

NEW ZEALAND DATA SHEET

NAME OF MEDICINE

SYMBICORT[®] 100/6 TURBUHALER[®]
SYMBICORT[®] 200/6 TURBUHALER[®]
SYMBICORT[®] 400/12 TURBUHALER[®]

Budesonide / Eformoterol fumarate dihydrate (100/6 µg, 200/6 µg or 400/12 µg per inhalation)

PRESENTATION

SYMBICORT TURBUHALER is a multidose inspiratory flow driven, dry powder inhaler. The inhaler is made of plastic parts.

SYMBICORT 100/6 TURBUHALER

SYMBICORT 100/6 TURBUHALER delivers the same amount of budesonide and eformoterol as the corresponding Turbuhaler monoproducs, i.e. budesonide 100 micrograms/inhalation (metered dose) and eformoterol fumarate dihydrate 6 micrograms/inhalation (metered dose).

Each delivered dose (the dose that leaves the mouthpiece) contains as active constituents: budesonide 80 micrograms/inhalation and eformoterol fumarate dihydrate 4.5 micrograms/inhalation.

Each inhaler contains 60 doses or 120 doses

SYMBICORT 200/6 TURBUHALER

SYMBICORT 200/6 TURBUHALER delivers the same amount of budesonide and eformoterol as the corresponding Turbuhaler monoproducs, i.e. budesonide 200 micrograms/inhalation (metered dose) and eformoterol fumarate dihydrate 6 micrograms/inhalation (metered dose).

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

Each inhaler contains 60 doses or 120 doses

SYMBICORT 400/12 TURBUHALER

SYMBICORT 400/12 TURBUHALER delivers the same amount of budesonide and eformoterol as the corresponding Turbuhaler monoproducs, i.e. budesonide 400 micrograms/inhalation (metered dose) and eformoterol fumarate dihydrate 12 micrograms/inhalation (metered dose).

Each delivered dose (the dose that leaves the mouthpiece) contains as active constituents: budesonide 320 micrograms/inhalation and eformoterol fumarate dihydrate 9 micrograms/inhalation.

Each inhaler contains 60 doses

Eformoterol fumarate dihydrate is hereafter referred to as eformoterol.

INDICATIONS

ASTHMA

SYMBICORT TURBUHALER is indicated in the regular treatment of asthma where use of a combination (inhaled corticosteroid and long acting beta₂-agonist) is appropriate. This includes:

- patients who are not adequately controlled with inhaled corticosteroid therapy and “as needed” inhaled short-acting beta-2 adrenoceptor agonists.
- patients who are already adequately controlled on regular separate long-acting β-agonist and inhaled corticosteroid therapies.

There are two alternative treatment regimens:

- SYMBICORT maintenance and reliever therapy (SMART)
- SYMBICORT maintenance therapy

The 400/12 strength should not be used for SYMBICORT maintenance and reliever therapy (SMART) regimen.

COPD

SYMBICORT TURBUHALER is indicated in the regular treatment of adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) [FEV₁ ≤50% of predicted normal], with frequent symptoms despite beta₂-agonist use and a history of exacerbations.

SYMBICORT should not be used for the initiation of bronchodilator therapy in COPD.

DOSAGE AND ADMINISTRATION

The dosage of SYMBICORT TURBUHALER should be individualised according to disease severity.

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

ASTHMA

There are two alternative dosage regimens for the treatment of asthma with SYMBICORT:

- SYMBICORT maintenance and reliever therapy (SMART)
- SYMBICORT maintenance therapy

For both dosing regimens, the patient should be instructed to take the maintenance dose of SYMBICORT TURBUHALER even when asymptomatic for optimal benefit.

SYMBICORT maintenance and reliever therapy (SMART):

SYMBICORT is taken as both regular maintenance treatment, and as needed in response to symptoms. The as-needed inhalations provide both rapid relief and improved asthma control. Patients should be advised to have SYMBICORT available for rescue use at all times. A separate inhaler for rescue use is not necessary.

