SYMBICORT RAPIHALER®
(budesonide/formoterol fumarate dihydrate)

1. NAME OF THE MEDICINAL PRODUCT

Symbicort Rapihaler
40/2.25, 80/2.25, 80/4.5 and 160/4.5 micrograms/actuation,
pressurised inhalation, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single actuation delivers budesonide 40 or 80 or 160 micrograms and formoterol fumarate dihydrate 2.25 or 4.5 micrograms. Each dose is administered as 2 actuations.

Formoterol fumarate dihydrate is hereafter referred to as "formoterol."

For excipients see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Pressurised inhalation, suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma

Symbicort Rapihaler is indicated in the treatment of asthma to achieve overall asthma control, including the prevention and relief of symptoms as well as the reduction of the risk of exacerbations.

Symbicort Rapihaler is indicated for treatment of asthma, where the use of inhaled corticosteroids is appropriate.

Chronic Obstructive Pulmonary Disease (COPD)

Symbicort Rapihaler is indicated in the regular treatment of patients with severe COPD (FEV1 <50% predicted normal), with frequent symptoms and a history of exacerbations despite regular bronchodilator therapy.

4.2 Posology and method of Administration

Asthma

The dosage of the components of Symbicort Rapihaler is individual and should be adjusted to the severity of the disease. This should be considered not only when treatment with combination products is initiated but also when the maintenance dose is adjusted. If an individual patient should require a combination of doses other than those available in the combination inhaler, appropriate doses of β_2-agonists and/or corticosteroids by individual inhalers should be prescribed.

Symbicort can be used according to different treatment approaches:

A. Symbicort anti-inflammatory reliever therapy.
B. Symbicort anti-inflammatory reliever plus maintenance therapy.

As an alternative, Symbicort can be used in a fixed dose therapy:

C. Symbicort maintenance therapy.

A. Symbicort anti-inflammatory reliever therapy (patients with mild disease):

Symbicort is taken as needed for the relief of asthma symptoms when they occur, and to prevent allergen- or exercise- induced bronchoconstriction (or to prevent symptoms in those circumstances recognised by the patient to precipitate an asthma attack). The formoterol component in Symbicort pMDI provides fast onset of effect (within 1-3 minutes) with long-acting (at least 12 hours after a single dose) bronchodilation in reversible airways obstruction. Patients should be advised to always have Symbicort available for relief of symptoms.

Clinical studies have demonstrated that Symbicort anti-inflammatory reliever therapy provides significant reductions in severe exacerbations and was statistically superior on daily asthma symptom control compared to a short-acting β_2 agonist therapy alone, and comparable to budesonide maintenance therapy given with as-needed short-acting β_2 agonist in reducing severe exacerbations (see Section 5.1 Pharmacodynamic properties). Asthma symptom control was inferior for Symbicort as needed compared to a maintenance dose of corticosteroid given with as needed short-acting β_2 agonist.

Recommended doses:

Physicians should discuss allergen exposure and exercise patterns with the patients and take these into consideration when recommending the dose frequency.

Table 1. Dosing instructions - Symbicort anti-inflammatory reliever therapy

AGE group	**40/2.25 mcg/actuation**	**80/2.25 mcg/actuation**
Adults and adolescents (12 years and older):	The efficacy and safety have not been studied for this strength.	Patients should take 1 dose (2 actuations) as needed in response to symptoms and for the prevention of allergen- or exercise-induced bronchoconstriction to control asthma. If symptoms persist after a few minutes, 1 additional dose (2 actuations) should be taken. Not more than 6 doses (12 actuations) should be taken on any single occasion. A total daily dose of more than 8 doses (16 actuations) is normally not needed, however a total daily dose of up to 12 doses (24 actuations) can be used

AGE group	40/2.25 mcg/actuation	80/2.25 mcg/actuation
		temporarily. Patients using more than 8 doses (16 actuations) daily should be reassessed for alternative explanations of persisting symptoms.
Children (6 years and older)	The efficacy and safety have not been studied for this strength.	The efficacy and safety have not been studied for this strength.

B. Symbicort anti-inflammatory reliever plus maintenance therapy:

When maintenance treatment with a combination of inhaled corticosteroid and long-acting β_2 agonist is required, Symbicort Rapihaler is taken both as an anti-inflammatory reliever and as regular maintenance treatment. The as needed inhalations provide both rapid relief of symptoms and improved asthma control. Patients should be advised to have Symbicort Rapihaler available for relief of symptoms at all times. A separate reliever inhaler is not necessary.

Clinical studies have demonstrated that Symbicort anti-inflammatory reliever plus maintenance therapy provides clinically meaningful reductions in severe exacerbations while maintaining symptom control, compared to Symbicort maintenance therapy with a separate short-acting bronchodilator (see Section 5.1 Pharmacodynamic properties).

Recommended doses:

Physicians should discuss allergen exposure and exercise patterns with the patients and take these into consideration when recommending the strength and dose frequency.

