

Symbicort Rapihaler®

80/4.5 and 160/4.5 micrograms/actuation, pressurised inhalation, suspension

Qualitative and Quantitative Composition

Symbicort Rapihaler 80/4.5 micrograms/actuation:

Each delivered dose (ex-actuator) contains: budesonide 80 micrograms/actuation and formoterol fumarate dihydrate 4.5 micrograms/actuation.

This is equivalent to a metered dose containing budesonide 100 micrograms/actuation and formoterol fumarate dihydrate 6 micrograms/actuation.

Symbicort Rapihaler 160/4.5 micrograms/actuation:

Each delivered dose (ex-actuator) contains: budesonide 160 micrograms/actuation and formoterol fumarate dihydrate 4.5 micrograms/actuation.

This is equivalent to a metered dose containing budesonide 200 micrograms/actuation and formoterol fumarate dihydrate 6 micrograms/actuation.

Clinical Particulars

Therapeutic Indications

Asthma

Symbicort Rapihaler 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.

Chronic Obstructive Pulmonary Disease (COPD)

Symbicort Rapihaler is indicated in adults, aged 18 and older, for the symptomatic treatment of patients with COPD with FEV₁ <70% predicted normal (post-bronchodilator) and an exacerbation history despite regular bronchodilator therapy.

Posology and method of administration

General information

The patient should be instructed that Symbicort Rapihaler must be used regularly even when asymptomatic for optimal benefit.

The medication from Symbicort Rapihaler is delivered to the lungs as the patient inhales. Therefore a correct handling of Symbicort Rapihaler is very important. The patients should be instructed accordingly (see “Other advices/instruction for use”).

The patient should be instructed to use Symbicort Rapihaler regularly, i.e. in asymptomatic times to get the best therapeutic benefit.

Asthma

The dosage of Symbicort Rapihaler should be regularly checked by the doctor, and should be individualised according to disease severity (for this see current guidelines, e.g. GINA, www.ginasthma.com). Initial dose should be adjusted so that effective symptomatic control is obtained. When the desired clinical effect has been achieved, the dose should be titrated to the lowest dose at which effective asthma control is maintained. If so, then the next step could include a test of inhaled corticosteroid alone.

In usual practice when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include Symbicort Rapihaler given once daily, when in the opinion of the prescriber, a long acting bronchodilator would be required to maintain control.

In case of discontinuance of Symbicort Rapihaler therapy, it is recommended to reduce the doses step by step.

Repeated assessments by a doctor at regular intervals are indicated in cases of severe asthma in view of the possible onset of life-threatening situations. Patients suffering from severe asthma show continuous symptoms, frequent exacerbations, PEF values (peak flow values) below 60% of normal with a peak flow variability in excess of 30% and which fail to return to normal despite the administration of a bronchodilator. High-dose inhalation therapy or oral corticosteroid therapy is indicated in these patients. A sudden worsening in symptoms may necessitate an increase in the corticosteroid dose, but only under medical supervision. However, this must not be achieved by administration of the combined product more frequently. In unstable situations, a switch to the individual monoproducts must be considered.

Symbicort Rapihaler is for oral inhalation only.

Dosage

Asthma

Symbicort Rapihaler should be used for a daily maintenance dose and a separate rapid-acting bronchodilator is needed for symptom relief.

Children (6 to 11 years)

Symbicort Rapihaler 80/4.5: 2 inhalations twice daily. The maximum daily dose is 4 inhalations.

Adolescents 12 to 17 years:

Symbicort Rapihaler 80/4.5: 2 inhalations once or twice daily. During worsening of asthma the dose may temporarily (1 week max.) be increased to a maximum of 4 inhalations twice daily.

Symbicort Rapihaler 160/4.5: 2 inhalations once to twice daily. During worsening of asthma the dose may temporarily (1 week max.) be increased to a maximum of 4 inhalations twice daily.

Adults (18 years and older)

Symbicort Rapihaler 80/4.5: 2 inhalations once or twice daily. In some cases up to a maximum of 4 inhalations twice daily may be required as maintenance dose or temporarily during worsening of asthma.

Symbicort Rapihaler 160/4.5: 2 inhalations once or twice daily. In some cases up to a maximum of 4 inhalations twice daily may be required as maintenance dose or temporarily during worsening of asthma.

Equivalence between Symbicort Turbuhaler and Symbicort Rapihaler has been confirmed statistically for doses of twice daily 2 inhalations of 80/4.5 or 160/4.5 µg, but has not been proved for all dosages.

