1. Name of the medicinal product
Symbicort® Turbuhaler® 160/4.5 micrograms/inhalation, inhalation powder.

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

Excipients with known effect:
Lactose monohydrate 730 micrograms per delivered dose.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Inhalation powder.
White powder.

4. Clinical particulars
4.1 Therapeutic indications
Asthma
Symbicort Turbuhaler 160/4.5 mcg/dose is indicated in adults and adolescents (12 years and older), for the treatment of asthma, to achieve overall asthma control, including the relief of symptoms and the reduction of the risk of exacerbations (see Section 4.2 Posology and Method of administration).

Chronic Obstructive Pulmonary Disease (COPD)
Symbicort Turbuhaler 160/4.5 mcg/dose is indicated in adults, aged 18 years and older, for the symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV_1)< 70% predicted normal (post-bronchodilator) and an exacerbation history despite regular bronchodilator therapy (see also section 4.4).

4.2 Posology and method of administration
Route of administration: For inhalation use.

Posology
Asthma
Symbicort Turbuhaler can be used according to different treatment approaches:

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

B. Symbicort maintenance therapy (fixed dose).

C. Symbicort anti-inflammatory reliever plus maintenance therapy.

A. Symbicort anti-inflammatory reliever therapy (patients with mild disease)
Symbicort Turbuhaler 160/4.5 is taken as needed for the relief of asthma symptoms when they occur, and as a preventative treatment of symptoms in those circumstances recognised by the patient to precipitate an asthma attack. Patients should be advised to always have Symbicort Turbuhaler 160/4.5 available for relief of symptoms.
Preventative use of Symbicort Turbuhaler 160/4.5 for allergen- or exercise-induced bronchoconstriction (AIB/EIB) should be discussed between physician and patient; the recommended dose frequency should take into consideration both allergen exposure and exercise patterns.
Adults and adolescents (12 years and older)
Patients should take 1 inhalation of Symbicort Turbuhaler 160/4.5 as needed in response to symptoms.

If symptoms persist after a few minutes, an additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion.A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. If the patient experiences a three-day period of deteriorating symptoms after taking additional as needed inhalations, the patient should be reassessed for alternative explanations of persisting symptoms.

B. Symbicort maintenance therapy (Fixed dose)

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

Increasing use of short-acting bronchodilators indicates a worsening of the underlying condition and warrants reassessment of the asthma therapy. The dosage of Symbicort Turbuhaler should be individualised according to disease severity. When control of asthma has been achieved, the maintenance dose should be titrated to the lowest dose at which effective asthma control is maintained.

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.

Children (6 years and older)*:* A lower strength (80 micrograms/4.5 micrograms/inhalation) is available for children 6-11 years.

Children under 6 years*:* As only limited data are available, Symbicort Turbuhaler 160/4.5 mcg/dose is not recommended for children younger than 6 years.

C. Symbicort anti-inflammatory reliever plus maintenance therapy

When maintenance treatment with a combination of inhaled corticosteroid (ICS) and long acting β2 agonist (LABA) is required patients take Symbicort anti-inflammatory reliever therapy and in addition take a daily maintenance dose of Symbicort Turbuhaler 160/4.5 mcg/dose. The as-needed inhalations provide both rapid relief of symptoms and improved overall asthma control. Patients should be advised to always have Symbicort Turbuhaler 160/4.5 mcg/dose available for relief of symptoms.

Preventative use of Symbicort Turbuhaler 160/4.5 for AIB/EIB should be discussed between physician and patient; the recommended dose frequency should take into consideration both allergen exposure and exercise patterns.

Recommended doses:

Adults and adolescents (12 years and older):

Patients should take 1 inhalation of Symbicort Turbuhaler /160/4.5 as needed in response to symptoms to control asthma. If symptoms persist after a few minutes, another inhalation should be taken. No more than 6 inhalations should be taken on any single occasion.

Patients also take the recommended maintenance dose of Symbicort Turbuhaler, which 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.

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

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 Turbuhaler 160/4.5 mcg/dose maintenance and reliever therapy is not recommended for children.