When control has been achieved, the dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

Table 2. Dosing instructions - Symbicort anti-inflammatory reliever plus maintenance therapy

AGE group	40/2.25 mcg/actuation	80/2.25 mcg/actuation
Adults and adolescents (12 years and older):	Patients should take 1 dose (2 actuations) as needed in response to symptoms. If symptoms persist after a few minutes, 1 additional dose (2 actuations) should be taken. Not more than 6 doses (12 actuations) should be taken on any single occasion. Patients also take the recommended maintenance dose, which is 2 doses (4 actuations) per day, given either as 1 dose (2 actuations) in the morning and evening or as 2 doses (4 actuations) in either the morning or the evening. A total daily dose of more than 8 doses (16 actuations) is normally not needed, however a total daily dose of up to 12 doses (24 actuations) can be used temporarily. If the patient experiences deteriorating symptoms after taking the appropriate maintenance therapy and additional as needed doses, the patient should be reassessed for alternative explanations of persisting symptoms.	Patients should take 1 dose (2 actuations) as needed in response to symptoms and for the prevention of allergen- or exercise-induced bronchoconstriction to control asthma. If symptoms persist after a few minutes, 1 additional dose (2 actuations) should be taken. Not more than 6 doses (12 actuations) should be taken on any single occasion. Patients also take the recommended maintenance dose, which is 2 doses (4 actuations) per day, given either as 1 dose (2 actuations) in the morning and evening or as 2 doses (4 actuations) in either the morning or the evening. For some patients, a maintenance dose of 2 doses (4 actuations) twice daily may be appropriate. A total daily dose of more than 8 doses (16 actuations) is normally not needed, however a total daily dose of up to 12 doses (24 actuations) can be used temporarily. If the patient experiences deteriorating symptoms after taking the appropriate maintenance therapy and additional as needed doses, the patient should be reassessed for alternative explanations of persisting symptoms.

Note: Symbicort Rapihaler pMDI 40/2.25 micrograms/actuation has not been studied in patients with mild asthma and is not appropriate in patients with severe asthma.

C. Symbicort maintenance therapy (fixed dose):

When maintenance treatment with a combination of inhaled corticosteroid and long-acting β_2 agonist is required, Symbicort is taken as a fixed daily dose treatment, with a separate short-acting bronchodilator as reliever. Patients should be advised to have their separate short-acting bronchodilator available for relief of symptoms at all times.

Recommended doses:

When control has been achieved, the dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

Increasing use of a separate rapid-acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy.

Table 3. Dosing instructions - Symbicort maintenance therapy

AGE group	40/2.25 mcg/actuation	80/2.25 mcg/actuation	80/4.5 mcg/actuation	160/4.5 mcg/actuation
Adults (18 years and older):	1 or 2 doses (2 or 4 actuations) twice daily. In some cases, up to a maximum of 4 doses (8 actuations) twice daily may be required as maintenance dose or temporarily during worsening of asthma.	1 or 2 doses (2 or 4 actuations) twice daily. In some cases up to a maximum of 4 doses (8 actuations) twice daily may be required as maintenance dose or temporarily during worsening of asthma.	1 dose (2 actuations) twice daily. In some cases, up to a maximum of 2 doses (4 actuations) twice daily may be required as maintenance dose or temporarily during worsening of asthma.	1 dose (2 actuations) twice daily. In some cases, up to a maximum of 2 doses (4 actuations) twice daily may be required as maintenance dose or temporarily during worsening of asthma.
Adolescents (12-17 years):	1 or 2 doses (2 or 4 actuations) twice daily. During worsening of asthma, the dose may temporarily be increased to a maximum of 4 doses (8 actuations) twice daily.	1 or 2 doses (2 or 4 actuations) twice daily. During worsening of asthma, the dose may temporarily be increased to a maximum of 4 doses (8 actuations) twice daily.	1 dose (2 actuations) twice daily. During worsening of asthma the dose may temporarily be increased to a maximum of 2 doses (4 actuations) twice daily.	1 dose (2 actuations) twice daily. During worsening of asthma the dose may temporarily be increased to a maximum of 2 doses (4 actuations) twice daily.
Children (6-11 years)	1 or 2 doses (2 or 4 actuations) twice daily. Maximum daily	1 dose (2 actuations) twice daily. Maximum daily dose: 2	1 dose (2 actuations) twice daily. Maximum daily dose: 2	A lower strength is available for children 6-11 years.

AGE group	40/2.25 mcg/actuation	80/2.25 mcg/actuation	80/4.5 mcg/actuation	160/4.5 mcg/actuation
	dose: 4 doses (8 actuations).	doses (4 actuations).	doses (4 actuations).	

Note: Symbicort Rapihaler pMDI 40/2.25 micrograms/actuation has not been studied in patients with mild asthma and is not appropriate in patients with severe asthma.

COPD

Table 4. Dosing instructions - COPD

AGE group	80/2.25 mcg/actuation	160/4.5 mcg/actuation
Adults (18 years and older):	2 doses (4 actuations) twice daily. Maximum daily dose: 4 doses (8 inhalations).	1 dose (2 actuations) twice daily. Maximum daily dose: 2 doses (4 actuations).

General information

If patients take Symbicort as a maintenance therapy, they should be instructed that Symbicort Rapihaler must be used even when asymptomatic for optimal benefit.

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 diseases.

Instructions for correct use of Symbicort Rapihaler

On actuation of Symbicort Rapihaler, a volume of the suspension is expelled from the canister at high velocity. When the patient inhales through the mouthpiece at the same time as actuating the inhaler, the substance will follow the inspired air into the airways.

Note: It is important to instruct the patient to:

- Carefully read the instructions for use/handling in the leaflet which is packed together with each inhaler.
- Shake the inhaler gently prior to each use to mix its contents properly.
- Prime the 40/2.25 mcg/actuation inhaler by actuating it three times into the air when the inhaler is new, and two times if it has not been used for more than one week or if it has been dropped.
- Prime the 80/2.25, 160/4.5 and 80/4.5 mcg/actuation inhaler by actuating it two times into the air when the inhaler is new, if it has not been used for more than one week or if it has been dropped.
- Place the mouthpiece in the mouth. While breathing in slowly and deeply, press the device firmly to release the medication. Continue to breathe in and hold the breath for approximately 10 seconds or as long as is comfortable.
- Shake the inhaler again and repeat.
- Rinse the mouth with water after inhaling the maintenance dose to minimise the risk of oropharyngeal thrush.

- Clean the mouthpiece of the inhaler regularly, at least once a week with a clean dry cloth.
- Do not put the inhaler into water.