A separate inhaler for rescue use is required. Patients should be advised to have their rapid acting bronchodilator available at all times. Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy.

Chronic Obstructive Pulmonary Disease (COPD)

Adults (18 years and older)

Symbicort Rapihaler 160/4.5: 2 inhalations twice daily.

General information

Special patient groups:

There are no special dosing requirements for elderly patients. There are no data available for use of Symbicort 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.

Paediatric Population

There is no relevant use of Symbicort 160 micrograms /4.5 micrograms in children 11 years of age and under or in adolescents 12 to 17 years of age in the symptomatic treatment of COPD.

Switching over of patients who are already receiving oral corticoid therapy see “Special warnings and precautions for use”.

Method of administration

Instructions for handling

Prior to initial use, if the inhaler has not been used for more than one week, or if it has been dropped, shake the inhaler gently and release 2 puffs in the air.

Administration

1. Hold the inhaler between thumb and index finger and shake it gently.
2. Remove the protective cap.
3. Breathe out. Close your lips around the mouthpiece. The canister should be pointing upwards.
4. While breathing in slowly and deeply, press down on the canister. Continue to breathe in.
5. Hold the breath for as long as is comfortable. Remove the inhaler from your mouth and do not press anymore on the canister.

6. Shake the inhaler again and repeat steps 3/4/5.
7. Replace the protective cap.

For cleaning, the protective cap must be removed and the mouthpiece wiped inside and outside with a dry cloth. Do not put the inhaler into water. Clean at least once a week.

To minimize the risk of oropharyngeal thrush, patients should thoroughly rinse their mouth and spit out after each application of the inhaler.

The counter on the top of the inhaler indicates the number of remaining doses. The inhaler must be replaced if the arrow is pointing to “0”, even if the inhaler does not yet seem to be empty. In this case, not enough active substance will be released.

Contraindications

Hypersensitivity to the active substances or to the excipient listed in section ‘List of excipients’.

Special warnings and precautions for use

It is recommended that the maintenance dose is tapered when long-term treatment is discontinued and the dosing should not be stopped abruptly. Complete withdrawal of inhaled corticosteroids should not be considered unless it is temporarily required to confirm the diagnosis of asthma.

If patients find the treatment ineffective, or exceed the highest recommended dose of Symbicort Rapihaler, medical attention must be sought (see section ‘Posology and method of administration’). Sudden and progressive deterioration in control of asthma or COPD is potentially life threatening and the patient should undergo urgent medical assessment. In this situation, consideration should be given to the need for increased therapy with corticosteroids e.g. a course of oral corticosteroids, or antibiotic treatment if an infection is present. For treatment of severe exacerbations, a combination product of inhaled corticosteroid and long-acting β_2 agonist alone is not sufficient.

Patients should be advised to have their rescue inhaler available at all times.

Patients should be reminded to take their Symbicort maintenance dose as prescribed even when asymptomatic.

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

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

There are no clinical study data on Symbicort available in COPD patients with a pre-bronchodilator FEV1 >50% predicted normal and with a post-bronchodilator FEV1 <70% predicted normal (see section 'Pharmacodynamic properties').

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, Symbicort 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 'Undesirable 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) (see section 'Undesirable effects').

Potential effects on bone density should be considered particularly in patients on high doses for prolonged periods that have coexisting risk factors for osteoporosis. Long-term studies with inhaled budesonide in children at mean daily doses of 400 micrograms (metered dose) or in adults at daily doses of 800 micrograms (metered dose) have not shown any significant effects on bone mineral density. No information regarding the effect of Symbicort 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 Symbicort therapy.

The benefits of inhaled budesonide therapy would normally minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Recovery may take a considerable amount of time after cessation of oral steroid therapy and hence oral steroid dependent patients transferred to inhaled budesonide may remain at risk from impaired adrenal function for some considerable time. In such circumstances HPA axis function should be monitored regularly.

The prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Therefore, additional systemic corticosteroid cover should be considered during periods of stress such as severe infections or elective surgery. Rapid reduction in the dose of steroids can induce acute adrenal crisis. 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 Symbicort, 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 ‘Undesirable effects’), 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.

Symbicort 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 adverse effects 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.

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.

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 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.

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patient with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Interaction with other medicinal products and other forms of interactions

Pharmacokinetic interactions

The metabolism of budesonide is primarily mediated by the enzyme CYP3A4. Potent CYP3A4 inhibitors may therefore increase systemic exposure to budesonide. This is of limited clinical importance for short-term (1-2 weeks) treatment with potent CYP3A4 inhibitors but should be taken into consideration during long-term treatment.

