SYMBICORT TURBUHALER®
(budesonide/formoterol fumarate dihydrate)

1. NAME OF THE MEDICINAL PRODUCT

Symbicort Turbuhaler
80/4.5, 160/4.5 and 320/9 µg/dose
budesonide/formoterol
Inhalation powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose that leaves the mouthpiece) contains: budesonide 80 or 160 or 320 micrograms/inhalation and formoterol fumarate dihydrate 4.5 or 9 micrograms/inhalation.

Symbicort Turbuhaler 80/4.5 micrograms/inhalation delivers the same amount of budesonide and formoterol as the corresponding Turbuhaler monoproducts, i.e. budesonide 100 micrograms/inhalation (metered dose) and formoterol 6 micrograms/inhalation (metered dose) alternatively labelled as 4.5 micrograms/inhalation (delivered dose). Excipient: Lactose monohydrate 810 micrograms per dose.

Symbicort Turbuhaler 160/4.5 micrograms/inhalation delivers the same amount of budesonide and formoterol as the corresponding Turbuhaler monoproducts, i.e. budesonide 200 micrograms/inhalation (metered dose) and formoterol 6 micrograms/inhalation (metered dose) alternatively labelled as 4.5 micrograms/inhalation (delivered dose). Excipient: Lactose monohydrate 730 micrograms per dose.

Symbicort Turbuhaler 320/9 micrograms/inhalation delivers the same amount of budesonide and formoterol as the corresponding Turbuhaler monoproducts, i.e. budesonide 400 micrograms/inhalation (metered dose) and formoterol 12 micrograms/inhalation (metered dose) alternatively labelled as 9 micrograms/inhalation (delivered dose). Excipient: Lactose monohydrate 491 micrograms per dose.

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

3. PHARMACEUTICAL FORM

Inhalation powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Table 1. Therapeutic Indications

	Symbicort Turbuhaler 80/4.5 µg/dose	**Symbicort Turbuhaler 160/4.5 µg/dose**	**Symbicort Turbuhaler 320/9 µg/dose**
Asthma	Symbicort is indicated in the regular treatment of	Symbicort Turbuhaler is indicated in the	Symbicort is indicated in the regular treatment

	asthma where use of a combination (inhaled corticosteroid and long acting β_2 agonist) is appropriate: - patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short acting β_2 agonists or - patients already adequately controlled on both inhaled corticosteroids and long acting β_2 agonists. **Note:** Symbicort Turbuhaler 80/4.5 micrograms/inhalation is not appropriate in patients with severe asthma.	treatment of asthma to achieve overall asthma control, including the prevention and relief of symptoms as well as the reduction of the risk of exacerbations. Symbicort Turbuhaler is indicated for treatment of asthma, where the use of inhaled corticosteroids is appropriate.	of asthma where use of a combination (inhaled corticosteroid and long acting β_2 agonist) is appropriate: - patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short acting β_2 agonists or - patients already adequately controlled on both inhaled corticosteroids and long acting β_2 agonists.
Chronic Obstructive Pulmonary Disease (COPD)	-	Symptomatic treatment of patients with COPD with FEV_1 <70% predicted normal (post-bronchodilator) and a history of repeated exacerbations, despite regular long-acting bronchodilator therapy (see Section 4.4 special warnings and precautions for use).	

4.2 Posology and method of administration

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

Asthma

Symbicort can be used according to different treatment approaches:

A. Symbicort anti-inflammatory reliever therapy.

B. Symbicort anti-inflammatory reliever plus maintenance therapy.

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

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

Symbicort Turbuhaler 160/4.5 µg/dose

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

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

Recommended doses:

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

Adults and adolescents (12 years and older): Patients should take 1 inhalation as needed in response to symptoms and for the prevention of allergen- or exercise-induced bronchoconstriction to control asthma. If symptoms persist after a few minutes, 1 additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion.