To enable patients with difficulty in coordinating inhalation with actuation to use Symbicort Rapihaler (such as young children or the elderly), a spacer device can be used. See Section 6.6 Instructions for use, handling and disposal for instructions for the correct use of Symbicort Rapihaler with a spacer device.

4.3 Contraindications

Hypersensitivity (allergy) to budesonide, formoterol or any of the excipients.

4.4 Special warnings and special precautions for use

Dosing advice

If patients take Symbicort as maintenance therapy, they should be reminded to take Symbicort Rapihaler as prescribed even when asymptomatic.

Patients should be advised to have their rescue inhaler available at all times, either Symbicort (for asthma patients using Symbicort as anti-inflammatory reliever - therapy A or B) or a separate short-acting bronchodilator (for all patients using Symbicort as maintenance therapy only - therapy C).

It is recommended that the maintenance dose is tapered when the 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.

To minimise the risk of oropharyngeal candida infection, the patient should be instructed to rinse the mouth with water after inhaling the maintenance dose.

Deterioration of disease

Serious asthma-related adverse events and exacerbations may occur during treatment with Symbicort Rapihaler. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation with Symbicort Rapihaler.

If patients find the treatment ineffective, or exceed the current dose of the fixed combination, medical attention must be sought. Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy. 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 or addition of systemic anti-inflammatory therapy, such as 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 β2 agonist alone is not sufficient.

Paradoxical bronchospasm

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. Symbicort Rapihaler should then be discontinued; treatment should be re-assessed and alternative therapy instituted if necessary.

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 adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

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

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

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 Symbicort Rapihaler therapy.

Particular care is needed in patients transferring from oral steroids, since they may remain at risk of impaired adrenal function for a considerable time. Patients who have required high-dose emergency corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroids, may also be at risk. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Interaction with other medicinal products

Concomitant treatment with Symbicort and a potent CYP3A4 inhibitor should be weighed against the increased risk of systemic corticosteroid side effects (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Caution with special diseases

Symbicort Rapihaler should be administered with caution in patients with severe cardiovascular disorders (including hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm, ischaemic heart disease, heart rhythm abnormalities or severe heart failure), phaeochromocytoma, diabetes mellitus, untreated hypokalaemia or thyrotoxicosis.

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 agonists. Concomitant treatment of β2 agonist with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine-derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the β2 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 β2 agonists, additional blood glucose controls should be considered in diabetic patients.

The need for, and dose of inhaled corticosteroids should be re-evaluated in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.

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. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed (see Section 5.1 Pharmacodynamic properties). 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.

COPD population

Clinical studies and meta-analyses indicate that maintenance treatment of COPD with inhaled corticosteroids may lead to an increased risk of pneumonia.

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

4.5 Interaction with other medical products and other forms of interaction

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

β-adrenergic blockers can weaken or inhibit the effect of formoterol. Symbicort Rapihaler should therefore not be given together with β-adrenergic blockers (including eye drops) unless there are compelling reasons.

Concomitant treatment with quindine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), monoamine oxidase inhibitors 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 β-adrenergic drugs can have a potentially additive effect.

Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

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

4.6 Pregnancy and lactation

For Symbicort Rapihaler or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Data from an embryo-fetal development study in the rat showed no evidence of any additional effect from the combination.

There are no adequate data from use of formoterol in pregnant women. In animal studies, formoterol has caused adverse effects in reproduction studies at very high systemic exposure levels.

Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies, glucocorticosteroids have been shown to induce malformations. 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 Rapihaler 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.

Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the nursing infant 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 Symbicort Rapihaler 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.

4.7 Effects on ability to drive and use machines

Symbicort Rapihaler is not expected to adversely affect the ability to drive or use machines.

4.8 Undesirable Effects

Since Symbicort Rapihaler contains both budesonide and formoterol, the same type and intensity of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side effects of β_2 agonist therapy, such as tremor and palpitations. These tend to be mild and disappear within a few days of treatment.

Adverse reactions, which have been associated with budesonide or formoterol, are given in Table 5.

Table 5 Adverse drug reactions by frequency and system organ class (SOC)

Frequency	**SOC**	**Reaction**
Common ≥1% - <10%	*Cardiac disorders:*	Palpitations
	Infections and infestations:	Candida infections in oropharynx Pneumonia (in COPD patients)
	Nervous system disorders:	Headache, tremor
	Respiratory, thoracic and mediastinal disorders:	Mild irritation in the throat, coughing, hoarseness
Uncommon ≥0.1% - <1%	*Cardiac disorders:*	Tachycardia
	Gastrointestinal disorders:	Nausea
	Musculoskeletal, connective tissue and bone disorders:	Muscle cramps
	Nervous system disorders:	Dizziness
	Psychiatric disorders:	Agitation, restlessness, nervousness, sleep disturbances, aggression, psychomotor hyperactivity, anxiety
	Skin and subcutaneous tissue disorders:	Bruises
Rare ≥0.01% - <0.1%	*Cardiac disorders:*	Cardiac arrhythmias, e.g., atrial fibrillation, supraventricular tachycardia, extrasystoles

Frequency	SOC	Reaction
	Immune system disorders:	Immediate and delayed hypersensitivity reactions, e.g., dermatitis, exanthema, urticaria, pruritus, angioedema and anaphylactic reaction
	Metabolic and nutrition disorders:	Hypokalaemia
	Respiratory, thoracic and mediastinal disorders:	Bronchospasm
Very rare <0.01%	*Cardiac disorders:*	Angina pectoris
	Endocrine disorders:	Signs or symptoms of systemic glucocorticosteroid effects, e.g. adrenal suppression, growth retardation, decrease in bone mineral density, cataract and glaucoma
	Metabolic and nutrition disorders:	Hyperglycaemia
	Psychiatric disorders:	Depression, behavioural disturbances (mainly in children)
	Vascular disorders:	Variations in blood pressure
Unknown	*Eye disorders:*	Blurred vision

As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases.

