Proposed packaging material		
Code	SYMBICORT RAPIHALER 80/4.5-PI-02.01	
Regulatory Objective	☐NDA ☒Renewal ☐ Variation change detail no.: RO-Obligation Event-0011687	
Code of previous version	SYMBICORT RAPIHALER 80/4.5-PIL-01.01	
Reference	☐ CDS version: N/A ☐ CPIL version: N/A	☐SmPC country/version/date: N/A ☐ RAM approval: N/A
Changes	Renewal submission	
Name	ADR	

Symbicort® Rapihaler 80/4.5 mcg/dose
budesonide/formoterol fumarate dihydrate
pressurised inhalation, suspension

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

Formoterol fumarate dihydrate is hereafter referred to as “formoterol.”

For excipients see section List of Excipients.

Pharmaceutical Form
Pressurised inhalation, suspension.

Therapeutic Indications
Asthma
Symbicort Rapihaler is indicated in the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting β2 agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting beta2-agonists, or

- patients already adequately controlled on both inhaled corticosteroids and long-acting beta2-agonists.

Note: Symbicort (80/4.5 micrograms/inhalation) is not appropriate in patients with severe asthma

Posology and Method of Administration
Asthma
Symbicort Rapihaler is not intended for the initial management of 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 product 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 dose of beta2-agonists and/or corticosteroid by individual inhalers should be prescribed.

The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Patients should be regularly reassessed by their prescriber/health care provider, so that the dosage of SYMBICORT remains optimal. When long term control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

SYMBICORT maintenance and reliever therapy
SYMBICORT is taken as both regular maintenance treatment, and also as needed in response to symptoms. The as needed inhalations provide both rapid relief and improved asthma control. Patients should be advised to have SYMBICORT available for rescue use at all times. A separate inhaler for rescue use is not necessary. Clinical studies have demonstrated that SYMBICORT maintenance and reliever therapy provides clinically meaningful reductions in severe exacerbations while maintaining symptom control, compared to SYMBICORT maintenance therapy with a separate rapid-acting bronchodilator (see section Pharmacodynamic properties).
Recommended doses:
Adults and adolescents (12 years and older)
The recommended maintenance dose is 2 inhalations per day, given either as one inhalation in the morning and evening or as 2 inhalations in either the morning or evening. Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion.

Children (6 years and older)
The usual maintenance dose is 1 inhalation once daily. Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 4 inhalations should be taken on any single occasion.

A reassessment of asthma therapy should be considered in patients using an increasing number of SYMBICORT inhalations for symptom relief without achieving improved asthma control within 2 weeks. A total daily dose of more than 8 inhalations for adults and adolescents and 4 inhalations for children is not normally needed, however a total daily dose of up to 12 inhalations for adults and adolescents and 8 inhalations for children could be used temporarily.

Symbicort maintenance therapy
Symbicort is 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.
Recommended doses:
Adults and adolescents (12 years and older)
1-2 inhalations twice daily.

Children (6 years and older)
2 inhalations twice daily.

In usual practice when control of symptoms is achieved with 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 maintan control.

Children under 6 years
SYMBICORT RAPIHALER is not recommended for children under 6 years of age.

Special patient groups
There are no special dosing requirements for elderly patients. There are no data available for use of SYMBICORT RAPIHALER in patients with hepatic or renal impairment. As budesonide and formoterol are primarily eliminated via hepatic metabolism, an increased exposure in patients with severe liver cirrhosis.

General information
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.

Hepatic/renal impairment
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 systemic availability can be expected in patients with severe liver disease.

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. Check the expiry date.

Note It is important to instruct the patient to:

- Carefully read the instructions for use in the patient information leaflet which is packed together with each inhaler of Symbicort Rapihaler.
- 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, 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 this step for the second inhalation.
- 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.

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

Special Warnings and Special Precautions for Use
Treatment of asthma should be in accordance with current national treatment guidelines.

Patients with asthma should have a personal asthma action plan designed in association with their general practitioner. This plan should incorporate a stepwise treatment regime which can be instituted if the patient's asthma improves or deteriorates. It is recommended that the dose is tapered when long-term treatment is discontinued and should not be stopped abruptly.

Sudden and progressive deterioration in control of asthma 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 (eg a course of oral corticosteroids) or antibiotic treatment if a bacterial infection is present. Patients should be advised to seek medical attention if they find the treatment ineffective or they have exceeded the prescribed dose of Symbicort.

Patients should be advised to have their rescue inhaler available at all times, either Symbicort (for asthma patients on *Symbicort maintenance and reliever therapy*) or a separate rapid-acting bronchodilator (for other patients using Symbicort as maintenance therapy only)

Symbicort therapy should not be initiated to treat a severe exacerbation.

Oral corticosteroid usage
Symbicort should not be used to initiate treatment with inhaled steroids in patients being transferred from oral steroids. Care should be taken when commencing Symbicort treatment, particularly if there is any reason to suspect that adrenal function is impaired from previous systemic steroid therapy.

Potential systemic effects of inhaled corticosteroids
Inhaled steroids are designed to direct glucocorticoid delivery to the lungs in order to reduce overall systemic glucocorticoid exposure and side effects. However, in higher than recommended doses, inhaled steroids may have adverse effects; possible systemic effects of inhaled steroids include depression of the HPA axis, reduction of bone density, cataract and glaucoma, and retardation of growth rate in children and adolescents. In steroid-dependent patients, prior systemic steroid usage may be a contributing factor but such effects may occur amongst patients who use only inhaled steroids regularly.

HPA axis suppression and adrenal insufficiency

Dose-dependant HPA axis suppression (as indicated by 24 hour urinary and/or plasma cortisol AUC) has been observed with inhaled budesonide, although the physiological circadian rhythms of plasma cortisol were preserved. This indicates that the HPA axis suppression represents a physiological adaption in response to inhaled budesonide, not necessarily adrenal insufficiency. The lowest dose that results in clinically relevant adrenal insufficiency has not been established. Very rare cases of clinically relevant adrenal dysfunction have been reported in patients using inhaled budesonide at recommended doses.

