Summary of Product Characteristics
FORMOCORT EASYCAP 12/400 mcg

(Formoterol Fumarate 12 micrograms / Budesonide 400 micrograms Inhalation Powder, Hard Capsule)

1 Name of the medicinal product

Formocort Easycap 12/400 mcg – Formoterol Fumarate 12 micrograms and Budesonide 400 micrograms Inhalation Powder, Hard Capsule

2 Qualitative and quantitative composition

Each hard capsule contains formoterol fumarate 12 micrograms (as formoterol fumarate dihydrate BP) and budesonide BP 400 micrograms as active substances.

Excipient(s) with known effect
Each capsule contains lactose monohydrate (less than 1 mg per inhalation). 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

Asthma
Formocort Easycap 12/400 mcg is indicated in the regular maintenance treatment of asthma in adults and adolescents (12 years and older), 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.

This strength is for maintenance therapy only and is not intended for the initial management of asthma, nor for maintenance and reliever therapy (MART) or as a reliever (see section 4.2).

Chronic obstructive pulmonary disease (COPD)
Formocort Easycap 12/400 mcg is indicated for the symptomatic treatment of patients with severe COPD (FEV1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

4.2 Posology and method of administration

Route of administration: for inhalation use.

Posology

Asthma

Formocort Easycap 12/400 mcg is used as regular maintenance treatment, with a separate rapid-acting bronchodilator taken as rescue medication. Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times. This strength must not be used as a reliever and is not suitable for the maintenance and reliever therapy (MART) regimen; lower strengths of budesonide/formoterol are available for that regimen.

Recommended doses:

- Adults (18 years and older): 1 inhalation twice daily. Some patients may require up to a maximum of 2 inhalations twice daily.
- Adolescents (12–17 years): 1 inhalation twice daily.

The maximum recommended dose is therefore 4 inhalations daily, corresponding to 1,600 micrograms of budesonide and 48 micrograms of formoterol fumarate per day.

The dosage is individual and should be adjusted according to disease severity, both when initiating treatment and when adjusting the maintenance dose. Patients should be regularly reassessed to ensure optimal control, and the dose titrated to the lowest dose at which effective control of symptoms is maintained. Patients should be provided with a written asthma action plan. If doses outside those available in the combination inhaler are required, appropriate doses of inhaled corticosteroids and/or β2-adrenoceptor agonists should be prescribed separately.

Increasing use of a separate rapid-acting bronchodilator indicates worsening asthma and warrants reassessment of therapy. Once asthma control is achieved, consideration should be given to stepping down to a lower strength of budesonide/formoterol.

Chronic obstructive pulmonary disease (COPD)
Adults: 2 inhalations twice daily.

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 12/400 mcg is not recommended for use in children under 12 years of age. Lower strengths of budesonide/formoterol are available for use in children.

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.

The patient may not taste or feel the medication, owing to the small quantity of powder delivered.

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

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose, including stepping down to a lower strength of budesonide/formoterol. Regular review of patients as treatment is stepped down is important, and the lowest effective dose should be used. Patients should be reminded to take their maintenance dose as prescribed, even when asymptomatic, and to have their separate rapid-acting bronchodilator available at all times.

To minimise the risk of oropharyngeal candida infection, the patient should be instructed to rinse the mouth out with water after inhaling the maintenance dose. It is recommended that the maintenance dose is tapered when treatment is discontinued; dosing should not be stopped abruptly. Complete withdrawal of inhaled corticosteroids should not be considered unless temporarily required to confirm a diagnosis of asthma.

Deterioration of disease

Serious asthma-related adverse events 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 less effective, or need more inhalations of their rescue medication than usual, 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; 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.

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 Formocort Easycap. 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.

Excipients

Formocort Easycap contains lactose monohydrate (< 1 mg 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.

Interactions 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 (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.

Potentially serious hypokalaemia may result from high doses of β2-adrenoceptor agonists. Concomitant treatment of β2-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. 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.

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, and fungal and viral infections of 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 who 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.

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.

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 of 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, 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.

Paediatric population
It is recommended that the height of children and adolescents 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.

COPD population
There are no clinical study data 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, and 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 and severe COPD.

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 (see section 4.4).

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).

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 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 or anticholinergic medicinal products can have a potentially additive bronchodilating effect. Hypokalaemia may increase the disposition towards arrhythmias in patients treated with digitalis glycosides. Hypokalaemia may result from β2-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 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 combination of 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 effects 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 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 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.

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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Common	Candida infections in the oropharynx
	Common	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
	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

Description of selected adverse reactions

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 antifungal treatment without the need to discontinue the inhaled corticosteroid.

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 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 prolonged 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 β2-adrenoceptor agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Paediatric population
It is recommended that the height of children and adolescents receiving prolonged treatment with inhaled corticosteroids is regularly monitored.

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 β2-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 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 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.

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 is a selective β2-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 – 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.

Clinical efficacy and safety – COPD
In two 12-month studies, the effect on lung function and the rate of exacerbations (defined as courses of oral steroids and/or courses of antibiotics and/or hospitalisations) was evaluated in patients with moderate to severe COPD. The inclusion criterion for both studies was a pre-bronchodilator FEV1 < 50% predicted normal; the median post-bronchodilator FEV1 at inclusion was 42% predicted normal.

The mean number of exacerbations per year was significantly reduced with budesonide/formoterol compared with treatment with formoterol alone or placebo (mean rate 1.4 compared with 1.8–1.9 in the placebo and formoterol groups). The mean number of days on oral corticosteroids per patient during the 12 months was slightly reduced in the budesonide/formoterol group (7–8 days per patient per 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.

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. 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 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-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.

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 β2-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” (yellow transparent cap, natural transparent body)

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 three-layer Alu-PVC/OPA film 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

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Manufacturer
Healthcare Pharmaceuticals Ltd

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8 Marketing authorisation number

CTD 12963

9 Date of first authorisation/renewal of the authorisation

22.07.2026

10 Date of revision of the text

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