If a patient requires long-term concomitant treatment with Symbicort and a potent CYP3A4 inhibitor, the benefit should be weighed against the increased risk of systemic corticosteroid side effects, patients should be monitored for corticosteroid side effects and/or a reduction of the inhaled corticosteroid dose could be considered.

Pharmacodynamic interactions

Beta-adrenergic blockers can weaken or inhibit the effect of formoterol. Symbicort 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 anti-depressants 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 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 beta₂-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids and diuretics (see section Special warning and precautions for use).

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

Pediatric population

Interaction studies have only been performed in adults.

Fertility, pregnancy and lactation

Pregnancy

For Symbicort 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, using the Symbicort Rapihaler formulation, showed no evidence of any additional effect from the combination or evidence of any effects attributable to the excipients on the rodent.

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 'Preclinical safety data').

Data in more than 17000 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 'Preclinical safety data'). 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, Symbicort 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

A clinical pharmacology study has shown that inhaled budesonide is excreted in breast milk. However, budesonide was not detected in nursing infant blood samples. Based on

pharmacokinetic parameters, the plasma concentration in the child is estimated to be less than 0.17% of the mother's plasma concentration. Consequently, no effects due to budesonide are anticipated in breast-fed children whose mothers are receiving therapeutic doses of Symbicort Rapihaler. 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 Symbicort to women who are breastfeeding 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 'Preclinical safety data').

Effect on the ability to drive and use machines

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

Undesirable effects

Since Symbicort 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 adrenoceptor agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment.

Adverse reactions, which have been associated with budesonide or formoterol, are given below, listed by system organ class (SOC) and frequency. Frequency 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 $< 1/1000$) and very rare $< 1/10\ 000$).

Table 1

SOC	Frequency	Adverse Drug Reaction
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Rare	Cardiac arrhythmias e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles
	Very rare	Angina pectoris. Prolongation of QT _C -interval
Endocrine disorders	Very rare	Cushing's syndrome, adrenal suppression, growth retardation, decrease in bone mineral density

Gastrointestinal disorders	Uncommon	Nausea
Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions, e.g., exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction
Infections and infestations	Common	Candida infections in the oropharynx Pneumonia (in COPD patients)
Metabolic and nutrition disorders	Rare	Hypokalaemia
	Very rare	Hyperglycaemia
Musculoskeletal, connective tissue and bone disorders	Uncommon	Muscle cramps
Nervous system disorders	Common	Headache, tremor
	Uncommon	Dizziness
	Very rare	Taste disturbances
Psychiatric disorders	Uncommon	Aggression, psychomotor hyperactivity, anxiety, sleep disorders
	Very rare	Depression, behavioural changes (predominantly in children)
Respiratory, thoracic and mediastinal disorders	Common	Mild irritation in the throat, coughing, hoarseness
	Rare	Bronchospasm
Skin and subcutaneous tissue disorders	Uncommon	Bruises
Vascular disorders	Very rare	Variations in blood pressure
Eye disorders	Uncommon	Vision blurred (see also section ‘Special warnings and precautions for use’)
	Very rare	Cataract and glaucoma

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. Symbicort should be discontinued immediately, the patient should be assessed and an alternative therapy instituted if necessary (see section ‘Special warnings and precautions for use’).

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 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 receiving prolonged treatment with inhaled corticosteroids is regularly monitored (see section ‘Special warnings and precautions for use’).

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 and when given three times daily as a total of 54 micrograms/day for 3 days to stable asthmatics 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 Symbicort therapy has to be withdrawn due to overdose of the formoterol component of the drug, provision of appropriate inhaled corticosteroid therapy must be considered.

Pharmacological Properties

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases: Adrenergics, Inhalants.

ATC-code: R03AK07

Mechanisms of action and pharmacodynamic effects

Symbicort Rapihaler contains budesonide and formoterol, which have different modes of action and show additive effects in case of obstructive airways diseases.

Budesonide

Budesonide is a glucocorticosteroid which when inhaled has a dose-dependent anti-inflammatory action in the airways, resulting in reduced symptoms and fewer COPD 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 agonist that when inhaled results in rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly (within 1-3 minutes after inhalation) and has a duration of 12 hours after a single dose.

Clinical efficacy of Symbicort Rapihaler

Asthma

Therapeutic equivalence between Symbicort Rapihaler and Symbicort Turbuhaler was demonstrated in two clinical efficacy and safety studies in medium and high doses, including asthmatic patients from 6 to 79 years of age. Clinical comparability was strengthened by a long-term safety study, which also showed that the safety profile and tolerability of Symbicort Rapihaler were similar to that of Symbicort Turbuhaler.