A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. Patients using more than 8 inhalations daily should be reassessed for alternative explanations of persisting symptoms.

Children under 12 years: Efficacy and safety of Symbicort anti-inflammatory reliever therapy in children under 12 years have not been studied.

B. Symbicort anti-inflammatory reliever plus maintenance therapy:

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

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

Recommended doses:

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

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

AGE Group	Symbicort Turbuhaler 80/4.5 µg/dose	Symbicort Turbuhaler 160/4.5 µg/dose
Adults and adolescents (12 years and older):	Patients should take 1 inhalation as needed in response to symptoms. If symptoms persist after a few minutes, 1 additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion. Patients also take the recommended maintenance dose, which is 2 inhalations per day, given either as 1 inhalation in the morning and evening or as 2 inhalations in either the morning or evening. A total daily dose of more than 8 inhalations is not normally needed, however a total daily dose of up to 12 inhalations could be used for a limited period. Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice. They should be reassessed and their maintenance therapy should be reconsidered.	Physicians should discuss allergen exposure and exercise patterns with the patients and take these into consideration when recommending the dose frequency. Patients should take 1 inhalation as needed in response to symptoms and for the prevention of allergen- or exercise-induced bronchoconstriction to control asthma. If symptoms persist after a few minutes, 1 additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion. Patients also take the recommended maintenance dose, which is 2 inhalations per day, given either as 1 inhalation in the morning and evening or as 2 inhalations in either the morning or the evening. For some patients, a maintenance dose of 2 inhalations twice daily may be appropriate. A total daily dose of more than 8 inhalations is not normally needed, however a total daily dose of up to 12 inhalations could be used for a limited period. Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice. They should be reassessed and their

AGE Group	Symbicort Turbuhaler 80/4.5 µg/dose	Symbicort Turbuhaler 160/4.5 µg/dose
		maintenance therapy should be reconsidered.
Children under 12 years:	Symbicort anti-inflammatory reliever plus maintenance therapy is not recommended for children under 12 years.	

C. Symbicort maintenance therapy (fixed dose):

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

Recommended doses:

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

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

Table 3. Dosing instructions – Symbicort maintenance therapy

AGE Group	Symbicort Turbuhaler 80/4.5 µg/dose	Symbicort Turbuhaler 160/4.5 µg/dose	Symbicort Turbuhaler 320/9 µg/dose
Adults (18 years and older):	1 or 2 inhalations twice daily. Some patients may require up to a maximum of 4 inhalations twice daily.	1 or 2 inhalations twice daily. Some patients may require up to a maximum of 4 inhalations twice daily.	1 inhalation twice daily. Some patients may require up to a maximum of 2 inhalations twice daily.
Adolescents (12-17 years):	1 or 2 inhalations twice daily.	1 or 2 inhalations twice daily. During worsening of asthma, the dose may temporarily be increased to a maximum of 4 inhalations twice daily.	1 inhalation twice daily.
Children (6 years and older):	2 inhalations twice daily.	A lower strength is available for children 6-11 years.	
Children under 6 years:	Symbicort Turbuhaler is not recommended for children under 6 years of age.		

COPD

Table 4. Dosing instructions – COPD

AGE Group	Symbicort Turbuhaler 160/4.5 µg/dose	Symbicort Turbuhaler 320/9 µg/dose
Adults:	2 inhalations twice daily.	1 inhalation twice daily.

General information

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

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

Instructions for correct use of Symbicort Turbuhaler:

Turbuhaler is inspiratory flow-driven, which means that when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

Note: It is important to instruct the patient

- To carefully read the instructions for use/handling written at the end of this leaflet.
- To breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs.
- Never to breathe out through the mouthpiece.
- To replace the cover of the Symbicort Turbuhaler after use.
- Rinse the mouth with water after inhaling the maintenance dose to minimise the risk of oropharyngeal thrush.

The patient may not taste or feel any medication when using Symbicort Turbuhaler due to the small amount of drug dispensed.