Clinically important disturbances of the HPA axis and/or adrenal insufficiency induced by severe stress (eg trauma, surgery, infection in particular gastroenteritis or other conditions associated with severe electrolyte loss) may be related to inhaled budesonide in specific patient populations. These are patients switched from oral corticosteroids (see *PRECAUTIONS – Oral corticosteroid usage*) and patients administering concomitant medication metabolised by CYP3A4 (see *Interactions with other medicines*). Monitoring for signs of adrenal dysfunction is advisable in these patient groups. For these patients additional systemic glucocorticosteroid treatment should be considered during periods of stress, a severe asthma attack or elective surgery.

Bone density

Whilst corticosteroids may have an effect on bone mass at high doses, long-term follow up (3 to 6 years) studies of budesonide treatment in adults at recommended doses, have not demonstrated a negative effect on bone mass compared to placebo, including a study

conducted in patients with a high risk of osteoporosis. The lowest dose that does effect bone mass has not been established.

Bone-mineral density measurements in children should be interpreted with caution as an increase in bone area in growing children may reflect an increase in bone volume. In 3 large, medium-to-long-term (12 months to 6 years) studies in children (5 to 16 years), no effects on bone-mineral density were observed after treatment with budesonide (189 to 1322 μg/day) compared to nedocromil, placebo or age matched controls. However, in a randomised 18 month paediatric study (n=176; 5 to 10 years), bone-mineral density was significantly decreased by 0.11 g/cm^2 (p=0.023) in the group treated with inhaled budesonide via Turbuhaler, compared with the group treated with inhaled disodium cromoglycate. The dose of budesonide was 400 μg twice daily for 1 month, 200 μg twice daily for 5 months, and 100 μg twice daily for 12 months, and the dose of disodium cromoglycate 10 mg three times daily. The clinical significance of this result remains uncertain.

Growth

Long-term studies show that children treated with inhaled budesonide ultimately achieve adult target height. However, an initial reduction of growth velocity (approximately 1 cm) has been observed and is generally within the first year of treatment. Physicians should closely follow the growth of children and adolescents taking long-term corticosteroids.

Rare individuals may be exceptionally sensitive to inhaled corticosteroids. Height measurements should be performed to identify patients with increased sensitivity. The potential growth effects of prolonged treatment should be weighed against the clinical benefit. To minimise the systemic effects of inhaled corticosteroids, each patient should be titrated to his/her lowest effective dose (see *DOSAGE & ADMINISTRATION*).

Infections/tuberculosis

Signs of existing infection may be masked by the use of high doses of glucocorticosteroids and new infections may appear during their use. Special care is needed in patients with active or quiescent pulmonary tuberculosis or fungal, bacterial or viral infections of the respiratory system.

Sensitivity to sympathomimetic amines

In patients with increased susceptibility to sympathomimetic amines (eg inadequately controlled hyperthyroidism), eformoterol should be used with caution.

Cardiovascular disorders

β_2-agonists have an arrhythmogenic potential that must be considered before commencing treatment for bronchospasm.

The effects of eformoterol in acute as well as chronic toxicity studies were seen mainly on the cardiovascular system and consisted of hyperaemia, tachycardia, arrhythmias and myocardial lesions. These are known pharmacological manifestations seen after administration of high doses of β_2-adrenoceptor agonists.

Patients with pre-existing cardiovascular conditions may be at greater risk of developing adverse cardiovascular effects following administration of β_2-adrenoreceptor agonists. Caution is advised when eformoterol is administered to patients with severe cardiovascular disorders such as ischaemic heart disease, tachyarrythmias or severe heart failure.

Hipokalaemia

High doses of β_2-agonists can lower serum potassium by inducing a redistribution of potassium from the extracellular to the intracellular compartment, via stimulation of Na^+/K^+-ATPase in muscle cells.

Potentially serious hypokalaemia may result. Particular caution is advised in acute exacerbation as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatments (see *PRECAUTIONS - Interactions with other medicines*). Patients receiving digoxin are particularly sensitive to hypokalaemia. Serum potassium levels should therefore be monitored in such situations.

Diabetes

Due to the blood-glucose increasing effects of β_2-stimulants, extra blood glucose controls are initially recommended when diabetic patients are commenced on eformoterol.

Impaired renal and hepatic function

The effect of decreased liver and kidney function on the pharmacokinetics of eformoterol and budesonide are not known. As budesonide and eformoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver disease.

Carcinogenicity

The carcinogenic potential of the budesonide/eformoterol combination has not been investigated in animal studies.

In eformoterol carcinogenicity studies performed by AstraZeneca, there was a dose dependent increase in the incidence of uterine leiomyomas in mice dosed orally at 0.1, 0.5, and 2.5 mg/kg/day for 2 years, and a mesovarian leiomyoma was observed in a female rat dosed by inhalation at 0.13 mg/kg/day for 2 years. The effects observed are expected findings with high-dose exposure to β_2-agonists.

Eformoterol carcinogenicity studies performed by other companies used systemic exposure levels 800 to 4800-fold higher than those expected upon clinical use of eformoterol (based on an 18 μg daily dose).

Some carcinogenicity activity was observed in rats and mice. However, in view of the dose levels at which these effects were observed and the fact that eformoterol is not mutagenic (except for very weak activity at high concentrations in one test system), it is concluded that the cancer risk in patients treated with eformoterol fumarate is no greater than for other β_2-adrenoceptor agonists.

The carcinogenic potential of budesonide has been evaluated in the mouse and rat at oral doses up to 200 and 50 μg/kg/day respectively. In male rats dosed with 10, 25, and 50 μg budesonide/kg/day, those receiving 25 and 50 μg/kg/day showed an increased incidence of primary hepatocellular tumours. In a repeat study, this effect was observed in a number of steroid groups (budesonide, prednisolone, triamcinolone acetonide), thus indicating a class effect of corticosteroids.