Systemic effects of inhaled corticosteroids may occur particularly at high doses prescribed for prolonged periods.

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

4.9 Overdose

An overdose of formoterol would likely lead to effects that are typical for β_2-adrenergic agonists: tremor, headache, palpitations, and tachycardia. Hypotension, metabolic acidosis, hypokalaemia and hyperglycaemia may also occur. 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. Another observation might be the plasma cortisol level will decrease and number and percentage of circulating neutrophils will increase. The number and percentage of lymphocytes and eosinophils will decrease concurrently. When used chronically in excessive

doses, systemic glucocorticosteroid effects, such as hypercorticism and adrenal suppression, may appear.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergics and other drugs for obstructive airway diseases.

ATC code: R03AK07

Mechanism of action and pharmacodynamic effects:

Symbicort contains budesonide and formoterol, which have different modes of action and show additive effects in terms of reduction of asthma and COPD exacerbations. The specific properties of budesonide and formoterol allow the combination to be used both as reliever therapy and as maintenance therapy.

Budesonide

Budesonide is a glucocorticosteroid which when inhaled has a rapid (within hours) and dose-dependent anti-inflammatory action in the airways, resulting in reduced symptoms and fewer asthma exacerbations. Inhaled budesonide has less severe adverse effects than systemic corticosteroids. The exact mechanism responsible for the anti-inflammatory effect of glucocorticosteroids is unknown.

Formoterol

Formoterol is a selective β_2-adrenergic agonist that when inhaled results in a 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 after inhalation. The duration of effect is at least 12 hours after a single dose.

Symbicort Rapihaler

Clinical efficacy in asthma

Therapeutic equivalence between Symbicort Rapihaler and Symbicort Turbuhaler was demonstrated in three clinical efficacy and safety studies, including asthmatic patients from 6 to 79 years of age and one long-term safety study in adolescents and adults with asthma. The safety profile of Symbicort Rapihaler has been shown to be as safe and well tolerated as Symbicort Turbuhaler. As a result of demonstrating therapeutic equivalence, the clinical efficacy for Symbicort Rapihaler in asthma described below is based on studies conducted with Symbicort Turbuhaler.

It has been shown in a separate study that Symbicort Rapihaler can be used safely with a named spacer device in children.

Symbicort Turbuhaler

Clinical efficacy for Symbicort as an anti-inflammatory reliever: anti-inflammatory reliever therapy (therapy A) and anti-inflammatory reliever plus maintenance therapy (therapy B) in asthma (see Section 4.2 Posology and method of administration)

Overall, 20140 asthma patients were included in 7 double-blind clinical studies, of which 7831 were randomised to a therapy which included Symbicort as an anti-inflammatory reliever, both with a maintenance (therapy B) and without a maintenance dosing (therapy A).

A total of 8064 asthma patients with mild asthma were included in 2 double blind efficacy and safety studies (SYGMA 1 and SYGMA 2 studies), of which 3384 patients were randomised to Symbicort anti-inflammatory reliever therapy (therapy A) for 12 months. Patients were required to be uncontrolled on only short-acting inhaled bronchodilator as needed or controlled on a low dose of inhaled corticosteroids or LTRA (leukotriene receptor antagonist) plus short-acting inhaled bronchodilator as needed.

In the SYGMA 2 study, Symbicort Turbuhaler 160/4.5 micrograms used as needed in response to symptoms (anti-inflammatory reliever therapy – therapy A) was comparable to a maintenance dose of budesonide (1 inhalation of 200 micrograms/inhalation twice daily) given with as-needed short-acting β_2 agonist in terms of the rate of severe exacerbations (Table 6). Protection against severe exacerbation was achieved with a 75% reduction in median inhaled steroid load. The SYGMA 1 study showed that Symbicort anti-inflammatory reliever therapy provided statistically significant and clinically meaningful reduction in the rate of annual severe exacerbation by 64% compared with as-needed use of a short-acting β_2 agonist (Table 6). Reduction in the annual rate of moderate to severe exacerbations was consistent (60%) with that observed for severe exacerbations ([RR] 0.40, 95% CI 0.32 to 0.49, p-value <0.001).

In the SYGMA 1 study, as-needed use of Symbicort Turbuhaler 160/4.5 micrograms provided superior daily asthma symptom control compared to as-needed short-acting β_2 agonist (OR 1.14, 95% CI 1.00 to 1.30, p-value 0.046), showing a mean percentage of weeks with well-controlled asthma of 34.4% and 31.1%, respectively. Asthma symptom control was inferior for Symbicort as needed compared to a maintenance dose of budesonide (1 inhalation of 200 micrograms/inhalation twice daily) given with as-needed short-acting β_2 agonist (OR 0.64, 2-sided 95% CI 0.57 to 0.73, lower limit of the CI $\geq$ 0.8 for non-inferiority), showing a mean percentage of well-controlled asthma weeks of 34.4% and 44.4%, respectively. Improvements in asthma control (as defined by ACQ5) in patients using Symbicort anti-inflammatory reliever therapy were superior to improvements in patients using a short-acting β_2 agonist as needed (-0.15, 95% CI -0.20 to -0.11, p-value < 0.001). Improvements in asthma control were lower for Symbicort as needed compared to a maintenance dose of budesonide (1 inhalation of 200 micrograms/inhalation twice daily) given with a short-acting β_2 agonist to be used as needed (SYGMA 1: 0.15, 95% CI 0.10 to 0.20; SYGMA 2: 0.11, 95% CI 0.07 to 0.15, both p-value < 0.001). For both comparisons, mean differences in treatments' effect upon ACQ5 are not clinically meaningful (as assessed by a difference of greater than or equal to 0.5). These results were observed in a clinical study setting with considerably higher adherence to budesonide maintenance dosing than expected in real life.