4.3 Contraindications

Hypersensitivity (allergy) to budesonide, formoterol or lactose (which contains small amounts of milk proteins).

4.4 Special warnings and precautions for use

Dosing advice

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

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

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

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

Symbicort Turbuhaler 80/4.5 µg/dose

The reliever inhalations of Symbicort should be taken in response to asthma symptoms but are not intended for regular prophylactic use, e.g. before exercise. For such use, a separate rapid-acting bronchodilator should be considered.

Deterioration of disease

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

If patients find the treatment ineffective or exceed the prescribed dose, 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, such as a course of oral corticosteroids, or antibiotic treatment if an infection is present. For treatment of severe exacerbations, a combination product of inhaled corticosteroid and long-acting β_2 agonist alone is not sufficient.

Paradoxical bronchospasm

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. Symbicort Turbuhaler should then be discontinued; treatment should be re-assessed and alternative therapy instituted if necessary. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway (see Section 4.8 Undesirable effects).

Systemic effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

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

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

Transfer from oral therapy

If there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy, care should be taken when transferring patients to Symbicort Turbuhaler therapy.

Particular care is needed in patients transferring from oral steroids, since they may remain at risk of impaired adrenal function for a considerable time. Patients who have required high-dose emergency corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroid, 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.

Excipients

Symbicort Turbuhaler contains lactose (<1 mg/inhalation). This amount does not normally cause problems in lactose-intolerant people. The excipient lactose contains small amounts of milk proteins, which may cause allergic reactions.

Interaction with other medicinal products

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

Caution with special diseases

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

Caution should be observed when treating patients with prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval.

Potentially serious hypokalaemia may result from high doses of β_2 agonists. Concomitant treatment of β_2 agonists with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g., xanthine-derivatives, steroids and diuretics may add to a possible hypokalaemic effect of the β_2 agonist. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalaemia adverse effects is increased. It is recommended that serum potassium levels are monitored during these circumstances.

As for all β_2 agonists, additional blood glucose controls should be considered in diabetic patients.

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

Paediatric population

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with

the aim of reducing the dose of inhaled corticosteroid. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide will ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment.

COPD population

There are no clinical study data on Symbicort Turbuhaler available in COPD patients with a pre-bronchodilator FEV_1 >50% predicted normal and with a postbronchodilator FEV_1 <70% predicted normal (see Section 5.1 Pharmacodynamic properties).

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

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

Pharmacodynamic interactions

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

Concomitant treatment with quindine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), monoamine oxidase inhibitors and tricyclic anti-depressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias.

In addition, L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards β_2-sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors including agents with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions.

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

Concomitant use of other β-adrenergic drugs can have a potentially additive effect.

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

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

4.6 Pregnancy and lactation

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

There are no adequate data from use of formoterol in pregnant women. In animal studies, formoterol has caused adverse effects in reproduction studies at very high systemic exposure levels (see Section 5.3 Preclinical safety data).

Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies, glucocorticosteroids have been shown to induce malformations (see Section 5.3 Preclinical safety data). This is not likely to be relevant for humans given recommended doses.

Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the teratogenic dose range.

During pregnancy, Symbicort Turbuhaler should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used.

Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the nursing infant are anticipated. It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of Symbicort Turbuhaler to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Since Symbicort Turbuhaler contains both budesonide and formoterol, the same pattern of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side-effects of β_2 agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment. In a 3-year clinical trial with budesonide in COPD,

skin bruises and pneumonia occurred at a frequency of 10% and 6%, respectively, compared with 4% and 3% in the placebo group ($p<0.001$ and $p<0.01$, respectively).

Adverse reactions, which have been associated with budesonide or formoterol, are given in Table 5, listed by system organ class and frequency. Frequency is defined as: very common ($\geq$1/10), common ($\geq$1/100 and <1/10), uncommon ($\geq$1/1000 and <1/100), rare ($\geq$1/10 000 and <1/1000) and very rare (<1/10 000).