Genotoxicity

Individually, budesonide and eformoterol were not genotoxic in a series of assays for gene mutations (except for a slight increase in reverse mutation frequency in *Salmonella typhimurium* at high concentrations of eformoterol), chromosomal damage and DNA repair. The combination of budesonide and eformoterol has not been tested in genotoxicity assays.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an opthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serious

chrorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Interactions

Pharmacokinetic interactions

The metabolism of budesonide is primarily mediated by the enzyme CYP3A4. Inhibitors of this enzyme, eg ketoconazole, may therefore increase systemic exposure to budesonide. This is of limited clinical importance for short-term (1 to 2 weeks) treatment with ketoconazole, but should be taken into consideration during long-term treatment with ketoconazole or other potent CYP 3A4 inhibitors.

Pharmacodynamic interactions

Neither budesonide nor eformoterol have been observed to interact with any other drug used in the treatment of asthma.

β-receptor blocking agents

β-receptor blocking agents, especially those that are non-selective, may partially or totally inhibit the effect of β_2-agonists. These drugs may also increase airway resistance, therefore the use of these drugs in asthma patients is not recommended.

Other sympathomimetic agents

Other β-adrenergic stimulants or sympathomimetic amines such as ephedrine should not be given concomitantly with eformoterol, since the effects will be cumulative. Patients who have already received large doses of sympathomimetic amines should not be given eformoterol.

Xanthine derivatives, mineralocorticosteroids, and diuretics

Hypokalaemia may result from β_2-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, mineralocorticosteroids, and diuretics (see *PRECAUTIONS - Hypokalaemia*).

Monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines and antihistamines

The adverse cardiovascular effects of eformoterol may be exacerbated by concurrent administration of drugs associated with QT-interval prolongation and increased risk of ventricular arrhythmia. For this reason caution is advised when eformoterol is administered to patients already taking monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines, or antihistamines associated with QT-interval prolongation (eg terfenadine, astemizole).

Fertility, pregnancy, and lactation

Fertility

There are no animal studies on the effect of the budesonide/eformoterol combination on fertility.

Long-term treatment of female mice and rats with eformoterol fumarate causes ovarian stimulation, the development of ovarian cysts, and hyperplasia of granulosa/theca cells as a result of the β-agonist properties of the compound. A study by another company showed no effect on fertility of female rats dosed orally with eformoterol fumarate at 60 mg/kg/day for two weeks. This finding was repeated in an AstraZeneca study where no effect was seen on the fertility of female rats dosed orally with eformoterol fumarate at 15 mg/kg/day for two weeks.

Testicular atrophy was observed in mice given eformoterol fumarate in the diet at 0.2 to 50 mg/kg/day for 2 years, but no effect on male fertility was observed in rats dosed orally at 60 mg/kg/day for 9 weeks, in studies undertaken by another company.

Pregnancy

For the concomitant treatment with budesonide and eformoterol, no clinical data on exposed pregnancies are available. Fetal malformations (umbilical hernia and cleft palate), typical of glucocorticoid toxicity in animals, occurred in rats dosed with the Symbicort Rapihaler formulation at the inhaled dose of 12 μg/kg/day budesonide and 0.66 μg/kg/day eformoterol, with plasma AUC values for both drugs below that expected in patients at the maximum recommended clinical dose. No teratogenic effect was detected at 2.5 μg/kg/day of budesonide and 0.14 μg/kg/day of eformoterol.

Symbicort Rapihaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Only after special consideration should Symbicort Rapihaler be used during the first 3 months and shortly before delivery.

Because β-agonists, including eformoterol, may potentially interfere with uterine contractility due to a relaxant effect on uterine smooth muscle, Symbicort Rapihaler should be used during labour only if the potential benefit justifies the potential risk.

Budesonide

Results from a large prospective epidemiological study and from world-wide post marketing experience indicate no adverse effects of inhaled budesonide during pregnancy on the health of the fetus/newborn child.

If treatment with glucocorticosteroids during pregnancy is unavoidable, inhaled corticosteroids such as budesonide should be considered due to their lower systemic effect. The lowest effective dose of budesonide to maintain asthma control should be used.

Eformoterol

No teratogenic effects were observed in rats receiving eformoterol fumarate at doses up to 60 mg/kg/day orally or 1.2 mg/kg/day by inhalation. Foetal cardiovascular malformations were observed in one study in which pregnant rabbits were dosed orally at 125 or 500 mg/kg/day during the period of organogenesis, but similar results were not obtained in another study at the same dose range. In a third study, an increased incidence of subcapsular hepatic cysts was observed in foetuses from rabbits dosed orally at 60 mg/kg/day. Decreased birth weight and increased perinatal/postnatal mortality were observed when eformoterol fumarate was given to rats at oral doses of 0.2 mg/kg/day or greater during late gestation.

Lactation

Budesonide is excreted in breast milk. However, due to the relatively low doses used via the inhalational route the amount of drug present in the breast milk, if any, is likely to be low.

It is not known whether eformoterol passes into human breast milk. In rats, eformoterol was excreted into breast milk. There are no studies in lactating animals using the budesonide/eformoterol combination. Increased postnatal mortality at maternal eformoterol

doses of 0.2 mg/kg/day PO or greater, and retardation of pup growth at 15 mg/kg/day PO were observed in a rat study. There are no well-controlled human studies using Symbicort Rapihaler in nursing mothers. Because many drugs are excreted in human breast 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.

Effects on Ability to Drive and Use Machines

Driving or using machinery should be undertaken with caution until the effect of Symbicort Rapihaler on the individual is established. Symbicort Rapihaler does not generally affect the ability to drive or use machinery.

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 beta$_2$-agonist therapy, such as tremor and palpitations. These tend to be mild and disappear within a few days of treatment.

In the clinical program comparing Symbicort Rapihaler with Symbicort Turbuhaler, 679 adults and adolescents (Study 681 and Study 715) were exposed to Symbicort Rapihaler 800/24 μg daily with a median duration of 359 days and a range of 1 to 427 days.

There were no apparent differences in the overall pattern of AE's between the Symbicort Rapihaler and Symbicort Turbuhaler groups in the clinical program. The AEs were generally mild to moderate in intensity and the pattern was that usually seen in a population with persistent asthma and dominated by symptoms of upper respiratory events.