Clinical studies have demonstrated that SYMBICORT Maintenance And Reliever Therapy provides clinically meaningful reductions in severe exacerbations while maintaining symptom control, compared to SYMBICORT maintenance therapy with a separate rapid-acting bronchodilator (see ACTIONS).

The maintenance dose should be titrated to the lowest dose at which effective control of asthma is maintained.

Adults and adolescents (12 years and older):

Maintenance dose: 2 inhalations of SYMBICORT TURBUHALER 100/6 or 200/6 per day, given either as one inhalation in the morning and one in the 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.

Reliever dose: 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 can be used temporarily. If the patient experiences deteriorating symptoms after taking the appropriate maintenance therapy and additional as needed inhalations, the patient should be reassessed for alternative explanations of persisting symptoms.

Note - SYMBICORT TURBUHALER 400/12 should not be used for the SYMBICORT maintenance and reliever therapy (SMART) regimen.

Children (4 years and older):

Maintenance dose: 1 inhalation of SYMBICORT TURBUHALER 100/6 once daily.

Reliever dose: 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken.

Not more than 4 inhalations should be taken on any single occasion.

A total daily dose of more than 4 inhalations is not normally needed, however a total daily dose of up to 8 inhalations could be used temporarily.

A reassessment of asthma therapy should be considered in patients using an increasing number of SYMBICORT inhalations for symptom relief without achieving improved asthma control within 2 weeks.

SYMBICORT maintenance therapy:

SYMBICORT taken as regular maintenance treatment, with a separate rapid-acting bronchodilator as rescue. Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

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

Adults and adolescents (12 years and older):

SYMBICORT 100/6: 1-2 inhalations once or twice daily
Maximum daily maintenance dose: 4 inhalations (2 inhalations twice daily).

SYMBICORT 200/6: 1-2 inhalations once or twice daily
Maximum daily maintenance dose: 4 inhalations. (2 inhalations twice daily).

During worsening of asthma the dose of SYMBICORT 100/6 and 200/6 may temporarily be increased to a maximum of 4 inhalations twice daily in adults.

SYMBICORT 400/12: 1 inhalation once or twice daily
Maximum daily maintenance dose: 2 inhalations (1 inhalation twice daily).

During worsening of asthma the dose of SYMBICORT 400/12 may temporarily be increased to a maximum of 2 inhalations twice daily in adults.

Children (4 years and older):

SYMBICORT 100/6: 1-2 inhalations twice daily.
Maximum daily maintenance dose: 4 inhalations;

SYMBICORT 200/6: 1 inhalation twice daily.
Maximum daily maintenance dose: 2 inhalations.

SYMBICORT 400/12: Efficacy and safety have not been fully studied in children for SYMBICORT 400/12.

Children under 4 years of age:

The use of SYMBICORT TURBUHALER is not recommended in children under four years of age.

COPD***Adults (40 years and older):***

SYMBICORT 200/6: 2 inhalations twice daily
Maximum daily maintenance dose: 4 inhalations

SYMBICORT 400/12: 1 inhalation twice daily
Maximum daily maintenance dose: 2 inhalations.

Special Populations

There is no special dosing requirement in elderly patients.

There are no data available for use of SYMBICORT TURBUHALER in patients with hepatic or renal impairment. As budesonide and eformoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver disease.

INSTRUCTIONS FOR CORRECT USE OF TURBUHALER

SYMBICORT 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 in the patient information leaflet which are packed together with each inhaler
- to breath 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 the mouth out 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 Turbuhaler due to the small amount of medicine dispensed.

CONTRAINDICATIONS

Hypersensitivity to budesonide, eformoterol or to lactose.

WARNINGS AND PRECAUTIONS**DOSING AND DISCONTINUATION**

The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.

Treatment with SYMBICORT TURBUHALER should not be initiated to treat a severe exacerbation or if patients have significantly worsening or acutely deteriorating asthma.

The lowest effective dose of SYMBICORT TURBUHALER should be used.