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

Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Rare	Cardiac arrhythmias, e.g., atrial fibrillation, supraventricular tachycardia, extrasystoles
	Very rare	Angina pectoris
Endocrine disorders	Very rare	Signs or symptoms of systemic glucocorticosteroid effects e.g. adrenal suppression, growth retardation, decrease in bone mineral density, cataract and glaucoma
Gastrointestinal disorders	Uncommon	Nausea
Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions, e.g., exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction
Infections and infestations	Common	Candida infections in the oropharynx Pneumonia (in COPD patients)
Metabolic and nutrition disorders	Rare	Hypokalaemia
	Very rare	Hyperglycaemia
Musculoskeletal, connective tissue and bone disorders	Uncommon	Muscle cramps
Nervous system disorders	Common	Headache, tremor
	Uncommon	Dizziness
	Very rare	Taste disturbances
Psychiatric disorders	Uncommon	Agitation, restlessness, nervousness, sleep disturbances
	Very rare	Depression, behavioural disturbances (mainly in children)
Respiratory, thoracic and mediastinal disorders	Common	Mild irritation in the throat, coughing, hoarseness
	Rare	Bronchospasm
Skin and subcutaneous tissue disorders	Uncommon	Bruises
Vascular disorders	Very rare	Variations in blood pressure

Eye disorders	Unknown	Blurred vision

As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases (see Section 4.4 Special warning and precautions for use).

Systemic effects of inhaled corticosteroids may occur particularly at high doses prescribed for prolonged periods. These may include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma (see Section 4.4 Special warnings and precautions for use).

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

The excipient lactose contains small amounts of milk proteins. These may cause allergic reactions.

4.9 Overdose

An overdose of formoterol would likely lead to effects that are typical for β_2-adrenergic agonists: tremor, headache, palpitations. Symptoms reported from isolated cases are tachycardia, hyperglycaemia, hypokalaemia, prolonged QTc-interval, arrhythmia, nausea and vomiting. Supportive and symptomatic treatment may be indicated. A dose of 90 micrograms administered during three hours in patients with acute bronchial obstruction and when given three times daily as a total of 54 micrograms/day for 3 days to stable asthmatics raised no safety concerns.

Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses, systemic glucocorticosteroid effects, such as hypercorticism and adrenal suppression, may appear.

If Symbicort therapy has to be withdrawn due to overdose of the formoterol component of the drug, provision of appropriate inhaled corticosteroid therapy must be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanisms of action and pharmacodynamic effects

Symbicort Turbuhaler contains formoterol and budesonide, which have different modes of action and show additive effects in terms of reduction of asthma exacerbations. The specific properties of budesonide and formoterol allow the combination to be used both as reliever therapy and as maintenance therapy. The mechanisms of action of the two substances, respectively 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 glucocortisteroids is unknown.

Formoterol

Formoterol is a selective β_2-adrenergic agonist that when inhaled results in a rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose dependent, with an onset of effect within 1-3 minutes after inhalation. The duration of effect is at least 12 hours after a single dose.

Symbicort Turbuhaler

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

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

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

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

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

clinically meaningful (as assessed by a difference of greater than or equal to 0.5). These results were observed in a clinical study setting with considerably higher adherence to budesonide maintenance dosing than expected in real life.

In the SYGMA studies, increases in lung function compared to baseline (mean prebronchodilator FEV_1) were statistically significantly larger for patients on Symbicort anti-inflammatory reliever therapy compared to patients on as-needed short-acting β_2 agonist treatment. Statistically significantly smaller increases were observed for Symbicort as needed compared to a maintenance dose of budesonide (1 inhalation of 200 micrograms/inhalation twice daily) given with a short-acting β_2 agonist to be used as needed. For both comparisons, mean differences in treatments' effect were small (approximately 30 to 55 mL, equating to approximately 2% of the baseline mean).

