0501300/6

Budesonide + Formoterol fumarate dihydrate

Symbicort® Rapihaler®

80 mcg/4.5 mcg per actuation Inhalation Aerosol
160 mcg/4.5 mcg per actuation Inhalation Aerosol
Pressurised Suspension for Inhalation

Adrenergics and Other Drugs for Obstructive Airway Disease

1. NAME OF THE MEDICINAL PRODUCT

Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) 80/4.5 micrograms/actuation, pressurised inhalation, suspension and
Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) 160/4.5 micrograms/actuation, pressurised inhalation, suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single actuation (delivered dose, the amount of drug that leaves the mouthpiece) contains budesonide 80 or 160 micrograms respectively and formoterol fumarate dihydrate 4.5 micrograms.

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

For excipients see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Pressurised suspension for inhalation

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma
Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) is indicated in the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting beta$_2$-agonist) is appropriate.

COPD
Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) is indicated in the regular treatment of patients with moderate to severe chronic obstructive pulmonary disease (COPD), with frequent symptoms and a history of exacerbations.

4.2 Dosage and method of administration

The dosage of Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) should be individualised according to disease severity.

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

Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) maintenance therapy: Budesonide + Formoterol fumarate dihydrate (Symbicort) taken as regular maintenance treatment, with a separate rapid-acting bronchodilator as rescue. Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

Table 1 Dosing instructions - Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) maintenance therapy

AGE group	80/4.5mcg/ actuation	160/4.5mcg/ actuation
Adults (18 years and older)	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.	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.
Adolescents (12-17 years)	2 inhalations once or twice daily. During worsening of asthma the dose may temporarily be increased to a maximum of 4 inhalations twice daily.	2 inhalations once or twice daily. During worsening of asthma the dose may temporarily be increased to a maximum of 4 inhalations twice daily.
Children (6-11 years)	2 inhalations twice daily. Maximum daily dose: 4 inhalations.	A lower strength is available for children 6-11 years.

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

Table 2 Dosing instructions - COPD

AGE group	160/4.5mcg/ actuation
Adults (18 years and older)	2 inhalations twice daily. Maximum daily dose: 4 inhalations.

General information

The patients should be instructed that Budesonide + Formoterol fumarate dihydrate (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 Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) 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 Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER)

On actuation of Budesonide + Formoterol fumarate dihydrate (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 in section 6.6.
- Shake the inhaler gently prior to each use to mix its contents properly.
- Prime the inhaler by actuating it twice into the air when the inhaler is new, 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.

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

It is recommended that the dose be tapered when long-term treatment is discontinued and should not be stopped abruptly.

If patient finds the treatment ineffective, or exceed the prescribed dose of Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER), medical attention must be sought. Sudden and progressive deterioration in control of asthma or COPD is potentially life threatening and the patient should undergo urgent medical assessment. In this situation, consideration should be given to the need for increased therapy with corticosteroids, e.g., a course of oral corticosteroids, or antibiotic treatment if an infection is present.

Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

Treatment with Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) should not be used to treat a severe exacerbation.

Physicians should closely follow the growth of children and adolescents taking long-term corticosteroids by any route, and weigh the benefits of the corticosteroid therapy against the possible risk of growth suppression (see section 5.3).

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.

Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) should be administered with caution in patients with severe cardiovascular disorders (including heart rhythm abnormalities), diabetes mellitus, untreated hypokalaemia or thyrotoxicosis.

High doses of $beta_{2}$-agonists can lower S-potassium by inducing a redistribution of potassium from the extracellular to the intracellular compartment, via stimulation of Na^{+}/K^{+}-ATPase in muscle cells. The clinical importance of this effect is uncertain.

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 medicinal products and other forms of interaction

Pharmacokinetic interactions

The metabolism of budesonide is primarily mediated by CYP3A4. Inhibitors of this enzyme, e.g. ketoconazole, itraconazole and ritonavir 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 with potent CYP3A4 inhibitors.