Patients should be reminded to take their SYMBICORT TURBUHALER maintenance dose as prescribed, even when asymptomatic. They should also be advised to have their rescue inhaler available at all times, either SYMBICORT TURBUHALER (for asthma patients on SYMBICORT maintenance and reliever therapy) or a separate rapid-acting bronchodilator (for asthma patients using SYMBICORT TURBUHALER as maintenance therapy only and for COPD patients).

In patients using the SYMBICORT maintenance and reliever therapy (SMART) regimen, the reliever inhalations of SYMBICORT TURBUHALER should be taken in response to asthma symptoms. Reliever inhalations are not intended for regular prophylactic use e.g. before exercise. For such use, a separate rapid-acting bronchodilator should be considered.

If the patient finds the treatment ineffective or exceeds the highest recommended dose of SYMBICORT TURBUHALER, the patient should be reviewed by a physician.

Once asthma symptoms are controlled, consideration may be given to stepping down treatment with SYMBICORT TURBUHALER. Regular review of patients as treatment is stepped down is important.

When long-term treatment with SYMBICORT TURBUHALER is to be discontinued, the dose should be tapered. Treatment should not be stopped abruptly.

DETERIORATION OF ASTHMA CONTROL

Increasing use of SYMBICORT TURBUHALER for reliever therapy or short-acting bronchodilators to relieve symptoms indicates deterioration of control.

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 seek medical attention if sudden deterioration of their asthma occurs, or if they find that short-acting relief bronchodilator treatment becomes less effective.

ASTHMA EXACERBATIONS

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

SYMBICORT TURBUHALER must not be initiated or the dose increased during an asthma exacerbation.

POTENTIAL SYSTEMIC EFFECTS OF INHALED CORTICOSTEROIDS

SYMBICORT TURBUHALER contains an inhaled corticosteroid (budesonide).

SYMBICORT TURBUHALER should not be used to initiate treatment with inhaled corticosteroids in patients being transferred from oral steroids.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. However, 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.

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. Therefore it is important that the patient is reviewed regularly and the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.

HPA AXIS SUPPRESSION AND ADRENAL INSUFFICIENCY

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

Clinically important disturbances of the HPA axis and/or adrenal insufficiency induced by severe stress (eg trauma, surgery, infection in particular gastroenteritis or other conditions associated with severe electrolyte loss) may be related to inhaled budesonide in specific patient populations. These are patients with prolonged treatment at the highest recommended dose of SYMBICORT and patients administered concomitant CYP3A4-inhibitors (see INTERACTIONS). Monitoring for signs of adrenal dysfunction is advisable in these patient groups. For these patients additional systemic glucocorticosteroid cover should be considered during periods of stress, a severe asthma attack or elective surgery.

Particular care is needed in patients transferring from oral steroids, since they may remain at risk of impaired adrenal function for a considerable time. Patients who have required high-dose emergency corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroids may also be at risk. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Care should be taken when commencing SYMBICORT TURBUHALER treatment, particularly if there is any reason to suspect that adrenal function is impaired from previous systemic steroid therapy.

BONE DENSITY

Whilst corticosteroids may have an effect on bone mass at high doses, studies with budesonide treatment in adults at recommended doses, have not demonstrated any significant effect on bone mineral density. No information regarding the effect of SYMBICORT TURBUHALER at higher doses is available.

Bone mineral density measurements in children should be interpreted with caution as an increase in bone area in growing children may reflect an increase in bone volume. In three large medium to long term (12 months - 6 years) studies in children (5-16 years), no effects on bone mineral density were observed after treatment with budesonide (189 - 1322µg/day) compared to nedocromil, placebo or age matched controls. However, in a randomised 18 month study (n=176; 5-10 years), bone mineral density was significantly decreased by 0.11 g/cm² (p=0.023) in the group treated with inhaled budesonide via Turbuhaler compared with the group treated with inhaled disodium cromoglycate. The dose of budesonide was 400µg bd for 1 month, 200µg bd for 5 months and 100µg bd for 12 months and the dose of disodium cromoglycate 10mg tid. The clinical significance of this result remains uncertain.

GROWTH

Long term studies suggest that children and adolescents treated with inhaled budesonide ultimately achieve their adult target height. However an initial small but transient reduction in growth (approx 1 cm) has been observed. This generally occurs within the first year of treatment.