Overall, the results of the SYGMA studies show that Symbicort anti-inflammatory reliever therapy is a more effective treatment than a short-acting β_2 agonist as needed in patients with mild asthma. In addition, these studies suggest that the as-needed use of Symbicort may be considered an alternative treatment option for patients with mild asthma who are eligible for inhaled corticosteroid treatment.

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

Symbicort anti-inflammatory reliever plus maintenance therapy provided statistically significant and clinically meaningful reductions in severe exacerbations for all comparisons in all 5 studies. This included a comparison with Symbicort at a higher maintenance dose with terbutaline as reliever (study 735) and Symbicort at the same maintenance dose with either formoterol or terbutaline as reliever (study 734) (Table 6). In Study 735, lung function, symptom control, and reliever use were similar in all treatment groups. In Study 734, symptoms and reliever use were reduced and lung function improved, compared with both comparator treatments. In the 5 studies combined, patients receiving Symbicort anti-inflammatory reliever plus maintenance therapy used, on average, no reliever inhalations on 57% of treatment days. There was no sign of development of tolerance over time.

Table 6. Overview of severe exacerbations in clinical studies

Study No. Duration	**Treatment groups[a]**	**N**	**Severe exacerbations[b]**	
			Events	**Events/ patient -year[c]**
SYGMA 1 (Therapy A*) >12 years	Symbicort 160/4.5 µg bd as needed	1277	77	0.07
	Terbutaline 0.4 mg as needed	1277	188	0.20[d]
	Budesonide 200 µg bd + terbutaline 0.4 mg as needed	1282	89	0.09[e]
SYGMA 2 (Therapy A*) >12 years	Symbicort 160/4.5 µg bd as needed	2084	217	0.11
	Budesonide 200 µg bd + terbutaline 0.4 mg as needed	2083	221	0.12[f]

Study No. Duration	Treatment groups[a]	N	Severe exacerbations[b]	
			Events	Events/ patient -year[c]
6-month double-blind studies				
Study 735 (Therapy B) 6 months**	Symbicort 160/4.5 µg bd + as needed	1103	125	0.23***
	Symbicort 320/9 µg bd + terbutaline 0.4 mg as needed	1099	173	0.32
	Salmeterol/fluticasone 2 x 25/125 µg bd + terbutaline 0.4 mg as needed	1119	208	0.38
12-month double-blind studies				
Study 734 (Therapy B) 12 months**	Symbicort 160/4.5 µg bd + as needed	1107	194	0.19***
	Symbicort 160/4.5 µg bd + formoterol 4.5 µg as needed	1137	296	0.29
	Symbicort 160/4.5 µg bd + terbutaline 0.4 mg as needed	1138	377	0.37

* Symbicort anti-inflammatory reliever therapy.

** Symbicort anti-inflammatory reliever plus maintenance therapy.

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

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

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

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

[d] Reduction in exacerbation rate is statistically significant (P value <0.01) for the comparison of Symbicort as needed vs Terbutaline as needed.