Pharmacodynamic interactions

Beta-adrenergic blockers (including eye drops) can weaken or inhibit the effect of formoterol.

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

4.6 Pregnancy and lactation

For Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) or the concomitant treatment with budesonide and formoterol no clinical data on exposed pregnancies are available. Data from an embryo-fetal development study in the rat, using the Budesonide + Formoterol fumarate dihydrate (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 5.3 Preclinical Safety Data).

Data on approximately 2500 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.

During pregnancy, Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) should only be used when the benefits outweigh the potential risk, especially during the first 3 months and shortly before delivery. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used.

A clinical pharmacology study has shown that inhaled budesonide Turbuhaler 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 Budesonide + Formoterol fumarate dihydrate (SYMBICORT). 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 Budesonide + Formoterol fumarate dihydrate (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.

4.7 Effects on ability to drive and use machines

Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) is not expected to adversely affect the ability to drive or use machines.

4.8 Undesirable effects

Since Budesonide + Formoterol fumarate dihydrate (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 beta$_2$-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 below:

Table 3 Adverse drug reactions by frequency and system order class (SOC)

Frequency	SOC	Reaction
Common 1% to 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% to 1%	*Cardiac disorders:*	Tachycardia
	Gastrointestinal disorders:	Nausea
	Musculoskeletal and connective tissue disorders:	Muscle cramps
	Nervous system disorders:	Dizziness
	Psychiatric disorders:	Agitation, restlessness, nervousness, sleep disturbances
	Skin and subcutaneous tissue disorders:	Bruises
Rare 0.01% to 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, purities, angioedema and anaphylactic reaction
	Metabolic and nutrition disorders:	Hypokalemia
	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
	Metabolism and nutrition disorders:	Hyperglycaemia
	Psychiatric disorders:	Depression, behavioural disturbances (mainly in children)
	Vascular disorders:	Variations in blood pressure

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

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

Treatment with beta$_2$-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 an exaggeration of effects that are typical for beta$_2$-adrenergic agonists: tremor, headache, palpitations, and tachycardia. Hypotension, metabolic acidosis, hypokalaemia and hyperglycemia 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 micograms/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 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:

Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) 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 as maintenance treatment of asthma. The respective mechanisms of action of both drugs are discussed below.

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 beta$_2$-adrenergic agonist that when inhaled results in rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose dependant, with an onset of effect within 1-3 minutes after inhalation. The duration of effect is at least 12 hours after a single dose.

Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER)

Clinical Efficacy in Asthma

Therapeutic equivalence between Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) and Budesonide + Formoterol fumarate dihydrate (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 Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) has been shown to be as safe and well tolerated as Budesonide + Formoterol fumarate dihydrate (SYMBICORT TURBUHALER). As a result of demonstrating therapeutic equivalence, the clinical efficacy of Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) in asthma described

below is based on studies conducted with Budesonide + Formoterol fumarate dihydrate (SYMBICORT TURBUHALER).

It has been shown in a separate study that Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) can be used safely with a named spacer device in children.

Budesonide + Formoterol fumarate dihydrate (SYMBICORT TURBUHALER)

Clinical Efficacy for Budesonide + Formoterol fumarate dihydrate (SYMBICORT TURBUHALER) maintenance therapy in Asthma

Clinical studies with Budesonide + Formoterol fumarate dihydrate (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 Budesonide + Formoterol fumarate dihydrate (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-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 Budesonide + Formoterol fumarate dihydrate (Symbicort) (2 inhalations of 80/4.5 micrograms/inhalation twice daily), and a short-acting beta$_2$-agonist as needed. Lung function was improved and the treatment was well tolerated compared to the corresponding dose of budesonide Turbuhaler.