General information

If patients take Symbicort Turbuhaler as an anti-inflammatory reliever (either alone or in combination with maintenance therapy) physicians should discuss allergen exposure and exercise patterns with the patients and take these into consideration when recommending the dose frequency for asthma treatment.

If patients take Symbicort Turbuhaler as a maintenance therapy, they should be instructed to take the maintenance dose of Symbicort Turbuhaler even when asymptomatic for optimal benefit.

COPD

Recommended doses:

Adults*:* 2 inhalations twice daily.

Special patient populations:

There are no special dosing requirements for elderly patients. There are no data available for use of Symbicort Turbuhaler 160/4.5 mcg/dose 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.

Method of Administration

Instructions for correct use of Symbicort Turbuhaler 160/4.5 mcg/dose:

The inhaler 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:

- Check the expiry dateTo carefully read the instructions for use in the patient information leaflet which is packed together with each Symbicort Turbuhaler 160/4.5 mcg/dose inhaler
- 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 Inhaler 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 Symbicort Turbuhaler 160/4.5 mcg/dose Inhaler due to the small amount of drug dispensed.

4.3 Contraindications

Hypersensitivity to the active substances or to the excipient listed in section 6.1 (lactose, which contains small amounts of milk proteins).

4.4 Special warnings and precautions for use

Dosing advice
Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Symbicort Turbuhaler 160/4.5 mcg/dose. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Symbicort should be used (see section 4.2).

Patients should be advised to have their reliever available at all times, either Symbicort Turbuhaler 160/4.5 mcg/dose (for asthma patients on *Symbicort anti-inflammatory reliever therapy* and *Symbicort anti-inflammatory reliever plus maintenance therapy*) or a separate short-acting bronchodilator (for other asthma patients using Symbicort as maintenance therapy only and for COPD Patients).
Patients should be reminded to take their Symbicort Turbuhaler 160/4.5 mcg/dose maintenance dose as prescribed, even when asymptomatic.

To minimise the risk of oropharyngeal candida infection (see section 4.8), 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.

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

Deterioration of disease
Serious asthma-related adverse events and exacerbations may occur during treatment with Symbicort Turbuhaler 160/4.5 mcg/dose. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation with Symbicort Turbuhaler 160/4.5 mcg/dose.
If patients find the treatment ineffective or exceed the highest recommended dose of Symbicort medical attention must be sought (see section 4.2). 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. For treatment of severe exacerbations, a combination product of ICS and LABA alone is not sufficient. Patients should be advised to seek medical attention if they find the

treatment ineffective or they have exceeded the prescribed dose of Symbicort Turbuhaler.

Patients should not be initiated on Symbicort Turbuhaler 160/4.5 mcg/dose during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Transfer from oral therapy
If there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy, care should be taken when transferring patients to Symbicort Turbuhaler 160/4.5 mcg/dose 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.

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 of oral glucocorticosteroids is sometimes necessary.

Excipients
Symbicort Turbuhaler 160/4.5 mcg/dose contains lactose monohydrate (<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.

Interactions with other medicinal products
Concomitant treatment with itraconazole, ritonavir or other potent CYP3A4 inhibitors should be avoided (see section 4.5). If this is not possible the time interval between administrations of the interacting drugs should be as long as possible. In patients using potent CYP3A4 inhibitors, Symbicort maintenance and reliever therapy is not recommended.

Caution with special diseases
Symbicort Turbuhaler 160/4.5 mcg/dose 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.

Potentially serious hypokalaemia may result from high doses of β_2 adrenoceptor-agonists. Concomitant treatment of β_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 β_2 adrenoceptor-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 is increased. It is recommended that serum potassium levels are monitored during these circumstances.

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

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

Systemic effects
Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, and 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) (see section 4.8).

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

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

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

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.

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 160/4.5 mcg/dose 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 straightaway (see section 4.8)

Paediatric populations
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 to the lowest dose at which effective control of asthma is maintained, if possible. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition consideration should be given to referring the patient to a paediatric respiratory specialist.