In the SYGMA studies, increases in lung function compared to baseline (mean pre-bronchodilator FEV1) were statistically significantly larger for patients on Symbicort anti-inflammatory reliever therapy compared to patients on as-needed short-acting β_2 agonist treatment. Statistically significantly smaller increases were observed for Symbicort as needed compared to a maintenance dose of budesonide (1 inhalation of 200 micrograms/inhalation twice daily) given with a short-acting β_2 agonist to be used as needed. For both comparisons, mean differences in treatments' effect were small (approximately 30 to 55 mL, equating to approximately 2% of the baseline mean).

Overall, the results of the SYGMA studies show that Symbicort anti-inflammatory reliever therapy is a more effective treatment than a short-acting β_2 agonist as needed in patients with

mild asthma. In addition, these studies suggest that the as-needed use of Symbicort may be considered an alternative treatment option for patients with mild asthma who are eligible for inhaled corticosteroid treatment.

In a separate clinical programme, a total of 12076 asthma patients were included in 5 double-blind efficacy and safety studies (4447 were randomised to Symbicort anti-inflammatory reliever plus maintenance therapy – therapy B) for 6 or 12 months. Patients were required to be symptomatic despite use of inhaled glucocorticosteroids.

Symbicort anti-inflammatory reliever plus maintenance therapy provided statistically significant and clinically meaningful reductions in severe exacerbations for all comparisons in all 5 studies. This included a comparison with Symbicort at a higher maintenance dose with terbutaline as reliever (study 735) and Symbicort at the same maintenance dose with either formoterol or terbutaline as reliever (study 734) (Table 6). 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 Symbicort maintenance and reliever therapy used, on average, no reliever inhalations on 57% of treatment days. There was no sign of development of tolerance over time.

Table 6. Overview of severe exacerbations in clinical studies

Study No. Duration	**Treatment groups**[a]	**N**	**Severe exacerbations**[b]	
			Events	**Events/ patient-year**[c]
SYGMA 1 (Therapy A*) > 12 years	**Symbicort 160/4.5 µg as needed**	1277	77	0.07
	Terbutaline 0.4 mg as needed	1277	188	0.20[d]
	Budesonide 200 µg bd + terbutaline 0.4 mg as needed	1282	89	0.09[e]
SYGMA 2 (Therapy A*) > 12 years	**Symbicort 160/4.5 µg as needed**	2084	217	0.11
	Budesonide 200 µg bd + terbutaline 0.4 mg as needed	2083	221	0.12[f]
6-month double-blind studies				
Study 735 (Therapy B) 6 months**	**Symbicort 160/4.5 µg bd + as needed**	**1103**	**125**	**0.23**[***]
	Symbicort 320/9 µg bd + terbutaline 0.4 mg as needed	1099	173	0.32
	Salmeterol/fluticasone 2 x 25/125 µg bd + terbutaline 0.4 mg as needed	1119	208	0.38
12-month double-blind studies				
Study 734 (Therapy B)**	**Symbicort 160/4.5 µg bd + as needed**	**1107**	**194**	**0.19**[***]
	Symbicort 160/4.5 µg bd + formoterol 4.5 µg as needed	1137	296	0.29

Study No. Duration	Treatment groups[a]	N	Severe exacerbations[b]	
			Events	Events/ patient-year[c]
12 months	Symbicort 160/4.5 µg bd + terbutaline 0.4 mg as needed	1138	377	0.37

* Symbicort anti-inflammatory reliever therapy.

** Symbicort anti-inflammatory reliever plus maintenance therapy.

*** Reduction in exacerbation rate is statistically significant (p-value <0.01) (for both comparisons where applicable).

[a] All doses expressed as delivered dose. Budesonide 160 µg and 320 µg (delivered doses) correspond to Pulmicort 200 µg and 400 µg (metered doses), respectively.

[b] Defined as hospitalisation/emergency room treatment or treatment with oral steroids due to asthma.

[c] Data normalised to 12 months for studies 735 and 734.

[d] Reduction in exacerbation rate is statistically significant (p value <0.001) for the comparison of Symbicort as needed vs Terbutaline as needed.

[e] Reduction in exacerbation rate is not statistically significantly different (p-value 0.279) when comparing Symbicort as needed vs Budesonide 200 µg bd + terbutaline 0.4 mg as needed in SYGMA 1.

[f] Symbicort as needed was non-inferior to Budesonide 200 µg bd + terbutaline 0.4 mg as needed in reducing the severe exacerbation rate in SYGMA 2. The upper limit (1.16) of the 95% CI for the rate ratio (RR) was below the pre-specified non-inferiority limit (1.20).

Analysis of time to first severe exacerbation in the SYGMA 1 study showed that the likelihood of experiencing a severe exacerbation was statistically significantly higher for the as-needed use of a short-acting β_2 agonist compared to the as-needed use of Symbicort (Symbicort anti-inflammatory reliever therapy - therapy A) over the 1 year treatment period (see Figure 1a), with a risk reduction of 56% ([HR] 0.44, 95% CI: 0.33-0.58, p-value <0.001). There were no differences in the probability of experiencing a severe exacerbation between Symbicort anti-inflammatory reliever therapy (therapy A) and a therapy including a maintenance dose of budesonide (1 inhalation of 200 micrograms/inhalation twice daily) and a short-acting β_2 agonist used as needed (see Figure 1a and 1b).