Overall, the AE profile was similar for patients receiving Symbicort Rapihaler and Symbicort Turbuhaler with regard to total daily dose, age, sex and ethnic group and no new safety concerns were identified with Symbicort Rapihaler.

If oropharyngeal *candidiasis* develops, it may be treated with appropriate anti-fungal therapy whilst still continuing with Symbicort therapy. The incidence of *candidiasis* can generally be held to a minimum by having patients rinse their mouth out with water after inhaling their maintenance dose.

Adverse reactions, which have been associated with budesonide or formoterol, are given below:

Table 4 Adverse drug reactions by frequency and system order class (SOC)

Frequency	SOC	Reaction
Common	*Cardiac disorders:*	Palpitations
≥1% - <10%	*Infections and infestations:*	Candida infections in oropharynx
	Nervous system disorders:	Headache, tremor
	Respiratory, thoracic and mediastinal disorders:	Mild irritation in the throat, coughing, hoarseness
Uncommon	*Cardiac disorders:*	Tachycardia
≥0.1% - <1%	*Gastrointestinal disorders:*	Nausea, diarrhoea
	Metabolism & nutrition disorders	Weight gain
	Musculoskeletal, connective tissue and bone disorders:	Muscle cramps
	Nervous system disorders:	Dizziness, bad taste, thrist,

Table 4	Adverse drug reactions by frequency and system order class (SOC)	
Frequency	**SOC**	**Reaction**
		tiredness
	Psychiatric disorders:	Agitation, restlessness, nervousness, sleep disturbances
	Eye disorders:	Vission blurred
Rare ≥0.01% - <0.1%	*Immune system disorders*	Immediate and delayed hypersensitivity reactions including dermatitis, exanthema, urticaria, pruritis, angioedema, and anaphylactic reaction.
	Cardiac disorders:	Cardiac arrhythmias, eg, atrial fibrillation, supraventricular tachycardia, extrasystoles
	Metabolic and nutrition disorders:	Hypokalemia
	Respiratory, thoracic and mediastinal disorders:	Bronchospasm
	Skin & subcutaneous tissue disorders	Skin bruising
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:	Hyperglycemia
	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 effects 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.

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 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. However, 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 hyper corticism and adrenal suppression, may appear.

Withdrawing Symbicort Rapihaler or decreasing the dose of budesonide will abolish these effects, although the normalization of the HPA-axis may be a slow process.

Pharmacological Properties

Pharmacodynamic Properties

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

ATC code: R03AK07

Mechanism of action and pharmacodynamic effects:
Symbicort contains formoterol and budesonide, which have different modes of action and show additive effects in terms of reduction of asthma. The specific properties of budesonide and formoterol allow the combination to be used as maintenance treatment of asthma.

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 a 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.

Clinical Trial

Asthma

Therapeutic equivalence between Symbicort Rapihaler and Symbicort Turbuhaler was demonstrated in three clinical efficacy and safety studies in adults and adolescents with asthma. They included two randomised, double-blind, active controlled, parallel-group studies, Studies 681 (12 weeks duration) and 003 (6 weeks duration); and one randomised, open-label, parallel group, long-term (12 months) study, Study 715.

No clinical studies have been conducted to directly compare the efficacy and safety of Symbicort Rapihaler 80/2.25 with Symbicort Turbuhaler 160/4.5.

In Study 681, Symbicort Rapihaler 160/4.5 (2 inhalations twice daily) was compared with the corresponding dose of budesonide pressurised metered dose inhaler (pMDI) (200 μg; 2 inhalations twice daily), or Symbicort Turbuhaler (160/4.5; 2 inhalations twice daily) in adults and adolescents (≥12 years) with moderate to severe asthma [eg mean forced expiratory volume during the first second (FEV_1) ≥50% and ≤90% of predicted normal (PN) and FEV_1 reversibility ≥12%]. Symbicort Rapihaler was shown to significantly improve morning peak expiratory flow rate (primary efficacy variable), other lung function parameters, symptom scores and use of rescue medication compared to budesonide and was equivalent to Symbicort Turbuhaler (see Table 1).

Table 1 Study 681 - Estimated treatment means and treatment contrasts: effects of 12 weeks of treatment with twice daily Symbicort Rapihaler 160/4.5, budesonide pMDI 200 and Symbicort Turbuhaler 160/4.5

Variable[†]	Symbicort Rapihaler n=234	budesonide pMDI n=217	Symbicort Turbuhaler n=229	Mean difference (95% confidence limits)	
				Symbicort Rapihaler vs budesonide pMDI	Symbicort Rapihaler vs Symbicort Turbuhaler
mPEF[§] (L/min)	29.3	0.6	32.0	28.6 (20.9, 36.4)	-2.8 (-10.4, 4.9)
ePEF (L/min)	24.3	-0.6	25.1	24.9 (17.5, 32.4)	-0.8 (-8.2, 6.6)
FEV_1 (L)	0.321	0.114	0.291	0.207 (0.135, 0.279)	0.030 (-0.042, 0.101)
Total asthma symptom score (0-6)	-0.70	-0.44	-0.84	-0.26 (-0.41, -0.11)	0.14 (-0.01, 0.29)
Nocturnal awakenings due to asthma (% nights)	-16.5	-9.7	-15.5	-6.7 (-10.6, -2.8)	-1.0 (-4.9, 2.9)

Variable[†]	Symbicort Rapihaler n=234	budesonide pMDI n=217	Symbicort Turbuhaler n=229	Mean difference (95% confidence limits)	
				Symbicort Rapihaler vs budesonide pMDI	Symbicort Rapihaler vs Symbicort Turbuhaler
Symptom-free days[Δ] (% days)	28.0	19.1	34.2	8.9 (3.1, 14.8)	-6.2 (-12.0, -0.4)
Asthma control days* (% of days)	26.5	18.3	33.1	8.2 (2.4, 14.0)	-6.5 (-12.3, -0.8)
Rescue medication use (inhalations/24 hours)	-0.94	-0.35	-0.92	-0.59 (-0.81, -0.37)	-0.02 (-0.23, 0.20)

[†] Mean change from mean of baseline to mean of the 12-week treatment period; [§]Primary efficacy variable; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; FEV_1 – forced expiratory volume during the first second; [Δ] day and night with no symptoms and a night with no awakenings; * day and night with no symptoms, no rescue medication use and a night with no awakenings.