Clinical Efficacy in COPD

Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER)

In one 12-month study and one 6-month study in patients with COPD, Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) 160/4.5 was superior to placebo, budesonide and formoterol for post-dose FEV1 and predose FEV1. In the 12-month study, Budesonide + Formoterol fumarate dihydrate (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 Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) was demonstrated. Budesonide + Formoterol fumarate dihydrate (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 Budesonide + Formoterol fumarate dihydrate (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 Pharmacokinetic properties

Absorption:

Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER)

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

In studies where Budesonide + Formoterol fumarate dihydrate (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 Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) was lower than when given via the monoproduct Budesonide (Budecort TURBUHALER). Collectively, the pharmacokinetic data from clinical efficacy and safety studies indicate that Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) delivers a comparable amount of budesonide to the systemic circulation, and thus the lung, as do budesonide pMDI and Budesonide (BUDECORT TURBUHALER). The results of the systemic exposure for formoterol were generally similar when administered via Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER).

Budesonide + Formoterol fumarate dihydrate (SYMBICORT TURBUHALER)

The systemic bioavailablity of budesonide and formoterol was comparable for the two treatments Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) and Budesonide + Formoterol fumarate dihydrate (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 beta-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% to13% 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). 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.

Budesonide + Formoterol fumarate dihydrate (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 Budesonide + Formoterol fumarate dihydrate (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 the expiry date on the label and carton. The shelf-life after removal from the foil pouch is 3 months.

6.4 Special precautions for storage

Store at temperatures not exceeding 30°C. Store the inhaler with the mouthpiece down. Keep out of reach of children. Always replace the mouthpiece cover after using Budesonide + Formoterol fumarate dihydrate (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 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

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

- This leaflet contains information about Budesonide + Formoterol fumarate dihydrate (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 it becomes loose, then place it back and continue to use it as instructed.

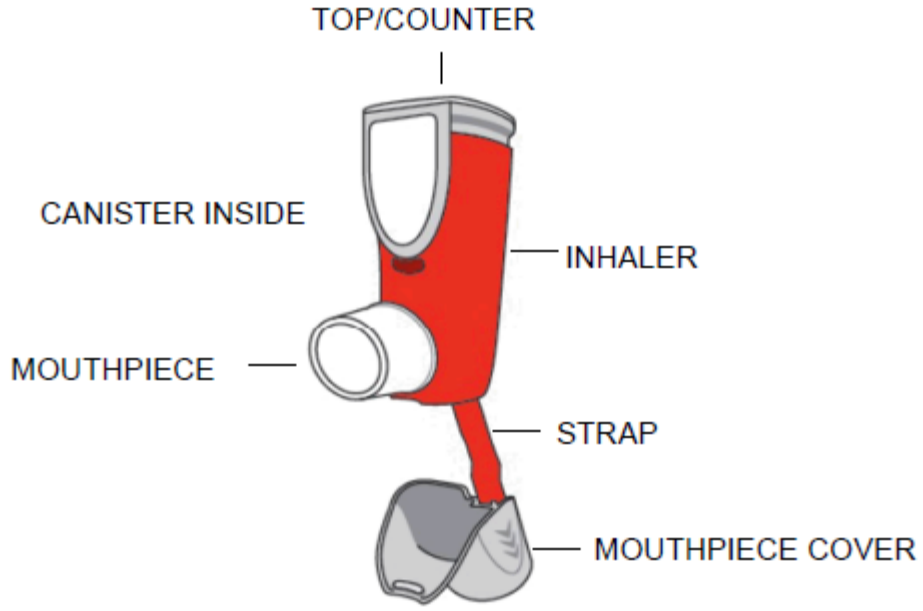


Figure 1

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, if it has not been used for a week or more, or it has been dropped, shake it gently and release 2 puffs or actuations (for the 80/4.5 and 160/4.5 micrograms/actuation strengths) in the air to prepare it for use.