Figure 1a Time to first severe asthma exacerbation in SYGMA 1 study

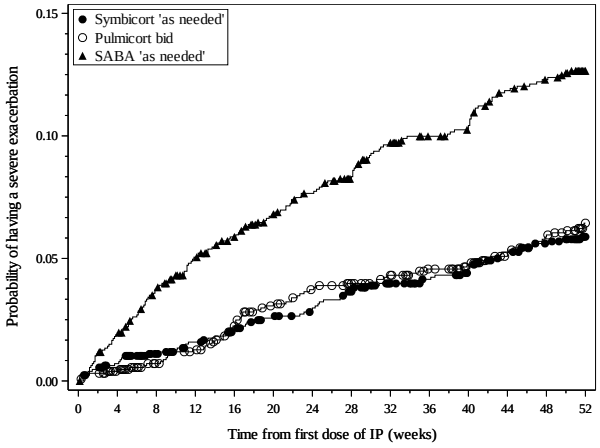
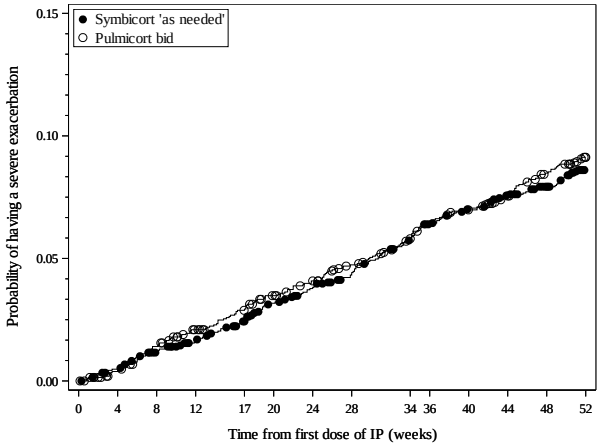


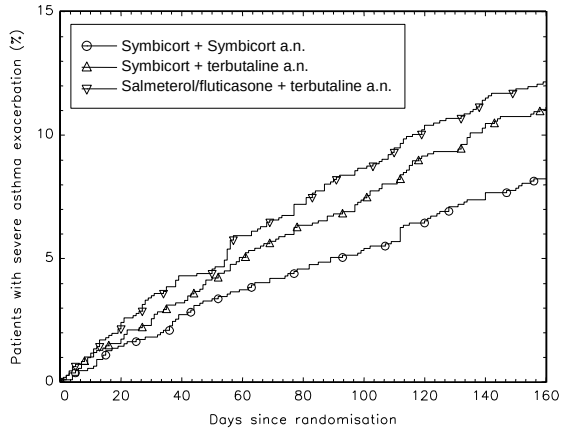
Figure 1b Time to first severe asthma exacerbation in SYGMA 2 study



In Study 735, Symbicort anti-inflammatory reliever plus maintenance therapy (therapy B) significantly prolonged the time to the first severe exacerbation (see Figure 2a) compared to

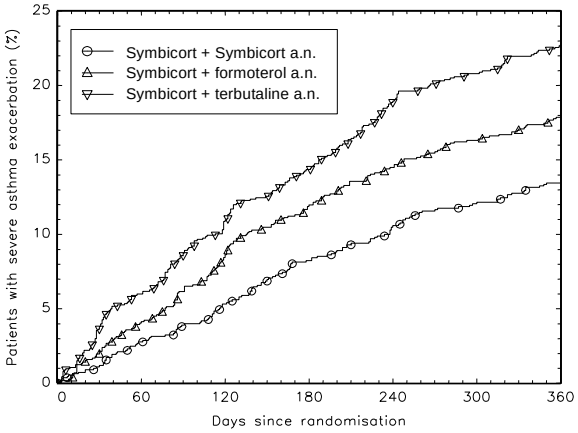
the other treatment groups. The rate of severe exacerbations was reduced by 28% compared to twice the maintenance dose of Symbicort with terbutaline as reliever. Lung function, symptom control, and reliever use were similar in all treatment groups.

Figure 2a Time to first severe asthma exacerbation in study 735



a.n. = as needed

Figure 2b Time to first severe asthma exacerbation in study 734



a.n. = as needed

In Study 734, Symbicort anti-inflammatory reliever plus maintenance therapy (therapy B) prolonged the time to the first severe exacerbation compared to Symbicort at the same maintenance dose with either formoterol or terbutaline as reliever (see Figure 2b). The rate of severe exacerbations was reduced by 33% and 48%, respectively. Symptoms and reliever use were reduced, and lung function improved, compared with both comparator treatments.

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

Clinical efficacy in asthma for Symbicort maintenance therapy (therapy C)

Clinical studies with Symbicort Turbuhaler have shown that the addition of formoterol to budesonide improved asthma symptoms and lung function, and reduced exacerbations. The effect on lung function of Symbicort Turbuhaler given as maintenance dose only was equal to that of budesonide and formoterol administered in separate inhalers in adults 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.

In a 12-week paediatric study 85 children aged 6-11 years were treated with a maintenance dose of Symbicort (2 inhalations of 80/4.5 micrograms/inhalation twice daily), and a short-acting β_2 agonist as needed. Lung function was improved and the treatment was well tolerated compared to the corresponding dose of budesonide Turbuhaler.

Clinical efficacy in Chronic Obstructive Pulmonary Disease (COPD)

Symbicort Rapihaler

In one 12-month study and one 6-month study in patients with COPD, Symbicort Rapihaler 160/4.5 was superior to placebo, budesonide and formoterol for post-dose FEV1 and predose FEV1. In the 12-month study, Symbicort Rapihaler was also superior to placebo and formoterol for both the number of, and the time to first severe COPD exacerbation (a worsening of COPD requiring oral steroid use of hospitalization.) Thus, the contribution of

both budesonide and formoterol to the effect of Symbicort Rapihaler was demonstrated. Symbicort Rapihaler 160/4.5 also significantly reduced breathlessness, daily rescue medication use, night-time awakenings and improved health-related quality of life compared with placebo in both studies. Serial FEV1 measures over 12 hours were obtained in subsets of patients in both studies. 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. Maximal improvement in FEV1 occurred at approximately 2 hours post-dose and post-dose bronchodilator effect was generally maintained over 12 hours. The treatment was well tolerated.