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

COPD population
There are no clinical study data on Symbicort Turbohaler 160/4.5 mcg/dose available in COPD patients with a prebronchodilator FEV_1 >50% predicted normal and with a post-bronchodilator FEV1 <70% predicted normal (see section 5.1).

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

4.5 Interaction with other medicinal products and other forms of interaction
Pharmacokinetic 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 μ g).

Pharmacodynamic interactions
Beta-adrenergic blockers can weaken or inhibit the effect of formoterol. Symbicort Turbuhaler 160/4.5 mcg/dose 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), and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias.

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

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

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

Concomitant use of other beta-adrenergic drugs or anticholinergic drugs can have a potentially additive bronchodilating effect.
Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides. Hypokalaemia may result from β_2-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids and diuretics (see section 4.4)

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.

4.6 Fertility, pregnancy and lactation
Pregnancy
For Symbicort Turbuhaler or the concomitant treatment with formoterol and budesonide, 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 formoterol in pregnant women. In animal studies formoterol, has caused adverse effects in reproduction studies at very high systemic exposure levels (see section 5.3).
Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies glucocorticosteroids have been shown to induce malformations (see section 5.3). This is not likely to be relevant for humans given recommended doses.

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

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

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

Fertility
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 5.3).

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

4.8 Undesirable effects
Since Symbicort Turbuhaler contains both budesonide and formoterol, the same pattern of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side-effects of β_2

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

Table 1

SOC	Frequency	Adverse Drug Reaction
Infections and infestations	Common	Candida infections in the oropharynx, Pneumonia (in COPD patients)
Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions, e.g. exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction
Endocrine disorders	Very rare	Cushing's syndrome, adrenal suppression, growth retardation, decrease in bone mineral density
Metabolism and nutrition disorders	Rare	Hypokalaemia
	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Aggression, psychomotor hyperactivity, anxiety, sleep disorders
	Very rare	Depression, behavioural changes (predominantly in children)
Nervous system disorders	Common	Headache, tremor
	Uncommon	Dizziness
	Very rare	Taste disturbances
Eye disorders	Uncommon	Vision blurred (see also section 4.4)
	Very rare	Cataract and glaucoma
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Rare	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles
	Very rare	Angina pectoris, prolongation of QTc-interval
Vascular disorders	Very rare	Variations in blood pressure
Respiratory, thoracic and mediastinal disorders	Common	Mild irritation in the throat, coughing, dysphonia including hoarseness
	Rare	Bronchospasm
Gastrointestinal disorders	Uncommon	Nausea
Skin and subcutaneous tissue disorders	Uncommon	Bruises
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps

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 very rarely affecting less than 1 in 10,000 people, with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. Symbicort Turbuhaler 160/4.5 mcg/dose should be discontinued immediately, the patient should be assessed and an alternative therapy instituted if necessary (see section 4.4).

Systemic effects of inhaled corticosteroids may occur particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur 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.

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

Paediatric populations
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il/

4.9 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 Turbuhaler 160/4.5 mcg/dose therapy has to be withdrawn due to overdose of the formoterol component of the drug, provision of appropriate inhaled corticosteroid therapy must be considered.

5. Pharmacological properties
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Drugs for obstructive airway diseases: Adrenergics, Inhalants.
ATC-code: R03AK07

Mechanisms of action and Pharmacodynamic effects

Symbicort Turbuhaler contains formoterol and budesonide, which have different modes of action and show additive effects in terms of reduction of asthma exacerbations. The specific properties of budesonide and formoterol allow the combination to be used either 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 β_2 adrenoceptor 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.

Clinical efficacy and safety

Asthma

Symbicort anti-inflammatory reliever therapy

A total of 8064 patients aged 12 and above with mild asthma were included in 2 double-blind efficacy and safety studies (SYGMA 1 and SYGMA 2), of which 3384 patients were randomised to *Symbicort anti-inflammatory reliever therapy* for 12 months. Patients were required to be uncontrolled on only short-acting β2 agonist (SABA) as needed or controlled on low dose ICS or leukotriene receptor agonist plus SABA as needed.