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

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

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

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

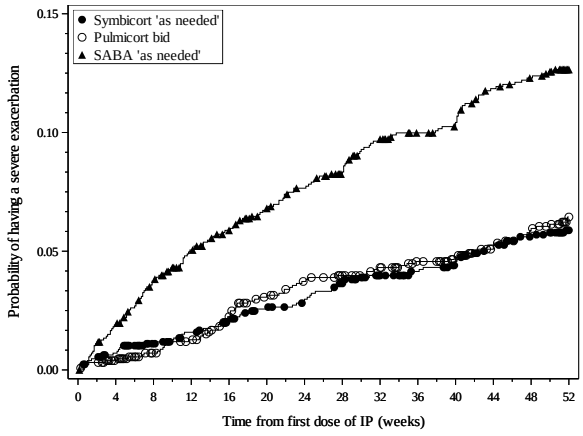
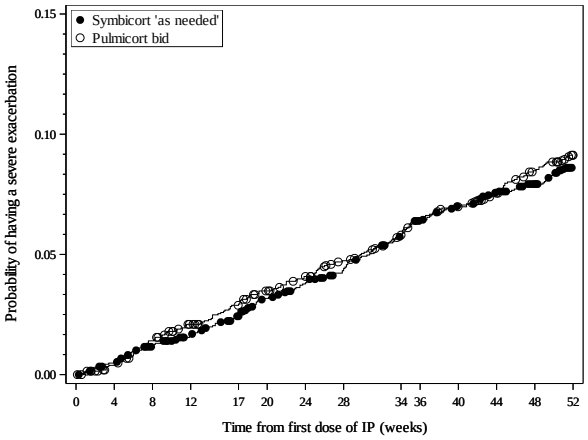
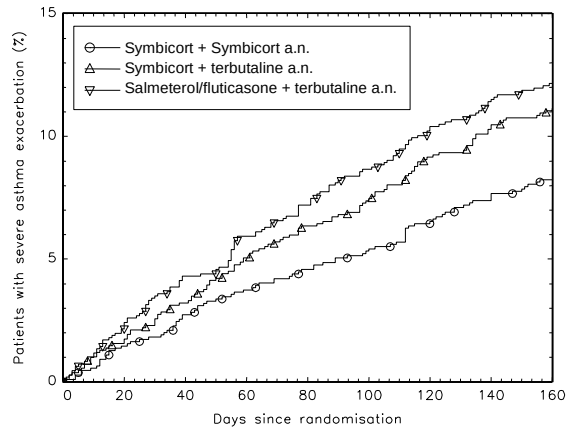


Figure 1b **Time to first severe asthma exacerbation in SYGMA 2 study**



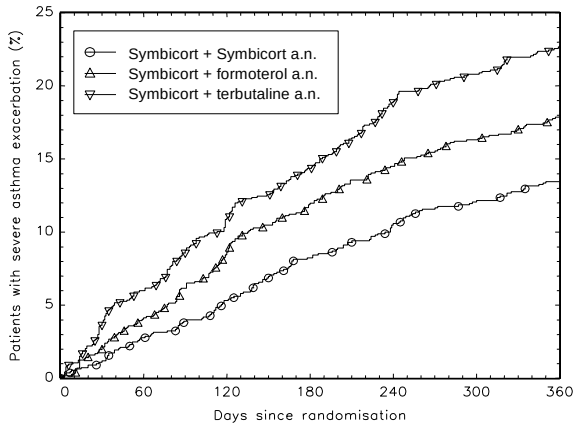
In Study 735, Symbicort anti-inflammatory reliever plus maintenance therapy (therapy B) significantly prolonged the time to the first severe exacerbation (see Figure 2a) compared to the other treatment groups. The rate of severe exacerbations was reduced by 28% compared to twice the maintenance dose of Symbicort with terbutaline as reliever. Lung function, symptom control, and reliever use were similar in all treatment groups.

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



a.n. = as needed

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



a.n. = as needed

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

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

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

Clinical studies with Symbicort Turbuhaler in adults, have shown that the addition of formoterol to budesonide improved asthma symptoms and lung function, and reduced exacerbations. In two 12-week studies, the effect on lung function of Symbicort was equal to that of the free combination of budesonide and formoterol, and exceeded that of budesonide alone. All treatment arms used a short-acting β_2 agonist as needed. There was no sign of attenuation of the anti-asthmatic effect over time.