5.2 Pharmacokinetics Properties

Absorption:

Symbicort Rapihaler

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

In studies where Symbicort Rapihaler was administered to healthy subjects and patients with moderate asthma, peak plasma concentrations for budesonide occurred approximately 30 minutes and for formoterol 10 minutes after dosing. Peak plasma concentrations were 30-40% higher in healthy subjects compared to asthma patients. However, the total systemic exposure was comparable to that in asthma patients.

In repeat dose studies plasma concentrations of budesonide and formoterol generally increased in proportion to dose.

Collectively, in pharmacokinetic studies conducted in adults with asthma, systemic exposure to budesonide and formoterol administered via Symbicort Rapihaler was lower than when given via the monoproducts Pulmicort Turbuhaler and Oxis Turbuhaler. Collectively, the pharmacokinetic data from clinical efficacy and safety studies indicate that Symbicort Rapihaler delivers a comparable amount of budesonide to the systemic circulation, and thus the lung, as do budesonide pMDI and Pulmicort Turbuhaler. The results of the systemic exposure for formoterol were generally similar when administered via Symbicort Rapihaler and Oxis Turbuhaler.

Symbicort Turbuhaler

The systemic bioavailability of budesonide and formoterol was comparable for the two treatments Symbicort Rapihaler and Symbicort Turbuhaler.

Distribution and Biotransformation:

Plasma protein binding is approximately 50% for formoterol and 90% for budesonide. Volume of distribution is about 4 L/kg for formoterol and 3 L/kg for budesonide. Formoterol is inactivated via conjugation reactions (active O-demethylated and deformylated metabolites are formed, but they are seen mainly as inactivated conjugates). Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6 β-hydroxy-budesonide and 16α-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 eliminated by metabolism in the liver followed by renal excretion. After inhalation of formoterol via Turbuhaler, 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 excreted 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.

Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 years old asthmatic children. Per kg body weight children have a clearance, which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. The pharmacokinetics of formoterol in children has not been studied.

The pharmacokinetics of budesonide or formoterol in elderly and in patients with renal failure is unknown. The exposure of budesonide and formoterol may be increased in patients with liver disease.

5.3 Preclinical safety data

The toxicity observed in animal studies with budesonide and formoterol was similar whether budesonide or formoterol were given in combination or separately. The effects were associated with pharmacological actions and dose dependent.

In animal reproduction studies, glucocorticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant in humans at the recommended doses (see Section 4.6 Pregnancy and Lactation). 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 to man.

Symbicort Rapihaler contains the excipients povidone (polyvinylpyrrolidone) K25, macrogol (polyethylene glycol) 1000 and the pressurised liquid propellant apaflurane (HFA 227). 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Apaflurane (HFA 227)
Povidone K25
Macrogol (polyethylene glycol) 1000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to expiry date on outer carton. The shelf life after removal from the foil pouch is 3 months.

6.4 Special precautions for storage

Store below 30°C. Store the inhaler with the mouthpiece down.

Keep out of the reach and sight of children.

Always replace the mouthpiece cover after using Symbicort Rapihaler.

6.5 Nature and contents of container

A pressurised container, comprising an internally coated aluminium can, sealed with a metering valve and fitted into a plastic actuator. Each inhaler delivers 120 actuations of budesonide/formoterol 40/2.25, 80/2.25, 80/4.5 or 160/4.5 micrograms/actuation respectively after initial priming. Each inhaler is individually wrapped in a foil laminate pouch containing a desiccant.

6.6 Instructions for use, handling and disposal

See Section 4.2 Posology and Method of Administration. The canister should not be broken, punctured or burnt, even when apparently empty.

The canister contains a pressurised liquid. Do not expose to temperatures above 50°C.

Instructions for the correct use of Symbicort Rapihaler with a spacer device

The use of Symbicort Rapihaler with a spacer device is recommended to enable patients with difficulty in co-ordinating inhalation with actuation, such as young children or the elderly, to derive greater therapeutic benefit.

It is important to instruct the patient to carefully read the instructions for use/handling in the leaflet.

Product Owner

AstraZeneca UK Limited
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Cambridge Biomedical Campus
Cambridge, CB2 0AA
United Kingdom

Date of revision of text

August 2022

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7. INSTRUCTIONS FOR USE/HANDLING

Please read all of this leaflet carefully before you start taking/using this medicine.

- This leaflet contains information about Symbicort Rapihaler and how to use and clean the device. Please read the leaflet carefully before using your inhaler and refer to it when you are using your medicine. You may find that you need to clean your inhaler regularly (at least weekly). Please follow the cleaning instructions at the end of the leaflet.
- This medicine has been prescribed for you personally and you should **not** pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you have further questions, please ask your doctor, nurse or your pharmacist.
- Your doctor, nurse or pharmacist should instruct you in the correct use of your inhaler.

YOUR INHALER:

Your inhaler will already be assembled when you first receive it. Please do not take your inhaler apart. If the canister becomes loose, then place it back and continue to use it as instructed.