Both studies compared *Symbicort anti-inflammatory reliever therapy* (Symbicort Turbuhaler 200/6 used as needed in response to symptoms) to budesonide Turbuhaler 200 µg (1 inhalation twice daily) given with as needed SABA. SYGMA 1 also compared *Symbicort anti-inflammatory reliever therapy* to as needed SABA alone.

In SYGMA 1 and SYGMA 2, respectively, based on physician assessment before enrolment, 44.5% and 46.3% of patients were uncontrolled on SABA as needed, and 55.5% and 53.7% of patients were controlled on low dose ICS or leukotriene receptor antagonists plus SABA as needed. At baseline, patients in SYGMA 1 and SYGMA 2, respectively, had a median age of 40 and 41 years (overall range across both studies 12 to 85 years), 12.5% and 9.8% of patients were adolescents (≥12 to <18 years) and approximately 7% and 9% of patients were over 65 years of age, 87.0% and 84.3% had never smoked, 10.3% and 13.1% were former smokers, 2.7% and 2.6% were current smokers, and 19.7% and 22.0% of patients had experienced a severe exacerbation within the 12 months prior to study enrolment.

In SYGMA 2, *Symbicort anti-inflammatory reliever therapy* was comparable to a maintenance dose of budesonide Turbuhaler given with as-needed SABA in terms of the rate of severe exacerbations (Table 2). Protection against severe exacerbation was achieved with a 75% reduction in median ICS load and without requiring adherence to maintenance ICS treatment. SYGMA 1 showed that *Symbicort anti-inflammatory reliever therapy* provided a statistically significant and clinically meaningful reduction in the rate of annual severe exacerbations by 64% compared with SABA as-needed alone (Table 2). Reduction in the annual rate of moderate to severe exacerbations was consistent (60%) with that observed for severe exacerbations (Risk Ratio (RR): 0.40 (95% Confidence Interval (CI): 0.32, 0.49); p<0.001).

In SYGMA 1, *Symbicort anti-inflammatory reliever therapy* provided superior daily asthma symptom control compared to as-needed SABA alone (Odds Ratio (OR): 1.14 (1.00 to 1.30); p=0.046), showing a mean percentage of weeks with well-controlled asthma of 34.4% and 31.1%,

respectively. Asthma symptom control was inferior for *Symbicort anti-inflammatory reliever therapy* compared to a maintenance dose of budesonide Turbuhaler given with as-needed SABA (OR: 0.64 (2-sided 95% CI 0.57, 0.73; lower limit of the CI ≥0.8 for non-inferiority), showing a mean percentage of well-controlled asthma weeks of 34.4% and 44.4%, respectively. Improvements in asthma control (as defined by Asthma Control Questionnaire (ACQ-5)) in patients using *Symbicort anti-inflammatory reliever therapy* were superior to improvements in patients using as needed SABA alone (estimate for difference: -0.15 (-0.20, -0.11); p<0.001). In accordance with the pre-specified hierarchical testing strategy, apart from well-controlled asthma weeks, all other efficacy results from this study were considered of nominal statistical significance. Improvements in asthma control were lower for *Symbicort anti-inflammatory reliever therapy* compared to a maintenance dose of budesonide Turbuhaler given with SABA as needed (SYGMA 1 estimate for difference: 0.15 (0.10, 0.20); SYGMA 2: 0.11 (0.07, 0.15); both p < 0.001). For both comparisons, mean differences in treatments' effect upon ACQ-5 are not clinically meaningful (as assessed by a difference of greater than or equal to 0.5). These results were observed in a clinical study setting with considerably higher adherence to budesonide maintenance dosing than expected in real life.
In the SYGMA studies, increases in lung function compared to baseline (mean pre-bronchodilator FEV1) were statistically significantly larger for patients on *Symbicort anti-inflammatory reliever therapy* compared to patients on as needed SABA alone. Statistically significantly smaller increases were observed for *Symbicort anti-inflammatory reliever therapy* compared to a maintenance dose of budesonide Turbuhaler given with SABA as needed. For both comparisons, mean differences in treatments' effect were small (approximately 30 to 55 mL, equating to approximately 2% of the baseline mean).

