Symbicort Turbuhaler 160/4.5 μg/dose

budesonide/formoterol

Inhalation powder

Composition

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

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).

Therapeutic indications

Asthma

Symbicort Turbuhaler is indicated in the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting $beta_2$-agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting $beta_2$-agonists

or

- patients already adequately controlled on both inhaled corticosteroids and long-acting $beta_2$-agonists.

COPD

Symptomatic treatment of patients with severe COPD (FEV_1 <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

Posology and method of administration

Asthma

Symbicort Turbuhaler is not intended for the initial management of asthma. 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 $beta_2$-agonists and/or corticosteroids 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 control of symptoms

is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

For Symbicort there are two treatment approaches:

A. Symbicort maintenance therapy: Symbicort is taken as regular maintenance treatment with a separate rapid-acting bronchodilator as rescue.

B. Symbicort maintenance and reliever therapy: Symbicort is taken as regular maintenance treatment and as needed in response to symptoms.

A. Symbicort maintenance therapy

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

Recommended doses:

Adults (18 years and older): 1-2 inhalations twice daily. Some patients may require up to a maximum of 4 inhalations twice daily.

Adolescents (12-17 years): 1-2 inhalations twice daily.

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

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

Children (6 years and older): A lower strength is available for children 6-11 years.

B. Symbicort maintenance and reliever therapy

Patients take a daily maintenance dose of Symbicort and in addition take Symbicort as needed in response to symptoms. Patients should be advised to always have Symbicort available for rescue use.

Symbicort maintenance and reliever therapy should especially be considered for patients with:

- inadequate asthma control and in frequent need of reliever medication
- asthma exacerbations in the past requiring medical intervention

Close monitoring for dose-related adverse effects is needed in patients who frequently take high numbers of Symbicort as-needed inhalations.

Recommended doses:

Adults (18 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. For some patients a maintenance dose of 2 inhalations twice daily may be appropriate. 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.

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.

Children and adolescents under 18 years: Symbicort maintenance and reliever therapy is not recommended for children and adolescents.

COPD
Recommended doses:
Adults: 2 inhalations twice daily.

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

Instructions for correct use of 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 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 rinse their mouth out with water after inhaling the maintenance dose to minimise the risk of oropharyngeal thrush. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.

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

Contraindications

Hypersensitivity (allergy) to budesonide, formoterol or inhaled lactose.

Special warning and precautions for use

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

If patients find the treatment ineffective, or exceed the highest recommended dose of Symbicort, medical attention must be sought (see section Posology and method of administration). Sudden and progressive deterioration in control of asthma or COPD is potentially life threatening and the patient should undergo urgent medical assessment. In this situation consideration should be given to the need for increased therapy with corticosteroids, e.g. a course of oral corticosteroids, or antibiotic treatment if an infection is present.

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

Patients should be reminded to take their Symbicort maintenance dose as prescribed, even when asymptomatic. The prophylactic use of Symbicort, e.g. before exercise, has not been studied. 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.

Therapy with Symbicort should not be initiated during an exacerbation.

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

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.

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.

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

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

The benefits of inhaled budesonide therapy would normally minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Patients who have required high dose emergency corticosteroid therapy in the past or prolonged treatment with high doses of inhaled corticosteroids, may also be at risk. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

To minimise the risk of oropharyngeal candida infection the patient should be instructed to rinse their mouth out with water after inhaling the maintenance dose. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.

Concomitant treatment with itraconazole and ritonavir or other potent CYP3A4 inhibitors should be avoided (see section Interactions). If this is not possible the time interval between administration of the interacting drugs should be as long as possible. In patients using potent CYP3A4 inhibitors, Symbicort maintenance and reliever therapy is not recommended.

Symbicort should be administered with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

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

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

Potentially serious hypokalaemia may result from high doses of $beta_2$-agonists. Concomitant treatment of $beta_2$-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 $beta_2$-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 $beta_2$-agonists, additional blood glucose controls should be considered in diabetic patients.

Symbicort Turbuhaler contains lactose (<1 mg/inhalation). This amount does not normally cause problems in lactose intolerant people.

Interactions

The metabolic conversion of budesonide is impeded by substances metabolized by CYP P450 3A4 (e.g. itraconazole, ritonavir). The concomitant administration of these potent inhibitors of CYP P450 3A4 may increase plasma levels of budesonide. The concomitant use of these drugs should be avoided unless the benefit outweighs the increased risk of systemic side effects. In patients using potent CYP3A4 inhibitors, Symbicort maintenance and reliever therapy is not recommended.

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

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), 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 $beta_2$-sympathomimetics.

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

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

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

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

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

Pregnancy and lactation

For Symbicort or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Animal studies with respect to reproductive toxicity of the combination have not been performed.

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

Data 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 Preclinical safety data). This is not likely to be relevant for humans given recommended doses.

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

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

It is not known whether formoterol or budesonide passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of Symbicort to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Effects on ability to drive and use machines

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

Undesirable effects

Since Symbicort contains both budesonide and formoterol, the same pattern of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side-effects of $beta_2$-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 below, listed by system organ class and frequency. Frequency are defined as:

very common (≥1/10), common (≥1/100) and <1/10), uncommon (≥1/1 000 and < 1/100), rare (≥1/10 000 and < 1/1000) and very rare (<1/10 000).

Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Rare	Atrial fibrillation, supraventricular tachycardia, extrasystoles
	Very rare	Angina pectoris
Endocrine disorders	Very rare	Signs or symptoms of systemic glucocorticosteroid effects (including hypofunction of the adrenal gland)
Gastrointestinal disorders	Uncommon	Nausea
Immune system disorders	Rare	Exanthema, urticaria, pruritus, dermatitis, angioedema
Infections and infestations	Common	Candida infections in the oropharynx
Metabolic and nutrition disorders	Rare	Hypokalemia
	Very rare	Hyperglycemia
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	Common	Mild irritation in the throat, coughing, hoarseness

disorders	Rare	Bronchospasm
Skin and subcutaneous tissue disorders	Uncommon	Bruises
Vascular disorders	Very rare	Variations in blood pressure

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

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 effects that are typical for beta$_2$-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 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.

Pharmacodynamic properties

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

ATC-code: R03AK07

Mechanisms 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 exacerbations. The specific properties of budesonide and formoterol allow the combination to be used both as maintenance and reliever therapy, or as maintenance treatment of asthma.

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

Formoterol
Formoterol is a selective $beta_2$-adrenergic agonist that when inhaled results in rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose dependant, with an onset of effect within 1-3 minutes. The duration of effect is at least 12 hours after a single dose.

Symbicort Turbuhaler
Asthma
Clinical efficacy for Symbicort maintenance therapy
Clinical studies 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 $beta_2$-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 Turbuhaler (2 inhalations of 80/4.5 micrograms/inhalation twice daily), and a short-acting $beta_2$-agonist as needed. Lung function was improved and the treatment was well tolerated compared to the corresponding dose of budesonide Turbuhaler.

Clinical efficacy for Symbicort maintenance and reliever therapy
A total of 12076 asthma patients were included in 5 double-blind efficacy and safety studies (4447 were randomised to Symbicort maintenance and reliever therapy) for 6 or 12 months. Patients were required to be symptomatic despite use of inhaled glucocorticosteroids.

Symbicort maintenance and reliever 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 1). In Study 735, lung function, symptom control, and reliever use were similar in all treatment groups. In Study 734, symptoms and reliever use were reduced and lung function improved, compared with both comparator treatments. In the 5 studies combined, patients

receiving Symbicort maintenance and reliever therapy used, on average, no reliever inhalations on 57% of treatment days. There was no sign of development of tolerance over time.

Table 1 Overview of severe exacerbations in clinical studies

Study No. Duration	Treatment groups	N	Severe exacerbations[a]	
			Events	Events/ patient-year
Study 735 6 months	**Symbicort 160/4.5 µg bd + as needed**	**1103**	**125**	**0.23[b]**
	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
Study 734 12 months	**Symbicort 160/4.5 µg bd + as needed**	**1107**	**194**	**0.19[b]**
	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

[a] Hospitalisation/emergency room treatment or treatment with oral steroids
[b] Reduction in exacerbation rate is statistically significant (P value <0.01) for both comparisons

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.

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 severe COPD was evaluated. Median FEV_1 at inclusion in the trials was 36% of 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.

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 Turbuhaler 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.

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 metabolism
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 16-alfa-hydroxy-prednisolone, is less than 1% of that of budesonide. There are no indications of any metabolic interactions or any displacement reactions between formoterol and budesonide.

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

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

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

In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant in humans at the recommended 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.

List of excipients

Lactose monohydrate (which contains milk proteins).

Incompatibilities

Not applicable.

Shelf-life

Please refer to expiry date on the outer carton.

Special precautions for storage

Do not store above 30° C. Keep the container tightly closed.

Pack size

Please refer to outer carton for pack size.

Date of revision of text

November 2006.

02/JF/RITA.000-017-677.5.0

INSTRUCTIONS FOR USE/HANDLING

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

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.

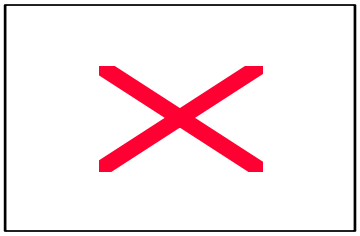

Figure 1

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.

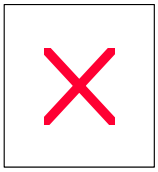

Figure 2

The inhaler is now prepared for use, and **you should not repeat the above 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 the device** (Fig. 3). Do not chew or bite on the mouthpiece.

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 after morning and evening doses. Do not swallow.

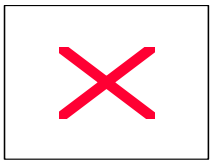

Figure 3

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 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.

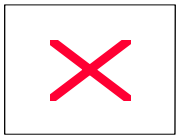

Figure 4

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.

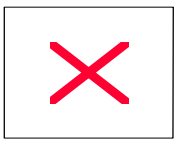

Figure 5

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.

AstraZeneca AB, Södertälje, Sweden