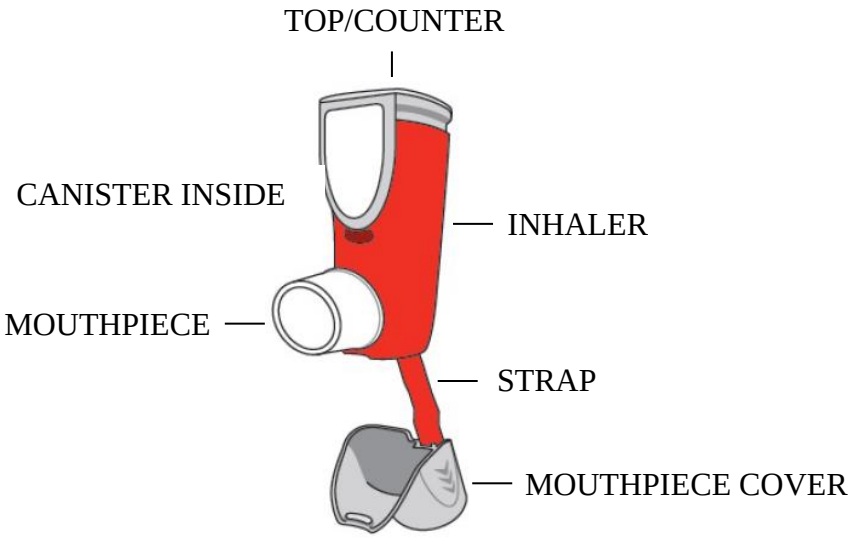


Figure 1

PREPARING YOUR INHALER FOR USE:

Take your inhaler out of the moisture-protective foil before you use it for the first time and throw away the foil. If your inhaler is new, shake it gently and release 3 puffs in the air if you use the 40/2.25 micrograms/actuation inhaler or 2 puffs if you use the 80/2.25 or 160/4.5 or

80/4.5 micrograms/actuation inhaler to prepare it for use. If your inhaler has not been used for a week or more, or it has been dropped, shake it gently and release 2 puffs in the air to prepare it for use.

WAYS TO HOLD THE INHALER FOR USE:

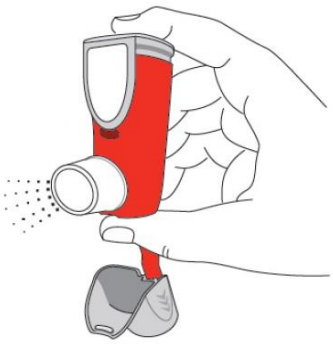


Figure 2

or

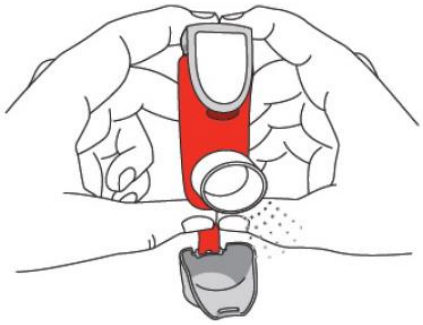


Figure 3

TAKING YOUR MEDICINE:

1. Shake the inhaler gently before each use.
2. Remove the mouthpiece cover.
3. Hold the inhaler upright in front of your mouth, using your thumb(s) at the base of the inhaler and your index finger(s) on the top, as shown on the pictures. Then breathe out as far as you can and put the mouthpiece gently in your mouth, between your teeth, and close your lips around it.
4. Start to breathe in deeply, comfortably and slowly through your mouth, press firmly down on the inhaler to release a puff of medicine.
5. Continue to breathe in and hold your breath for approximately 10 seconds or as long as it is comfortable, take the inhaler from your mouth and your finger from the top of the inhaler.
6. Take another puff, as directed by your doctor, shake the inhaler gently then repeat steps 3 to 5.
7. Put the mouthpiece cover back to keep dust and other debris from getting into your medicine.
8. Rinse your mouth with water to remove any excess medicine. Do not swallow.

Figure 4

IMPORTANT INFORMATION:

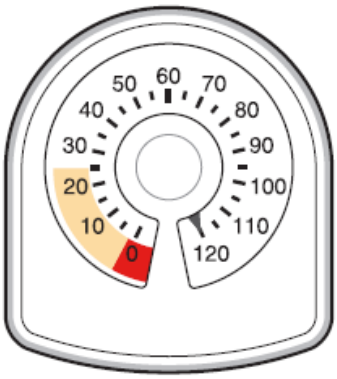
CLEANING INSTRUCTIONS:

Your inhaler mouthpiece will need to be cleaned regularly, at least once a week. And to do this you will need to:

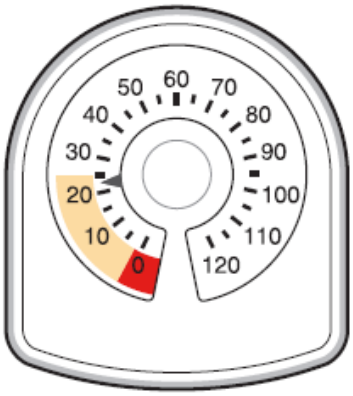
1. Remove the mouthpiece cover.
2. Wipe the inside and outside of the mouthpiece opening with a clean, dry cloth.
3. Replace the mouthpiece cover.
4. Do not put the inhaler in water.
5. Do not try to take the inhaler apart.

READING THE COUNTER:

- The arrow on the counter on the top of the inhaler points to the number of puffs remaining in your inhaler. It starts with 120 puffs when it is full.



- The counter will count down toward zero (“0”) each time you release a puff of medicine (either when preparing your inhaler for use or when taking the medicine).
- When the arrow on the counter enters the yellow area, this means that there are about 20 puffs left.



- It is very important that you note the number of puffs remaining in your SYMBICORT inhaler by reading the counter. Discard SYMBICORT after the counter reaches zero (“0”), indicating that you have used the number of puffs on the product label and box. Your inhaler may not feel empty and it may continue to operate, but you will not get the right amount of medicine if you keep using it.