It is recommended that the height of children and adolescents 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 to the lowest dose at which effective control of asthma is maintained, if possible.

Physicians should carefully weigh the benefits of the corticosteroid therapy against the possible risk of growth suppression.

OROPHARYNGEAL CANDIDA INFECTION

Candida infection in the oropharynx has been reported due to drug deposition in association with inhalation therapy. 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 treated with SYMBICORT maintenance and reliever therapy should also rinse their mouth with water after the as-needed inhalations. Oropharyngeal Candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroids.

PARADOXICAL BRONCHOSPASM

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

PATIENTS WITH OTHER MEDICAL CONDITIONS

Infections / Tuberculosis

Signs of existing infection may be masked by the use of high doses of glucocorticosteroids and new infections may appear during their use.

As with all inhaled medication containing corticosteroids, SYMBICORT TURBUHALER should be administered with caution in patients with active or quiescent pulmonary tuberculosis or fungal, bacterial or viral infections of the respiratory system.

Sensitivity to sympathomimetic amines

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

Thyrotoxicosis

SYMBICORT TURBUHALER should be administered with caution in patients with thyrotoxicosis.

Cardiovascular disorders

Beta₂-agonists have an arrhythmogenic potential that must be considered before commencing treatment for bronchospasm. Cardiovascular effects, such as increases in systolic blood pressure and heart rate, may occasionally be seen with all sympathomimetic medicines, especially at higher than therapeutic doses.

The effects of eformoterol in acute as well as chronic toxicity studies were seen mainly on the cardiovascular system and consisted of hyperaemia, tachycardia, arrhythmias and myocardial lesions. These are known pharmacological manifestations seen after administration of high doses of beta₂-adrenoceptor agonists.

Patients with pre-existing cardiovascular conditions may be at greater risk of developing adverse cardiovascular effects following administration of beta₂-adrenoceptor agonists. Caution is advised when eformoterol is administered to patients with severe cardiovascular disorders such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

QTc-interval prolongation

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

Hypokalaemia

SYMBICORT TURBUHALER should be administered with caution in patients predisposed to low levels of serum potassium.

High doses of β₂-agonists can lower serum potassium by inducing a redistribution of potassium from the extracellular to the intracellular compartment, via stimulation of Na⁺/K⁺-ATPase in muscle cells.

Concomitant treatment of beta-2 adrenoceptor 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 adrenoceptor agonist. Potentially serious hypokalaemia may result.

Particular caution is advised in unstable or acute severe asthma as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatments (see INTERACTIONS). Patients receiving digoxin are particularly sensitive to hypokalaemia. Serum potassium levels should therefore be monitored in such situations.

Diabetes mellitus

SYMBICORT TURBUHALER should be administered with caution in patients with diabetes mellitus.

Due to the blood-glucose increasing effects of beta₂-stimulants extra blood glucose controls are initially recommended when diabetic patients are commenced on eformoterol.

LACTOSE INTOLERANCE

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.

DRUG INTERACTION POTENTIAL

Concomitant treatment with ritonavir, itraconazole, ketoconazole or other potent CYP3A4 inhibitors should be avoided (see 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 (SMART) is not recommended.

In vivo studies have shown that oral administration of ketoconazole or itraconazole (known inhibitors of CYP3A activity in the liver and in the internal mucosa, also see INTERACTIONS) may cause an increase in the systemic exposure to budesonide, and consequently lead to systemic adverse reactions, such as Cushing's Syndrome. This is of limited importance for short-term (1-2 weeks) treatment, but should be taken into consideration during long-term treatment.

EFFECT ON ABILITY TO DRIVE AND USE MACHINES

SYMBICORT TURBUHALER is not expected to adversely affect the ability to drive or use machines.

USE IN PREGNANCY AND LACTATION

Pregnancy

SYMBICORT TURBUHALER should only be used in pregnancy if the potential benefits outweigh the potential risks to the foetus. Only after special consideration should SYMBICORT TURBUHALER be used during the first 3 months and shortly before delivery.