WAYS TO HOLD THE INHALER FOR USE:

Figure 2

or

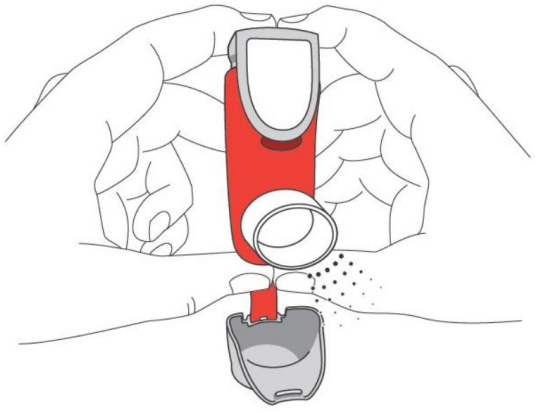


Figure 3

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.

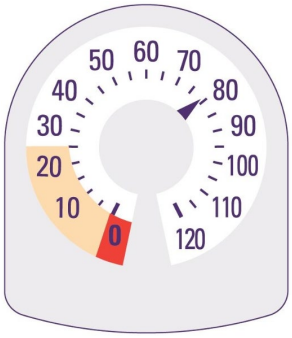
Figure 4

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.

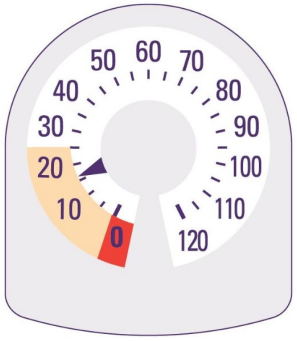
READING THE COUNTER:

- The arrow on the counter on the top of the inhaler points to the number of inhalations (puffs) remaining in your inhaler.



- 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 inhalations (puffs) remaining in your inhaler by reading the counter. Discard the inhaler after the counter reaches zero (“0”), indicating that you have used the number of inhalations 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.

See also section 4.2. 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 Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) with a spacer device

The use of Budesonide + Formoterol fumarate dihydrate (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.

Note: It is important to instruct the patient to:

- Carefully read the instructions for use in this leaflet.

On actuation of the aerosol, the dose is released into the inhalation chamber. The inhalation chamber is then emptied by two slow deep breaths. Young children may need to breathe 5–10 times through the mouthpiece. For further actuations, the procedure is repeated. For young children who are unable to breathe through the mouthpiece, a face mask can be used. Compatible face masks are available separately and care should be taken to ensure a good fit is achieved.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, please report to the Food and Drug Administration (FDA) at www.fda.gov.ph and to AstraZeneca at https://contactazmedical.astrazeneca.com/. The patient should seek medical attention immediately at the first sign of any adverse drug reaction.

AVAILABILITY

Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) 80 mcg/4.5 mcg/actuation Pressurised Suspension for Inhalation – 1 x 120 actuations or doses
Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) 160 mcg/4.5 mcg/actuation Pressurised Suspension for Inhalation – 1 x 120 actuations or doses

REGISTRATION NUMBERS

DR-XY45700 – Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) 80 mcg/4.5 mcg/actuation Pressurised Suspension for Inhalation
DR-XY45701 – Budesonide + Formoterol fumarate dihydrate (SYMBICORT RAPIHALER) 160 mcg/4.5 mcg/actuation Pressurised Suspension for Inhalation

DATE OF FIRST AUTHORIZATION

9 December 2016

Date of Revision of Text: March 2023
Philippine-specific Text ANGEL Reference: Doc ID-000368542 v.9.0
Based on CDS dated June 2020 with ANGEL Ref.: Doc ID-000392736 v.5.0

Imported by the Marketing Authorization Holder
AstraZeneca Pharmaceuticals (Phils.), Inc.

16th Floor, Inoza Tower, 40th Street
Bonifacio Global City, Taguig, Philippines
Manufactured by AstraZeneca Dunkerque Production
224 Avenue de la Dordogne, 59640, Dunkerque, France