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

Table 2 Overview of severe exacerbations in SYGMA 1 and 2 Study

Study	Treatment groups [a]	N	Severe exacerbations [b]	
			Number of events	Exacerbations / patient-year
SYGMA 1	Symbicort Turbuhaler 200/6 as needed	1277	77	0.07
	Terbutaline Turbuhaler 0.4 mg as needed	1277	188	0.20[c]
	Budesonide Turbuhaler 200 µg twice daily + terbutaline Turbuhaler 0.4 mg as needed	1282	89	0.09[d]
SYGMA 2	Symbicort Turbuhaler 200/6 as needed	2084	217	0.11
	Budesonide Turbuhaler 200 µg twice daily + terbutaline Turbuhaler 0.4 mg as needed	2083	221	0.12[e]

a Budesonide Turbuhaler 200 µg (metered dose; Pulmicort Turbuhaler); Terbutaline Turbuhaler 0.4 mg (delivered dose; M3 version).

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

c Reduction in exacerbation rate is statistically significant (p<0.001) for the comparison of Symbicort Turbuhaler as needed vs terbutaline 0.4 mg as needed.

[d] Reduction in exacerbation rate is not statistically significantly different (p=0.279) when comparing Symbicort Turbuhaler as needed vs budesonide 200 µg twice daily + terbutaline 0.4 mg as needed in SYGMA 1.

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

Analysis of time to first severe exacerbation in SYGMA 1 showed that the likelihood of experiencing a severe exacerbation was statistically significantly higher for SABA as needed use compared to *Symbicort anti-inflammatory reliever therapy* over the 1 year treatment period, with a risk reduction of 56% (Hazard Ratio (HR): 0.44 (0.33, 0.58); p<0.001). There were no differences in the probability of experiencing a severe exacerbation between *Symbicort anti-inflammatory reliever therapy* and a maintenance dose of budesonide given with SABA as needed.

Symbicort anti-inflammatory reliever therapy (SYGMA 1 and 2)

Overall, Symbicort anti-inflammatory reliever therapy is generally well tolerated, based on the frequency and nature of adverse effects. No new safety concerns were identified for the use of Symbicort Turbuhaler 160.4.5 as needed in a mild asthma population.

Clinical efficacy for budesonide/formoterol 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 budesonide/formoterol 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.

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 micrograms/4.5 micrograms/inhalation twice daily), and a short-acting β_2 adrenoceptor-agonist as needed. In both studies, Lung function was improved, and the treatment was well tolerated compared to the corresponding dose of budesonide Turbuhaler alone.

Clinical efficacy for budesonide/formoterol maintenance and reliever therapy

A total of 12076 asthma patients were included in 5 double-blind efficacy and safety studies (4447 were randomised to budesonide/formoterol maintenance and reliever therapy) for 6 or 12 months. Patients were required to be symptomatic despite use of inhaled glucocorticosteroids. Budesonide/formoterol 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 budesonide/formoterol at a higher maintenance dose with terbutaline as reliever (study 735) and budesonide/formoterol at the same maintenance dose with either formoterol or terbutaline as reliever (study 734) (Table 3). 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 budesonide/formoterol 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 3 Overview of severe exacerbations in clinical

Study No. Duration	Treatment groups	N	Severe exacerbations[a]	
			Events	**Events/ Patient year**
Study 735 6 months	**Budesonide/formoterol 160/4.5 µg bd + as needed**	**1103**	**125**	**0.23[b]**
	Budesonide/formoterol 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	**Budesonide/formoterol 160/4.5 µg bd + as needed**	**1107**	**194**	**0.19 [b]**
	Budesonide/formoterol 160/4.5 µg bd + formoterol 4.5 µg as needed	1137	296	0.29
	Budesonide/formoterol 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, budesonide/formoterol provided rapid and effective relief of bronchoconstriction similar to salbutamol and formoterol.