Study 003 was a 6-week study with similar design to Study 681. In this study, Symbicort Rapihaler 40/2.25 (2 inhalations twice daily) was compared primarily (as regular therapy) with the corresponding dose of budesonide Turbuhaler 100 μg (1 inhalation twice daily), or and secondarily with Symbicort Turbuhaler 80/4.5 (1 inhalation twice daily) in adults and adolescents (≥12 years) with asthma (mean FEV_1 74% PN and FEV_1 reversibility 24%). The primary efficacy variable was the change in morning peak expiratory flow (mPEF) from baseline (mean of the 10 last days of the run-in period) to the treatment period (mean of the 6-week treatment period). The primary objective was to demonstrate that Symbicort Rapihaler 40/2.25 was more efficacious than budesonide Turbuhaler 100 μg. The adjusted mean mPEF increased by 12.2 L/min with Symbicort Rapihaler 40/2.25, 4.15 L/min with budesonide Turbuhaler, and 13.1 L/min with Symbicort Turbuhaler 80/4.5. The results showed that the mean change from baseline in mPEF was greater with Symbicort Rapihaler 40/2.25 than with budesonide Turbuhaler, and that the mean difference was statistically significant (mean difference of 8.07 L/min [95% CI: 3.26 to 12.9], p=0.001). The secondary objective was to demonstrate therapeutic equivalence of Symbicort Rapihaler 40/2.25 and Symbicort Turbuhaler 80/4.5. The results supported equivalence of the two Symbicort formulations as regular treatment in both the ITT and per-protocol analyses. There was no statistically significant difference between the two Symbicort formulations for any outcome variable in this study.

Study 715 investigated primarily the safety of Symbicort Rapihaler 160/4.5 (2 inhalations twice daily) during 12 months. The reference treatment was the corresponding dose of Symbicort Turbuhaler 160/4.5 and in a population consisting of adults and adolescents (≥12 years) with moderate to severe asthma (eg mean FEV_1 of ≥50% of PN and FEV_1 reversibility ≥12%). The study was of an open-label design.

There was no statistically significant difference between Symbicort Rapihaler and Symbicort Turbuhaler regarding FEV_1 and FVC (forced vital capacity). The percentage of patients experiencing one or more severe asthma exacerbations did not differ between the two Symbicort groups: 11% in the Symbicort Rapihaler group and 13% in the Symbicort Turbuhaler group. The maximum number of severe exacerbations per patient was 6 in the Symbicort Rapihaler group and 4 in the Symbicort Turbuhaler group. There was no statistical significant difference in time to first severe asthma exacerbation between the two treatment groups.

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 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.

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 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.

List of Excipients
Apaflurane (HFA 227)
Povidone K25
Macrogol (polyethylene glycol) 1000

Incompatibilities
Not applicable.

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

Special precautions for storage
Do not store above 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.

Instructions for use, handling and disposal
See section 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.

Note: It is important to instruct the patient to:

- Carefully read the instructions for use in the Patient Information Leaflet, which is packed with each inhaler.
- Carefully read the instructions for use in the instruction leaflet which is packed with each spacer device

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.

Pack size

Box, 1 Rapihaler 80/4.5µg/dose, 120 doses in box (Reg. No.: DKI2004900268A1)

HARUS DENGAN RESEP DOKTER

Imported by:
PT AstraZeneca Indonesia,
Cikarang, Bekasi - Indonesia

Manufactured by:
AstraZeneca Dunkerque Production
224 Avenue de la Dordogne,
BP 41 F-59944 Dunkerque Cedex2 France

Latest revision	: 06 February 2025
Document number	: VV-RIM-07868679

Proposed packaging material		
Code	SYMBICORT RAPIHALER 80/4.5-PIL-02.01	
Regulatory Objective	☐NDA ☒Renewal ☐Variation change detail no.: RO-Obligation Event-0011687	
Code of previous version	SYMBICORT RAPIHALER 160/4.5-PIL-01.01	
Reference	☐CDS version: N/A ☐CPIL version: N/A	☐SmPC country/version/date: N/A ☐RAM approval: N/A
Changes	Renewal submission	
Name	ADR	

Informasi Leaflet untuk Pasien
Symbicort® Rapihaler 80/4.5, Suspensi (*Pressured Metered Dose Inhaler* / pMDI)
budesonide/formoterol fumarate dihydrate

Bacalah leaflet ini secara keseluruhan dengan seksama sebelum Anda menggunakan obat ini karena obat ini mengandung informasi penting untuk Anda

- Simpanlah leaflet ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan berikan obat ini kepada orang lain. Karena ini bisa membahayakan mereka, bahkan jika tanda-tanda penyakit mereka sama dengan Anda.
- Jika Anda mendapatkan efek samping, konsultasikanlah dengan dokter atau apoteker Anda. Ini termasuk kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Lihat bagian 4.

Apa yang ada dalam leaflet ini:

1. Apa itu Symbicort Rapihaler dan untuk apa obat ini digunakan

Asma

Symbicort Rapihaler diindikasikan dalam pengobatan asma secara teratur di mana penggunaan kombinasi (kortikosteroid inhalasi dan agonis β2 kerja panjang) sesuai. Ini termasuk :

- pasien tidak cukup terkontrol dengan kortikosteroid inhalasi dan agonis β2 kerja pendek “jika perlu”, atau
- pasien yang sudah terkontrol dengan kortikosteroid inhalasi dan agonis β2 kerja panjang.

2. Apa yang perlu Anda ketahui sebelum Anda menggunakan Symbicort Rapihaler

Jangan gunakan Symbicort Rapihaler:

- Jika Anda alergi terhadap budesonide, formoterol, atau bahan lain dari obat ini (tercantum dalam bagian 6).