SYMBICORT TURBUHALER should be used during labour only if the potential benefit justifies the potential risk.

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

There are no adequate data from use of eformoterol in pregnant women. In animal studies eformoterol has caused adverse effects in reproduction studies at very high systemic exposure levels (See PHARMACOLOGICAL PROPERTIES – Pre-Clinical Safety Data).

Data on approximately 2,500 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide.

Lactation

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.

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

Consequently, no adverse effects due to budesonide are anticipated in breast-fed children whose mothers are receiving therapeutic doses of SYMBICORT.

It is not known whether eformoterol passes into human breast milk. In rats, small amounts of eformoterol have been detected in maternal milk.

INTERACTIONS

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

EFORMOTEROL

Beta-receptor blocking agents:

Beta-receptor blocking agents (including eye drops), especially those that are non-selective, may partially or totally inhibit the effect of beta₂-agonists, such as eformoterol. These medicines may also increase airway resistance, therefore the use of these medicines in asthma patients is not recommended.

Other sympathomimetic agents:

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

Xanthine derivatives, mineralocorticosteroids and diuretics:

Hypokalaemia may result from beta₂-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, mineralocorticosteroids, and diuretics, such as thiazides and loop diuretics (see WARNINGS AND PRECAUTIONS - HYPOKALAEMIA section).

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

The adverse cardiovascular effects of eformoterol may be exacerbated by concurrent administration of medicines associated with QT interval prolongation. For this reason caution is advised when eformoterol is administered to patients already taking monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines or antihistamines associated with QT interval prolongation (eg terfenadine, astemizole) as these can prolong the QTc-interval and increase the risk of cardiovascular effects such as ventricular arrhythmias.

L-Dopa, L-thyroxine, oxytocin and alcohol:

L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta₂-sympathomimetics.

BUDESONIDE

CYP3A4 Inhibitors

The metabolism of budesonide is primarily mediated by CYP3A4. Inhibitors of this enzyme, e.g. ketoconazole and itraconazole can therefore increase plasma levels and thus systemic exposure to budesonide. (See WARNINGS and PRECAUTIONS.) The concomitant use of these medicines 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 (SMART) is not recommended.

At recommended doses, cimetidine has a slight but clinically insignificant effect and omeprazole has no effect on the pharmacokinetics of oral budesonide

ADVERSE EFFECTS

Since SYMBICORT TURBUHALER contains both budesonide and eformoterol, 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 disappear within a few days of treatment.

Adverse events which have been associated with budesonide and / or eformoterol are given below listed by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1000$) and very rare ($< 1/10\ 000$).

Table 1 Adverse Drug Reactions by frequency and system organ class (SOC)

Frequency	SOC	Reaction
Common	<i>Cardiac disorders:</i>	Palpitations
	<i>Infections and infestations:</i>	Candida infections in oropharynx
	<i>Nervous system disorders:</i>	Headache, tremor
	<i>Respiratory, thoracic and mediastinal disorders:</i>	Mild irritation in the throat Coughing Hoarseness
Uncommon	<i>Cardiac disorders:</i>	Tachycardia

	<i>Gastrointestinal disorders:</i>	Nausea, diarrhoea
	<i>Metabolism and nutrition disorders</i>	Weight gain
	<i>Musculoskeletal and connective tissue disorders:</i>	Muscle cramps
	<i>Nervous system disorders:</i>	Dizziness, taste disturbances, thirst, tiredness
	<i>Psychiatric disorders:</i>	Agitation, restlessness, nervousness, sleep disturbances
Rare	<i>Cardiac disorders:</i>	Cardiac arrhythmias, e.g.atrial fibrillation, supraventricular tachycardia, extrasystoles
	<i>Immune system disorders:</i>	Immediate and delayed hypersensitivity reactions, e.g. dermatitis, exanthema, urticaria, pruritus, angioedema and anaphylactic reaction
	<i>Respiratory, thoracic and mediastinal disorders:</i>	Bronchospasm
	<i>Skin and subcutaneous tissue disorders:</i>	Skin bruising
	<i>Metabolism and nutrition disorders</i>	Hypokalaemia
Very rare	<i>Cardiac disorders:</i>	Angina pectoris Prolongation of the QTc-interval
	<i>Endocrine disorders:</i>	Signs or symptoms of systemic glucocorticosteroid effects, e.g. Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents,