Clinical studies in adults have shown that the addition of formoterol to budesonide improved asthma symptoms and lung function, and reduced asthma exacerbations.

The effect on lung function of Symbicort Turbuhaler in adults, given as maintenance dose only, was equal to that of the free combination of budesonide and formoterol in separate inhalers and exceeded that of budesonide alone in adults and children. All treatment arms used a short acting β_2 -agonist as needed. There was no sign of attenuation of the anti-asthmatic effect over time.

COPD

The efficacy and safety of Symbicort Rapihaler in the treatment of patients with moderate to severe COPD (pre-bronchodilator $FEV_1 \leq 50\%$ predicted normal) has been evaluated in: one 12-month and one 6-month study (studies 001 and 002, respectively).

Studies 001 and 002: In both studies, Symbicort Rapihaler 160/4.5 was compared with placebo and formoterol Turbuhaler 6 μ g, and, in Study 002, it was also compared with budesonide pMDI 200 μ g, all taken as two inhalations twice daily. A total of 1964 and 1704 patients with mainly severe COPD were randomised, of which 494 and 277 were treated with Symbicort Rapihaler 160/4.5. The study populations had a mean age of 63 years and mean FEV_1 of 1.04-1.05 L or 34% of predicted normal at baseline.

Study 001

In Study 001, efficacy was evaluated over 12 months using the co-primary efficacy variables of change from baseline in average pre-dose and 1-hour post-dose FEV₁ over the treatment period.

Symbicort Rapihaler 160/4.5 significantly improved 1-hour pre-dose FEV₁ compared with formoterol and placebo by 0.04 L (p=0.008) and 0.09 L (p<0.001), respectively.

Symbicort Rapihaler 160/4.5 significantly improved post-dose FEV₁ over the treatment period compared with formoterol and placebo by 0.03 L (p=0.023) and 0.18 L (p<0.001), respectively.

Serial FEV₁ measures over 12 hours were obtained in a subset of patients (N=491). The median time to onset of bronchodilation (>15% improvement in FEV₁) was seen within 5 minutes at the end of treatment time point in patients receiving Symbicort Rapihaler 160/4.5 (N=121). Maximum improvement in FEV₁ occurred at approximately 2 hours post-dose, and clinically significant improvement was maintained over 12 hours.

Symbicort Rapihaler significantly reduced the number of severe exacerbations (defined as a worsening of COPD requiring oral steroid use and/or hospitalisation), compared with placebo and formoterol by 37% (p<0.001) and 25% (p=0.004), respectively. Symbicort Rapihaler significantly prolonged the time to first severe COPD exacerbation compared to placebo, reducing the instantaneous risk of experiencing a severe COPD exacerbation by 26% (p=0.009). Symbicort Rapihaler provided a statistically significant improvement in patient quality of life (as measure by St. George's Respiratory Questionnaire total score) compared with placebo (-2.39 units; p=0.006).

Study 002

In Study 002, efficacy was evaluated over 6 months using the co-primary efficacy variables of change from baseline in average pre-dose and 1-hour post-dose FEV₁ over the treatment period.

Symbicort Rapihaler 160/4.5 significantly improved pre-dose FEV₁ compared with formoterol by 0.04 L (p=0.026) and compared with placebo and budesonide by 0.08 L (p<0.001) for both comparators.

Symbicort Rapihaler 160/4.5 significantly improved 1-hour post-dose FEV₁ compared with formoterol by 0.04 L (p=0.039) and compared with placebo and budesonide by 0.17 L (p<0.001) for both comparators.

Study 002 was not powered for showing effect on severe COPD exacerbations. However, the estimates for treatment differences, though not statistically significant, were consistent with Study 001, with 20% fewer exacerbations with Symbicort Rapihaler 160/4.5 as compared with placebo and formoterol.

Serial FEV₁ measures over 12 hours were obtained in subsets of patients (n=618). The median time to onset of bronchodilation (>15% improvement in FEV₁) was seen within 5 minutes at the end of treatment in patients receiving Symbicort Rapihaler 160/4.5 (N=101). Maximum improvement in FEV₁ occurred at approximately 2 hours post-dose, and clinically significant improvement was maintained over 12 hours.

Symbicort Rapihaler 160/4.5 provided a statistically significant improvement in patient quality of life (as measure by St. George's Respiratory Questionnaire total score) compared with placebo (-3.12 units; $p=0.003$), budesonide (- 2.42 units; $p=0.024$), and formoterol (-2.56 units; $p=0.017$).

