printed three-layer Alu-PVC/OPA foil base), packed in an inner carton containing 3 blisters of 10 capsules (30 capsules per pack).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The capsules must not be swallowed. Each capsule should be inserted into the inhaler device provided and used as directed. The capsule should be removed from the blister pack immediately prior to use, as capsules exposed to moisture may not tear easily.

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

7 Marketing authorisation holder

Dawa Limited

Plot No. 7879/8, Baba Dogo Road, Ruaraka

P.O. Box 16633-00620

Nairobi, Kenya

Manufacturer

Healthcare Pharmaceuticals Ltd

Gazariapara, Rajendrapur

Gazipur-1703

Bangladesh

8 Marketing authorisation number

CTD 13210

9 Date of first authorisation/renewal of the authorisation

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