- Beberapa gejala reaksi alergi yang mungkin termasuk:
  - ❖ Ruam, gatal atau gatal-gatal pada kulit,
  - ❖ Sesak napas, mengi atau kesulitan bernapas, dan
  - ❖ Pembengkakan wajah, bibir, lidah atau bagian lain dari tubuh.
- Jangan berikan Symbicort Rapihaler 160/4.5 kepada anak dengan usia < 12 tahun. Terdapat dosis lebih rendah untuk terapi asma pada anak-anak.
- Dokter Anda harus memberikan Anda Rencana Tindakan Asma pribadi untuk membantu mengelola asma Anda. Rencana ini akan mencakup obat-obatan apa yang harus dikonsumsi secara teratur untuk mengendalikan asma Anda, serta obat pereda apa yang harus digunakan ketika asma tiba-tiba menyerang anda. Dokter Anda mungkin telah memberi resep Symbicort Rapihaler untuk Anda gunakan sebagai obat pencegah dan penghilang.
- Jangan gunakan Symbicort rapihaler setelah tanggal kadaluarsa (EXP) yang tercantum pada kemasan atau jika kemasannya sobek atau menunjukkan tanda kerusakan.
- Jika telah kadaluarsa atau rusak, kembalikan pada apoteker anda untuk dibuang.
- Jika anda tidak yakin apakah anda harus memulai menggunakan obat ini, hubungi dokter anda.
- Hubungi dokter anda jika anda memiliki alergi terhadap obat lain, makanan, bahan tambahan atau pewarna.

Peringatan dan pencegahan

Bicaralah dengan dokter atau apoteker Anda sebelum menggunakan Symbicort Rapihaler jika :

- Anda memiliki masalah dengan kelenjar tiroid atau adrenal.
- Anda memiliki riwayat penyakit diabetes
- Anda memiliki masalah dengan jantung
- Anda memiliki masalah dengan hati
- Anda memiliki kadar potasium yang rendah dalam darah.
- Anda memiliki riwayat penyakit tuberkulosis (TB)

Mungkin tidak aman bagi Anda untuk menggunakan Symbicort Rapihaler jika Anda memiliki, atau pernah mengalami, salah satu kondisi ini.

Obat-obatan lain dan Symbicort Rapihaler

Katakan kepada dokter atau apoteker Anda jika Anda baru-baru ini menggunakan obat lain.

Secara khusus, beri tahu dokter atau apoteker Anda jika menggunakan salah satu obat berikut.

- Obat-obatan yang digunakan untuk mengobati masalah jantung atau tekanan darah tinggi seperti beta-blocker, diuretik dan antiaritmia (disopiramide, procainamide dan quinidine)
- Obat-obatan yang digunakan untuk mengobati glaucoma seperti beta-bloker.
- Obat-obatan yang digunakan untuk mengobati depresi atau mood/mental disorder lainnya seperti tricyclic antidepresan, monoamine oxidase inhibitor and phenothiazines.
- Obat-obatan yang digunakan untuk mengobati demam tinggi, batuk, pilek seperti antihistamin.
- Obat-obatan yang digunakan untuk mengobati infeksi jamur seperti ketoconazole.

- Turunan xantin (misalnya teofilin) yang merupakan kelas obat yang digunakan untuk mengobati asma dan PPOK.

Obat-obatan ini mungkin dapat dipengaruhi oleh Symbicort Rapihaler atau dapat mempengaruhi seberapa baik kerjanya. Anda mungkin memerlukan jumlah obat yang berbeda, atau Anda mungkin perlu menggunakan obat-obatan yang berbeda. Dokter atau apoteker Anda akan menyarankan Anda.
Dokter dan apoteker Anda memiliki informasi lebih lanjut tentang obat-obatan untuk berhati-hati atau menghindari saat menggunakan Symbicort Rapihaler.

Kehamilan, menyusui dan kesuburan

- Jika Anda hamil, atau berencana untuk hamil, bicaralah dengan dokter Anda sebelum menggunakan Symbicort Rapihaler - jangan gunakan Symbicort Rapihaler kecuali dokter Anda menyuruh Anda mengkonsumsinya.
- Jika Anda hamil saat menggunakan Symbicort Rapihaler, jangan berhenti menggunakan Symbicort Rapihaler tetapi segera hubungi dokter Anda.
- Jika Anda sedang menyusui, bicarakan dengan dokter Anda sebelum menggunakan Symbicort Rapihaler.

Mengemudi dan menggunakan mesin

Symbicort Rapihaler dapat menyebabkan pusing, lelah atau mengantuk pada beberapa orang ketika mereka mulai menggunakannya.

3. Bagaimana cara menggunakan Symbicort Rapihaler

- Bacalah dengan cermat instruksi untuk digunakan dalam leaflet informasi pasien yang dikemas bersama dengan setiap inhaler Symbicort Rapihaler.
- Kocok inhaler dengan lembut sebelum digunakan untuk mencampur isinya dengan benar.
- Menghirup inhaler dengan menggerakkannya dua kali ke udara ketika inhaler baru, jika belum digunakan selama lebih dari satu minggu atau jika telah dijatuhkan.
- Tempatkan corong di mulut. Sambil bernapas perlahan dan dalam, tekan perangkat dengan kuat untuk melepaskan obat. Lanjutkan untuk bernapas dan tahan nafas selama kurang lebih 10 detik atau selama itu nyaman. Kocok inhaler lagi dan ulangi langkah ini untuk inhalasi kedua.
- Bilas mulut dengan air setelah menghirup dosis pemeliharaan untuk meminimalkan risiko sariawan orofaringeal.
- Bersihkan corong inhaler secara teratur, setidaknya sekali seminggu dengan lap kering yang bersih. Jangan masukkan inhaler ke dalam air.

Jika asma Anda telah terkendali untuk beberapa waktu, dokter Anda mungkin mengatakan kepada Anda untuk mengambil kurang semburan Symbicort Rapihaler atau memberi Anda kekuatan yang lebih rendah dari Symbicort Rapihaler.
Jika Anda menggunakan lebih banyak pernafasan obat pereda atau Anda mengi atau sesak napas lebih dari biasanya memberitahu dokter Anda sebagai asma Anda mungkin semakin parah.