Pharmacokinetics 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 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 Turbuhaler 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 fall 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 Turbuhaler 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 deformed 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 formoterol in children have not been studied. The pharmacokinetics of budesonide and formoterol in 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.

Preclinical Data

The toxicity observed in animal studies with budesonide and formoterol given in combination or separately, were effects associated with an 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 dose. 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.

Symbicort Rapihaler contains the excipients povidone (polyvinylpyrrolidone) K25, macrogol (polyethylene glycol) 1000 and the pressurised liquid propellant apaflurane (HFA227). The safe use of apaflurane has been fully evaluated in preclinical studies. Povidones have a history of safe use in man for many years, which supports the view that povidones are essentially biologically inert. Macrogols are recognized as safe excipients in pharmaceuticals, food and cosmetic products. Furthermore, toxicity studies carried out using Symbicort Rapihaler have shown no evidence of any local or systemic toxicity or irritation attributable to the excipients.

Pharmaceutical Particulars

List of excipients

Apaflurane (HFA 227)

Povidone

Macrogol 1000

Incompatibilities

Not applicable.

Shelf-life

Please see outer carton pack. The shelf life for Symbicort Rapihaler after first opening of the foil is 3 months.

Special precautions for storage

Symbicort Rapihaler should not be stored above 30 °C, but out of the reach of children.

The canister contains a pressurised liquid. It should not be exposed to temperatures above 50 °C, or be damaged, or opened with force, or burnt.

Pack size

Each inhaler delivers 120 actuations.

Manufacturer

AstraZeneca Dunkerque Production (AZ DP), Dunkerque, France.

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INSTRUCTIONS FOR USE/HANDLING

Please read the complete instructions carefully before you start to take your medication.

Application

Before your first application, note the last date you can use the metered dose inhaler. This is 3 months from the moment after opening the protective foil.

Preparing the metered dose inhaler

Before using it for the first time, take the metered dose inhaler out of the protective foil and throw the foil away. Your metered dose inhaler is ready to use, please do not disassemble it (Figure 1). Before using the metered dose inhaler for the first time, if you have not used it for more than a week or if it has been dropped, gently shake it and release two puffs into the air (see Figure 2).

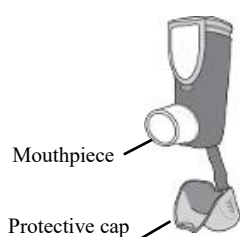


Figure 1



Figure 2



Figure 3



Figure 4

Method of administration

1. Shake the metered dose inhaler gently.
2. Remove the protective mouthpiece cap by gently squeezing it (Figure 3).
3. Hold the metered dose inhaler upright between your thumb and index finger (Figure 2). Breathe out as far as possible, hold the mouthpiece in your mouth between your teeth and wrap your lips around it (Figure 4).
4. Start breathing slowly and deeply through your mouth while pressing firmly on the canister (Figure 2, 4).
5. Continue to breathe in and hold your breath for approximately 10 seconds or as long as it is comfortable. Then take the metered dose inhaler out of your mouth and stop pressing down on the canister.
6. Shake the inhaler again and repeat points 3 to 5.
7. After application, put the protective cap back on.
8. Rinse your mouth with water to prevent any drug residue.

Routine care for mouthpiece

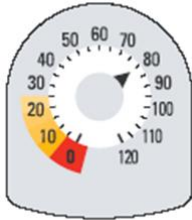
The mouthpiece must be cleaned regularly, at least once a week. Proceed as follows:

1. Remove the protective cap.
2. Wipe the inside and outside of the mouthpiece with a clean, dry cloth.
3. Put the protective cap back on.
4. Do not try to disassemble the metered dose inhaler.

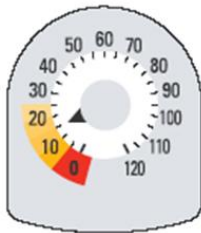
Never put the metered dose inhaler in water!

When is your Symbicort Rapihaler used up?

On the top of the metered dose inhaler is a counter that shows how many doses are still available. The counter, indicated by a small arrow, starts at 120. Each time you inhale a dose or spray it into the air, the arrow will move towards “0”.



Once the arrow reaches the yellow mark, there are about 20 doses left. If the arrow points to “0”, you must use a new metered dose inhaler, even if the metered dose inhaler does not yet appear to be empty. You would no longer be inhaling the correct dose.



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