	decrease in bone mineral density
<i>Eye disorders</i>	Cataract Glaucoma
<i>Metabolism and nutrition disorders:</i>	Hyperglycaemia
<i>Psychiatric disorders:</i>	Anxiety Depression, Behavioural disturbances
<i>Vascular disorders</i>	Variations in blood pressure

Treatment with beta-2 adrenoceptor agonists may also result in an increase in blood levels of insulin, free fatty acids, glycerol, and ketone bodies.

OVERDOSAGE

EFORMOTEROL

An overdose of eformoterol would likely lead to effects that are typical for beta₂-adrenergic agonists: tremor, headache, palpitations, and tachycardia. Hypotension, metabolic acidosis, prolonged QTc-interval, arrhythmia, nausea, vomiting, hypokalaemia and hyperglycaemia may also occur.

Supportive and symptomatic treatment may be indicated. Beta-blockers should be used with care because of the possibility of inducing bronchospasm in sensitive individuals.

If SYMBICORT TURBUHALER therapy has to be withdrawn due to overdose of the eformoterol component, provision of appropriate inhaled corticosteroid therapy must be considered.

BUDESONIDE

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

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES

SYMBICORT contains eformoterol 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 eformoterol allow the combination to be used both as maintenance and reliever therapy, and as maintenance treatment for asthma.

Budesonide

Budesonide is a glucocorticosteroid which when inhaled has a rapid (within hours) and dose-dependent anti-inflammatory action in the airways, resulting in reduced symptoms and fewer asthma exacerbations. Inhaled budesonide has less severe adverse effects than systemic

corticosteroids. The exact mechanism responsible for the anti-inflammatory effect of glucocorticosteroids is unknown.

Eformoterol

Eformoterol 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 dependent, with an onset of effect within 1-3 minutes. The duration of effect is at least 12 hours after a single dose.

PHARMACOKINETIC PROPERTIES

Absorption

SYMBICORT TURBUHALER and the corresponding monoproducts (Pulmicort Turbuhaler and Oxis Turbuhaler, respectively) have been shown to be bioequivalent with regard to systemic exposure of budesonide and eformoterol, respectively.

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

Pharmacokinetic parameters, for the respective substances were comparable after the administration of budesonide and eformoterol as monoproducts or as SYMBICORT TURBUHALER.

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 Pulmicort Turbuhaler ranged from 32 to 44% of the delivered dose. The systemic bioavailability is approximately 49% of the delivered dose.

Inhaled eformoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation. In studies, the mean lung deposition of eformoterol after inhalation via Oxis Turbuhaler ranged from 28-49% of the delivered dose. The systemic availability is about 61% of the delivered dose.

Distribution and Metabolism

Plasma protein binding is approximately 50% for eformoterol and 90% for budesonide. Volume of distribution is about 4 L/kg for eformoterol and 3 L/kg for budesonide. Eformoterol 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 β -hydroxy-budesonide and 16 α -hydroxy-prednisolone, is less than 1% of that of budesonide. There are no indications of any metabolic interactions or any displacement reactions between eformoterol and budesonide.

Elimination

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

Budesonide is eliminated via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites of budesonide are excreted in urine as such or in conjugated form. Only

negligible amounts of unchanged budesonide have been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 L/min) and the plasma elimination half-life after iv dosing averages 4 hours.

Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 year old asthmatic children. Per kg body weight children have a clearance which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. The pharmacokinetics of eformoterol in children has not been studied.

The pharmacokinetics of budesonide or eformoterol in elderly and patients with renal failure is unknown. The exposure of budesonide and eformoterol may be increased in patients with liver disease.

PRECLINICAL SAFETY DATA

The toxicity observed in animal studies with budesonide and eformoterol was similar whether budesonide or eformoterol were given in combination or separately. The effects were associated with pharmacological actions and dose dependent.