Lama penggunaan
Jika dokter anda memberitahu untuk menggunakan Symbicort Rapihaler setiap hari, penting untuk anda gunakan setiap hari meskipun anda merasa sudah baik.

Tetap gunakan selama dokter masih meminta anda untuk menggunakannya. Jangan berhenti kecuali atas perintah dokter.

Informasi penting tentang gejala asma Anda

Dosis yang biasa digunakan adalah 1 sampai 2 inhalasi Symbicort Rapihaler 80/4.5 dua kali sehari untuk orang dewasa dan anak-anak berusia 6 tahun atau lebih.

Dokter Anda harus memberi tahu Anda cara terbaik untuk mengelola gejala dan flare up Anda. Ini mungkin termasuk obat-obatan tambahan (seperti obat-obatan pereda) untuk digunakan ketika Anda mengalami serangan sesak napas mendadak.

Jika Anda menggunakan lebih banyak pernafasan obat pereda atau Anda mengalami sesak napas lebih dari biasanya memberitahu dokter Anda.

Jika Anda melewatkan dosis Symbicort Rapihaler, ambil dosis Anda segera setelah Anda ingat. Jangan gunakan dosis ganda untuk menebus dosis yang Anda lewatkan.
Ini dapat meningkatkan kemungkinan Anda mendapatkan efek samping yang tidak diinginkan.

Membersihkan Symbicort Rapihaler

Bersihkan bagian luar corong dengan kain/tisu kering. Jangan gunakan air atau cairan.

4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mendapatkannya.

Jika salah satu dari hal berikut terjadi pada Anda, bicaralah kepada dokter Anda:

- perih, kekuningan, bercak di mulut (sariawan)
- suara serak
- iritasi pada lidah dan mulut
- batuk

(Ini kurang mungkin terjadi jika Anda berkumur setelah setiap kali Anda menggunakan dosis Symbicort Rapihaler di pagi dan / atau malam hari)

- Gemetar
- Merasa cemas, gugup, gelisah atau kesal
- Denyut jantung cepat atau tidak teratur atau jantung berdebar
- Sakit pada bagian dada
- Sakit kepala
- Pusing
- Haus
- Rasa tidak enak di mulut Anda
- Mual
- Diare
- Kesulitan tidur
- Otot berkedut atau kram
- Ruam kulit
- Kelelahan
- Kenaikan berat badan
- Memar kulit

Jika salah satu dari hal berikut terjadi pada Anda, bicaralah segera kepada dokter Anda:

- Kesulitan bernapas atau memburuknya masalah pernapasan Anda
- Pembengkakan wajah, bibir, lidah atau bagian lain dari tubuh
- Ruam yang parah
- Suasana hati berubah

Ini mungkin efek samping yang serius. Anda mungkin membutuhkan tindakan medis secepatnya. Efek samping yang serius jarang terjadi.

Pelaporan efek samping

Jika anda mengalami efek samping, diskusikan dengan dokter, apoteker atau perawat anda. Ini dapat termasuk efek samping yang tidak disebutkan dalam leaflet ini. Dengan melaporkan efek samping, anda juga dapat menambah informasi mengenai keamanan obat ini. Untuk melaporkan efek samping, anda dapat menghubungi nomor: +628121064222 atau email: AE.Indonesia@astrazeneca.com.

5. Cara menyimpan Symbicort Rapihaler

- Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
- Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tercantum pada karton atau pada label inhaler. Tanggal kadaluwarsa mengacu pada hari terakhir bulan itu.
- Obat ini tidak memerlukan kondisi penyimpanan khusus.
- Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.
- Bagian *mouthpiece* dari rapihaler harus dibersihkan dengan kain bersih dan kering/tisu dan tidak boleh terbasahi.
- Simpan Symbicort Rapihaler dalam tempat yang sejuk dan kering, dimana suhu tetap terjaga dibawah 30 derajat celcius.
- Selalu ganti penutup *mouthpiece* setelah menggunakan Symbicort Rapihaler
- Buang Symbicort Rapihaler 3 bulan setelah dikeluarkan dari *foil puch*
- Jangan simpan Symbicort Rapihaler atau obat-obatan lain di kamar mandi atau dekat dengan lubang pembuangan. Jangan tinggalkan di dalam mobil pada hari yang panas di bawah *windowsill*. Panas dan lembab dapat merusak obat.
- Tabung di rapihaler Symbicort berisi cairan bertekanan. Jangan sampai terkena suhu tinggi dari 50 derajat celcius. Jangan menusuk tabung. Tabung tidak boleh rusak, tertusuk atau terbakar, bahkan ketika terlihat kosong.

6. Isi kemasan dan informasi lainnya

Apa kandungan Symbicort Rapihaler 80/4.5

Symbicort Rapihaler mengandung budesonide dan formoterol (eformoterol) fumarate dihydrate sebagai bahan aktif. Bahan lainnya adalah apaflurane (HFA-227), macrogol 1000 dan povidone. Symbicort Rapihaler tidak mengandung laktosa, sukrosa, gluten, tartrazine atau pewarna azo lainnya.

Seperti apa Symbicort Rapihaler 80/4.5 dan isi kemasannya

Symbicort Rapihaler adalah inhaler dosis terukur bertekanan dengan penghitung dosis. Inhaler terdiri dari kanister aluminium bertekanan dengan penghitung dosis terlampir, casing plastik merah dengan corong putih dan penutup corong abu-abu yang melekat. Setiap inhaler secara individual dibungkus dalam kantong laminasi foil (mengandung sachet zat pengering).

Symbicort Rapihaler berisi 120 puff (penarikan) dan tersedia dalam dua kekuatan: 80/4.5 dan 160/4.5. Setiap paket berisi 1 rapihaler.

Tidak semua ukuran paket dapat dipasarkan.