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

Clinical Efficacy in Chronic Obstructive Pulmonary Disease (COPD)

In two 12-month studies, the effect on lung function and the rate of exacerbation (defined as courses of oral steroids and/or course of antibiotics and/or hospitalisations) in patients with moderate to severe COPD was evaluated. The inclusion criteria for both studies was pre-bronchodilator FEV_1 <50% predicted normal. Median post-bronchodilator FEV_1 at inclusion in the trials was 42% predicted normal. The mean number of exacerbations per year (as defined above) was significantly reduced with Symbicort as compared with treatment with formoterol alone or placebo (mean rate 1.4 compared with 1.8-1.9 in the placebo/formoterol group). The mean number of days on oral corticosteroids/patient during the 12 months was slightly reduced in the Symbicort group (7-8 days/patient/year compared with 11-12 and 9-12 days in the placebo and formoterol groups, respectively). For changes in lung-function parameters, such as FEV_1, Symbicort was not superior to treatment with formoterol alone.

5.2 Pharmacokinetic properties

Absorption

Symbicort Turbuhaler and the corresponding monoproducts have been shown to be bioequivalent with regard to systemic exposure of budesonide and formoterol, respectively. In spite of this, a small increase in cortisol suppression was seen after administration of Symbicort compared to the monoproducts. The difference is considered not to have an impact on clinical safety.

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

Pharmacokinetic parameters for the respective substances were comparable after the administration of budesonide and formoterol as monoproducts or as Symbicort Turbuhaler. For budesonide, AUC was slightly higher, rate of absorption more rapid and maximal plasma concentration higher after administration of the fixed combination. For formoterol, maximal plasma concentration was similar after administration of the fixed combination. Inhaled budesonide is rapidly absorbed and the maximum plasma concentration is reached within 30 minutes after inhalation. In studies, mean lung deposition of budesonide after inhalation via Turbuhaler ranged from 32% to 44% of the delivered dose. The systemic bioavailability is approximately 49% of the delivered dose. In children aged 6-16 years, lung deposition fall in the same range as in adults for the same given dose, the resulting plasma concentrations were not determined.

Inhaled formoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation. In studies, the mean lung deposition of formoterol after

inhalation via Turbuhaler ranged from 28% to 49% of the delivered dose. The systemic bioavailability is about 61% of the delivered dose.

Distribution and Biotransformation

Plasma protein binding is approximately 50% for formoterol and 90% for budesonide. Volume of distribution is about 4 L/kg for formoterol and 3 L/kg for budesonide. Formoterol is inactivated via conjugation reactions (active O-demethylated and deformylated metabolites are formed, but they are seen mainly as inactivated conjugates). Budesonide undergoes an extensive degree (approx. 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6-beta-hydroxy-budesonide and 16-alfa-hydroxy-prednisolone, is less than 1% of that of budesonide. There are no indications of any metabolic interactions or any displacement reactions between formoterol and budesonide.

Elimination

The major part of a dose of formoterol is transformed by liver metabolism followed by renal elimination. After inhalation of formoterol via Turbuhaler, 8% to 13% of the delivered dose of formoterol is excreted unmetabolised in the urine. Formoterol has a high systemic clearance (approximately 1.4 L/min) and the terminal elimination half-life averages 17 hours.

Budesonide is eliminated via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites of budesonide are eliminated in urine as such or in conjugated form. Only negligible amounts of unchanged budesonide have been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 L/min) and the plasma elimination half-life after i.v. dosing averages 4 hours.

The pharmacokinetics of budesonide or formoterol in children 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, given in combination or separately, were effects associated with exaggerated pharmacological activity.

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. Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure and implantation losses as well as decreased early postnatal survival and birth weight at considerably higher systemic exposures than those reached during clinical use. However, these animal experimental results do not seem to be relevant in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (which contains milk proteins).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to expiry date on outer carton.

6.4 Special precautions for storage

Store below 30°C. Keep the container tightly closed.

6.5 Pack size

Please refer to outer carton for pack size.

Product Owner

AstraZeneca UK Limited
1 Francis Crick Avenue
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Cambridge, CB2 0AA
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7. INSTRUCTIONS FOR USE

Please read all the following instructions carefully before using your inhaler

Your doctor, nurse or pharmacist should instruct you in the correct use of your inhaler.

