

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 monoproductions, 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.

Therapeutic indications

Asthma

Symbicort Turbuhaler is indicated in adults and adolescents (12 years and older) for the regular treatment of asthma where use of a combination (inhaled corticosteroid and long-acting beta₂-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.

COPD

Symbicort Turbuhaler is indicated in adults, and 18 years and older, for the symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV₁) <70% predicted normal, (post bronchodilator) and an exacerbation history despite regular bronchodilator therapy.

Posology and method of administration

Asthma

Symbicort 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 beta₂-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 long-term 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 in combination with an inhaled corticosteroid 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 (80 micrograms /4.5 micrograms / inhalation) 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 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. 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 under 12 years: Symbicort maintenance and reliever therapy is not recommended for children..

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 replace the cover of the Symbicort Turbuhaler after use.
- 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 lactose (which contains small amounts of milk proteins).

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.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Symbicort. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Symbicort should be used (see section Posology and method of administration).

Patients should not be initiated on Symbicort during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

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.

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 post-bronchodilator $FEV_1 < 70\%$ predicted normal.

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. If the patient experiences paradoxical bronchospasm Symbicort should be discontinued immediately. The patient should be assessed and alternative therapy instituted if necessary. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straight away.

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

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. Recovery may take a considerable amount of time after cessation of oral steroid therapy and hence oral steroid-dependent patients transferred to inhaled budesonide may remain at risk from impaired adrenal function for some considerable time. In such circumstances HPA axis function should be monitored regularly.

The prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Therefore, additional systemic corticosteroid cover should be considered

during periods of stress such as severe infections or elective surgery. Rapid reduction in the dose of steroids can induce acute adrenal crisis. Symptoms and signs which might be seen in acute adrenal crisis may be somewhat vague, but may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, seizures, hypotension and hypoglycaemia.

Treatment with supplementary systemic steroids or inhaled budesonide should not be stopped abruptly.

During transfer from oral therapy to Symbicort, a generally lower systemic steroid action will be experienced which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema and muscle and joint pain. Specific treatment should be initiated for these conditions. A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases a temporary increase in the dose or oral glucocorticosteroids is sometime necessary.

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, 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 beta₂-agonists. Concomitant treatment of beta₂-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 beta₂-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 beta₂-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. The excipient lactose contains small amounts of milk proteins, which may cause allergic reactions.

Clinical studies and meta-analyses indicate that treatment of COPD with inhaled corticosteroids may lead to an increased risk of pneumonia. However, the absolute risk for budesonide is small. A meta-analysis of 11 COPD double blind trials including 10,570 patients did not demonstrate a statistically significant increased risk of pneumonia in patients treated with budesonide (with or without formoterol) compared to non-budesonide containing treatments (placebo or formoterol). The incidence rate of pneumonia reported as a serious adverse event was 1.9% per year on budesonide containing treatments and 1.5% per year on non-budesonide containing treatments. The pooled hazard ratio comparing all budesonide-containing versus non-budesonide containing treatments was 1.15 (95% CI: 0.83, 1.57). The pooled hazard ratio comparing budesonide/formoterol versus formoterol or placebo was 1.00 (95% CI: 0.69, 1.44). A causal relationship with budesonide-containing products has not been established.

Interactions

Potent inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors) are likely to markedly increase plasma levels of budesonide and concomitant use should be avoided. If this is not possible the time interval between administration of the inhibitor and budesonide should be as long as possible (section 4.4). In patients using potent CYP3A4 inhibitors, Symbicort maintenance and reliever therapy is not recommended.

The potent CYP3A4 inhibitor ketoconazole, 200 mg once daily, increased plasma levels of concomitantly orally administered budesonide (single dose of 3 mg) on average six-fold. When ketoconazole was administered 12 hours after budesonide the concentration was on average increased only three-fold showing that separation of the administration times can reduce the increase in plasma levels. Limited data about this interaction for high-dose inhaled budesonide indicates that marked increase in plasma levels (on average four fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 µg).

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 beta₂-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.

Hypokalaemia may result from beta₂-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids and diuretics (see Special warnings and precautions for use).

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

Paediatric population

Interaction studies have only been performed in adults.

Fertility, 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 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.

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

There is no data available on the potential effect of budesonide on fertility. Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure (see section Preclinical safety data).

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 beta₂-agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment.

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

Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Rare	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles
	Very rare	Angina pectoris. Prolongation of QTc-interval
Endocrine disorders	Very rare	Cushing's syndrome, adrenal suppression, growth retardation, decrease in bone mineral density, cataract and glaucoma
Eye Disorders	Very rare	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	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	Aggression, psychomotor hyperactivity, anxiety, sleep disorders.
	Very rare	Depression, behavioural changes (predominantly 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

Candida infection in the oropharynx is due to drug deposition. Advising the patient to rinse the mouth out with water after each maintenance dose will minimise the risk. Oropharyngeal Candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroid. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.

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 Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. Increased susceptibility to infections and impairment of the ability to adapt to stress may also occur. Effects are probably dependent on dose, exposure time, concomitant and previous steroid exposure and individual sensitivity (see section Special warning and precautions for use).

Treatment with beta₂-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.

Paediatric population

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored (see Special warnings and precautions for use).

Overdose

An overdose of formoterol would likely lead to effects that are typical for beta₂-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: Drugs for obstructive airway diseases: Adrenergics, Inhalants

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 beta₂-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 beta₂-agonist as needed. There was no sign of attenuation of the anti-asthmatic effect over time.

Two 12-week paediatric studies have been performed in which 265 children aged 6-11 years were treated with a maintenance dose of budesonide/formoterol (2 inhalations of 80/4.5 micrograms/inhalation twice daily), and a short-acting beta₂-agonist as needed. In both studies, lung function was improved, and the treatment was well tolerated compared to the corresponding dose of budesonide alone.

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

Comparable efficacy and safety in adolescents and adults was demonstrated in 6 double-blind studies, comprising the 5 studies mentioned above and an additional study using a higher maintenance dose of 160/4.5 micrograms, two inhalations twice daily. These assessments were based on a total of 14385 asthma patients of whom 1847 were adolescents. The number of adolescent patients taking more than 8 inhalations on at least one day as part of budesonide/formoterol maintenance and reliever therapy was limited, and such use was infrequent.

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 moderate to severe COPD was evaluated. The inclusion criteria for both studies was pre-bronchodilator FEV₁ <50% predicted normal. Median post-bronchodilator FEV₁ 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 FEV₁, 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 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 deformedylated 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

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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.

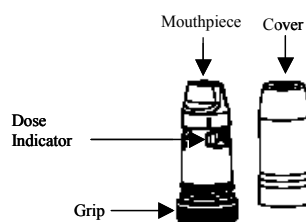


Figure 1

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 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.

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.

Please note that even when the dose indicator registers zero, it is still possible to turn the grip.

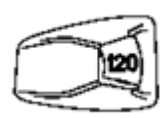


Figure 4

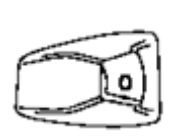


Figure 5

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.

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