Kemasan:
Dus, terdiri dari 1 rapihaler berisi 120 dosis dengan kekuatan 160/4.5 µg
Dus, terdiri dari 1 rapihaler berisi 120 dosis dengan kekuatan 80/4.5 µg

Diproduksi oleh
AstraZeneca Dunkerque Production
224 Avenue de la Dordogne,
BP 41 F-59944 Dunkerque Cedex2 France

Diimport oleh:
PT. AstraZeneca Indonesia
Cikarang, Bekasi – Indonesia

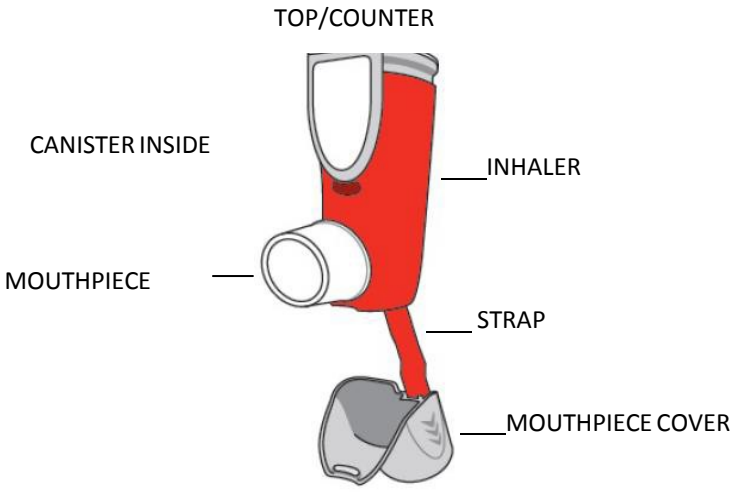
HARUS DENGAN RESEP DOKTER

Nomor Izin Edar : DKI2004900268A1 (80/4.5 mcg)
DKI2004900268B1 (160/4.5 mcg)

Latest revision : 06 February 2025
Document number : VV-RIM-07868733

Inhaler Anda :

Inhaler Anda sudah akan dipasang saat Anda pertama kali menerimanya. Tolong jangan pisahkan bagian inhaler Anda. Jika inhaler menjadi longgar, maka tempatkan kembali dan terus gunakan seperti yang diinstruksikan.



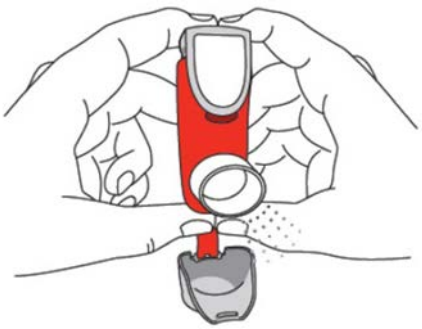
Gambar 1

Persiapkan inhaler anda untuk digunakan :

Ambil inhaler Anda dari foil pelindung sebelum digunakan untuk pertama kalinya dan buang foil pelindung. Jika inhaler Anda baru, jika belum digunakan selama satu minggu atau lebih, atau telah jatuh, kocok perlahan dan lepaskan 2 puff di udara untuk mempersiapkannya sebelum digunakan.

ı digı

atau



Gambar 2 **Gambar 3**

Cara Menggunakan Obat anda :
1. Kocok inhaler dengan perlahan sebelum digunakan.
2. Lepaskan penutup corong.
3. Pegang inhaler tegak di depan mulut Anda, dengan menggunakan ibu jari Anda di dasar

inhaler dan jari telunjuk Anda di atas, seperti yang ditunjukkan pada gambar. Lalu bernapas sejauh yang Anda bisa dan letakkan corong dengan lembut di mulut Anda, di antara gigi Anda, dan tutup bibir Anda di sekitarnya.
4. Mulailah bernapas dalam-dalam, nyaman dan perlahan melalui mulut Anda, tekan dengan kuat pada inhaler untuk melepaskan obat.
5. Lanjutkan untuk bernapas dan tahan napas Anda selama sekitar 10 detik atau selama itu nyaman, ambil inhaler dari mulut dan jari Anda dari bagian atas inhaler.
6. Ambil puff lain, seperti yang diarahkan oleh dokter Anda, kocok inhaler dengan lembut lalu ulangi langkah 3 hingga 5.
7. Letakkan penutup corong untuk mencegah debu dan kotoran lainnya masuk ke obat Anda.
8. Bilas mulut Anda dengan air untuk menghilangkan kelebihan obat.

Gambar 4

Informasi Penting:

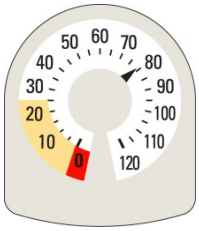
Instruksi Pembersihan :

Alat inhaler Anda harus dibersihkan secara teratur, setidaknya sekali seminggu dan untuk melakukan ini Anda perlu :

1. Lepaskan penutup corong.
2. Bersihkan bagian dalam dan luar corong dengan kain bersih yang kering.
3. Pasang kembali penutup corong.
4. Jangan memasukkan inhaler ke dalam air.
5. Jangan mencoba untuk memisahkan bagian inhaler.

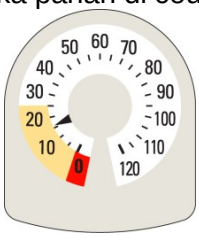
Cara membaca indikator :

- Panah di bagian atas inhaler menunjukkan jumlah penarikan (puff) yang tersisa di inhaler Anda.



- Penghitung akan menghitung mundur ke nol (“0”) setiap kali Anda melepaskan obat (baik saat menyiapkan inhaler untuk digunakan atau saat meminum obat).

- Ketika panah di counter masuk ke area kuning, ini berarti ada sekitar 20 puff tersisa.



• Sangat penting untuk dicatat jumlah inhalasi (puff) yang tersisa di inhaler SYMBICORT Anda dengan membaca counter. Buang SYMBICORT setelah penghitung mencapai nol ("0"), menunjukkan bahwa Anda telah menggunakan jumlah inhalasi pada label dan kotak produk. Inhaler Anda mungkin tidak terasa kosong dan mungkin terus beroperasi, tetapi Anda tidak akan mendapatkan jumlah obat yang tepat jika Anda tetap menggunakannya.