Turbuhaler is a multidose inhaler from which very small amounts of powder are administered (Fig 1). When you breathe in through Turbuhaler the powder is delivered to your lungs. It is therefore important that **you inhale forcefully and deeply** through the mouthpiece.

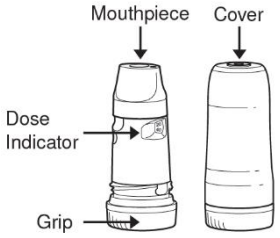

Figure 1

How to prepare a new inhaler for use

Before using Turbuhaler **for the first time** you need to prepare the inhaler for use.

1. Unscrew and lift off the cover. A rattling sound is heard when you unscrew the cover.

2. Hold the inhaler upright with the red grip downwards (Fig. 2). Do not hold the mouthpiece when you turn the grip. Turn the grip as far as it will go in one direction and then back again as far as it will go. It does not matter which way you turn first. During this procedure you will hear a click. Perform this procedure twice.

Figure 2

The inhaler is now ready for use, and **you should not repeat this procedure again.** To take a dose, please continue according to the instructions below.

How to use Symbicort Turbuhaler

To administer one dose, simply follow the instructions below.

1. Unscrew and lift off the cover. A rattling sound is heard when you unscrew the cover.

2. **Hold the inhaler upright** with the red grip downwards (Fig. 2). Do not hold the mouthpiece when you turn the grip. To load the inhaler with a dose **turn the grip as far as it will go in one direction, and then back again as far as it will go.** It does not matter which way you turn first. During this procedure you will hear a click.

3. **Breathe out.** Do **not** breathe out **through** the mouthpiece.

4. Place the mouthpiece gently between your teeth, close your lips and **inhale forcefully and deeply through your mouth** (Fig. 3). Do not chew or bite on the mouthpiece.

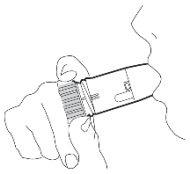

Figure 3

5. **Remove the inhaler from your mouth, before breathing out.**

6. If more than one dose has been prescribed, repeat steps 2-5.

7. **Replace the cover** by screwing it back on tightly.

8. Rinse your mouth out with water. Do not swallow.

NOTE!

Do not try to remove the mouthpiece since it is fixed to the inhaler. The mouthpiece can be rotated, but do not twist it unnecessarily.

As the amount of the powder dispensed is very small, you may not be able to taste it after inhalation. However, you can still be confident that you have inhaled the dose if you have followed the instructions.

If you by mistake perform the loading procedure more than once before taking your dose, you will still only receive one dose. The dose indicator will, however, register all the loaded doses.

The sound heard if you shake the inhaler is not produced by the medication but by a drying agent.

How will I know when to replace the inhaler?

The dose indicator (Fig. 4) tells you approximately how many doses are left in the inhaler, starting with either 60 or 120 when full.

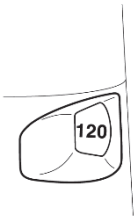

Figure 4

The indicator is marked in intervals of 10 doses. Therefore, it does not show the loading of each individual dose.

You should be reassured that Turbuhaler delivers the dose even if you may not notice a movement in the dose indicator.

For the last 10 doses, the background of the indicator is red. When the zero reaches the middle of the window (Fig. 5), it is time for you to discard the inhaler.

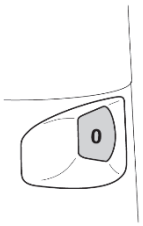

Figure 5

Please note that even when the dose indicator registers zero, it is still possible to turn the grip. However, the indicator stops moving and the zero remains in the window.

Cleaning

Wipe the outside of the mouthpiece regularly (once a week) with a **dry** tissue. **Do not use water or liquids when you clean the mouthpiece.**

Disposal

Always be sure to dispose of your used Turbuhaler responsibly/in the recommended way, since some of the medicine will remain inside it. Ask your pharmacist for advice.

Remember

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.