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 (See WARNINGS AND PRECAUTIONS – Pregnancy And Lactation). Animal reproduction studies with eformoterol have shown a somewhat reduced fertility in male rats at high systemic exposure and implantation losses as well as decreased early postnatal survival and birth weight at considerably higher systemic exposures than those reached during clinical use. However, these animal experimental results do not seem to be relevant to man.

CLINICAL TRIAL DATA

Symbicort Turbuhaler

Clinical Efficacy for Symbicort maintenance and reliever therapy (SMART) in asthma

A total of 12076 asthma patients were included in 5 double-blind clinical studies (4447 were randomised to SYMBICORT maintenance and reliever therapy) for 6 or 12 months. Patients were required to be symptomatic despite daily use of inhaled glucocorticosteroids. SYMBICORT maintenance and reliever therapy provided statistically significant and clinically meaningful reductions in severe exacerbations by prolonging time to first event and reducing the event rate (Table 1), as compared with all comparator treatments, including SYMBICORT at a higher maintenance dose (in Study 735). Symptom control, lung function and reliever use were similar compared with a higher maintenance dose of SYMBICORT, and all three parameters were improved compared with SYMBICORT at the same maintenance dose or budesonide at a 2 to 4 times higher maintenance dose.

Table 2 Overview of severe exacerbations in clinical studies

Study No., Age group	Treatment groups ^a	N	Severe exacerbations ^b	
			Number of events	Exacerbations/patient-year ^c
6-month double-blind studies				
Study 735, ≥ 12 years	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 2x25/125 µg bd + terbutaline 0.4 mg as needed	1119	208	0.38
Study 667, 12-80 years	SYMBICORT 2 x 80/4.5 µg od + as needed	354	14	0.08**
	Budesonide 2 x 160 µg od + terbutaline 0.4 mg as needed	342	57	0.35
12-month double-blind studies				
Study 734, ≥ 12 years	SYMBICORT 160/4.5 µg bd + as needed	1107	194	0.19**
	SYMBICORT 160/4.5 µg bd + eformoterol 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
Study 673, 4-80 years^d	SYMBICORT 80/4.5 µg bd + as needed	922	160	0.19**
	SYMBICORT 80/4.5 µg bd + terbutaline 0.4 mg as needed	906	330	0.40
	Budesonide 320 µg bd + terbutaline 0.4 mg as needed	925	294	0.35
4-11 years	SYMBICORT 80/4.5 µg od + as needed	118	11	0.10**
	SYMBICORT 80/4.5 µg od + terbutaline 0.4 mg as needed	117	52	0.46
	Budesonide 320 µg od + terbutaline 0.4 mg as needed	106	32	0.33
Study 668, 12-80 years	SYMBICORT 2 x 160/4.5 µg od + as needed	947	197	0.23**
	Budesonide 2 x 160 µg bd + terbutaline 0.4 mg as needed	943	349	0.42

** 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 (and for children, also an increase in inhaled steroid dose or additional asthma treatment).

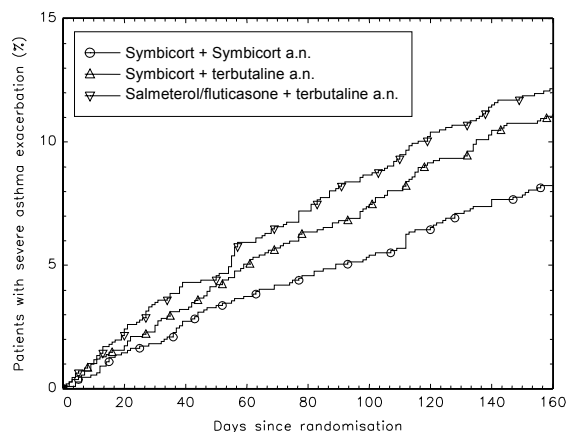
^c Data normalised to 12 months.

^d Includes children ages 4 to 11 that received half the maintenance dose, who are also presented separately.

In Study 735, SYMBICORT maintenance and reliever therapy significantly prolonged the time to the first exacerbation (see Figure 1a) compared to the other treatment groups. The rate of exacerbations was reduced by 28% compared to twice the maintenance dose of SYMBICORT

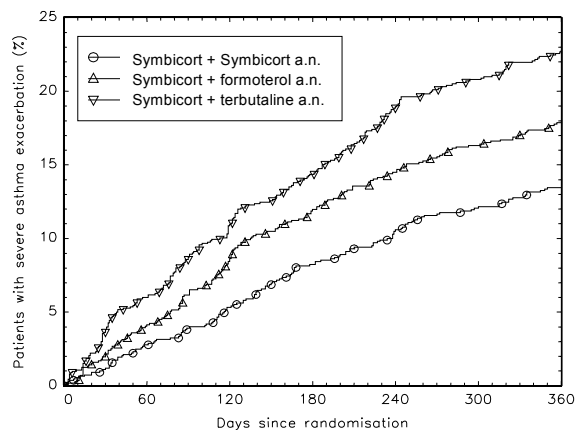
with terbutaline as reliever. Lung function, symptom control, and reliever use were similar in all treatment groups.

Figure 1a Time to first severe asthma exacerbation in study 735



a.n.. = as needed

Figure 1b Time to first severe asthma exacerbation in study 734



a.n. = as needed

In Study 734, SYMBICORT maintenance and reliever therapy prolonged the time to the first exacerbation compared to SYMBICORT at the same maintenance dose with either formoterol or terbutaline as reliever (see Figure 1b). The rate of exacerbations was reduced by 33% and 48%, respectively. Symptoms and reliever use were reduced and lung function improved, compared with both comparator treatments.

In Studies 673, 668 and 667, SYMBICORT maintenance and reliever therapy prolonged the time to the first exacerbation compared to SYMBICORT at the same maintenance dose with terbutaline as reliever and compared to a 2- to 4-fold higher maintenance dose of budesonide with terbutaline as reliever. Across the 3 studies, the rate of exacerbations was reduced by 45-76%. Symptoms and reliever use were reduced and lung function improved compared with all other treatments. For children (118 randomised to SYMBICORT maintenance and reliever therapy in study 673), the exacerbation rate was reduced by 70-79%.

In the 5 long-term studies, patients (adults and adolescents) receiving SYMBICORT maintenance and reliever therapy were allowed 12 inhalations per day (maintenance and as needed) without being reassessed. On average, no reliever inhalation was used on 57% of treatment days and 0-2 reliever inhalations on 87% of treatment days. There was no sign of development of tolerance over time.

In two 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

Clinical studies have shown that the addition of formoterol to budesonide improved asthma symptoms and lung function, and reduced exacerbations. The effect on lung function of SYMBICORT TURBUHALER, given as a maintenance dose only, was equal to that of budesonide and formoterol in separate inhalers in adults and exceeded that of budesonide alone in adults and children. All treatment arms used a short acting beta₂-agonist as needed. There was no sign of attenuation of the anti-asthmatic effect over time.

Clinical Efficacy in Chronic Obstructive Pulmonary Disease (COPD)

In two 12-month studies in patients with COPD, SYMBICORT TURBUHALER was superior to placebo, eformoterol and budesonide regarding lung function, and showed a significant reduction in the exacerbation rate compared to eformoterol and placebo. Thus, the contribution of both budesonide and eformoterol to the effect of SYMBICORT TURBUHALER was demonstrated. SYMBICORT TURBUHALER was also superior to placebo regarding symptoms and quality of life. The treatment was well tolerated.

PHARMACEUTICAL PARTICULARS

LIST OF EXCIPIENTS

Lactose monohydrate (which may contain milk protein residue).

STORAGE CONDITIONS

Do not store above 30°C. Store with cover tightened.

SHELF-LIFE

24 months.

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

SYMBICORT 100/6 AND 200/6 TURBUHALER:

Each inhaler contains 60 doses or 120 doses

SYMBICORT 400/12 TURBUHALER

Each inhaler contains 60 doses.

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