Exercise-induced and allergen-induced bronchoconstriction

The use of Symbicort Turbuhaler 160/4.5 in relation to exercise-induced and allergen-induced bronchoconstriction has been studied in three clinical trials for patients with mild / intermittent asthma.
Study D5890L00032 was a 6-week, 3-arm study in 66 adults and adolescents with mild asthma and episodic exercise-induced bronchoconstriction, in which the primary variable was change in maximum decrease in post-exercise FEV1 calculated before and after 6 weeks of treatment. This study demonstrated that Symbicort Turbuhaler 160/4.5, taken as 1 inhalation before exercise plus additional inhalations as needed in response to symptoms, improved asthma control by reducing exercise-induced bronchoconstriction to the same order of magnitude as regular maintenance treatment with budesonide 400 µg plus terbutaline 0.5 mg as needed, despite a substantially lower steroid dose. Both treatments were superior to terbutaline as needed when taken alone.

Study AF-039-0001 was a 6-month, 2-arm study in 92 adult and adolescents with mild intermittent asthma who used SABA for symptom relief, in which the primary variable of efficacy was the change in level of fractional exhaled nitric oxide (FENO) in the two treatment groups over the duration of the study. This study demonstrated that the budesonide component in Symbicort Turbuhaler 160/4.5taken before exercise and as needed, reduced airway inflammation and improved airway function, and showed the beneficial effect of the budesonide component when taken as needed together with formoterol (for symptom relief) as Symbicort Turbuhaler 160/4.5.

Study D5890L00007 was a 3-arm, placebo-controlled, cross-over study in 15 adult patients with mild allergic asthma, in which the primary efficacy variable was change in PD20 (the provocative dose causing a 20% fall in FEV1) methacholine (MCh) during each treatment period. This study showed that when administered 30 minutes after a low-dose allergen challenge, Symbicort Turbuhaler 160/4.5 abolished allergen-induced components of asthma deterioration whilst improving baseline pulmonary function, whereas, formoterol 6 ug alone inhibited the rise in symptoms but did not protect against allergen-induced airway inflammation. This study indicated that deteriorating asthma, provoked by low-dose allergen, is managed more effectively with Symbicort Turbuhaler 160/4.5 than with 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 FEV_1<50% predicted normal. Median post-bronchodilator FEV_1 at inclusion in the trials was 42% predicted normal.

The mean number of exacerbations per year (as defined above) was significantly reduced with budesonide/formoterol 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 budesonide/formoterol 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, budesonide/formoterol was not superior to treatment with formoterol alone.

5.2 Pharmacokinetic properties

Absorption

The fixed-dose combination of budesonide and formoterol, 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 the fixed-dose combination 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 the fixed-dose combination. 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 powder inhaler ranged from 32% to 44% of the delivered dose. The systemic bioavailability is approximately 49% of the delivered dose. In children 6-16 years of age the lung deposition falls in the same range as in adults for the same given dose. The resulting plasma concentrations were not determined. Inhaled formoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation. In studies the mean lung deposition of formoterol after inhalation via powder inhaler ranged from 28-49% of the delivered dose. The systemic bioavailability is about 61% of the delivered dose.

Distribution and biotransformation
Plasma protein binding is approximately 50% for formoterol and 90% for budesonide. Volume of distribution is about 4 L/kg for formoterol and 3 L/kg for budesonide. Formoterol is inactivated via conjugation reactions (active O-demethylated and deformylated metabolites are formed, but they are seen mainly as inactivated conjugates). Budesonide undergoes an extensive degree (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%-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.

Linearity/non-linearity
Systemic exposure for both budesonide and formoterol correlates in a linear fashion to administered dose.

5.3 Preclinical safety data
The toxicity observed in animal studies with budesonide and formoterol, given in combination or separately, were effects associated with exaggerated pharmacological activity.
In animal reproduction studies, 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.

6. Pharmaceutical particulars
6.1 List of excipients
Lactose monohydrate (which contains milk proteins).

6.2 Incompatibilities
Not applicable.
6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Registration Number
123 77 30317 00.

6.6 Nature and contents of container
Symbicort Turbuhaler is an inspiratory flow driven, multidose powder inhaler. The inhaler is white with a red turning grip. The inhaler is made of different plastic materials (PP, PC, HDPE, LDPE, , PBT). Each inhaler contains 60 or 120 doses.

6.7 Special precautions for disposal and other handling
No special requirements.

7 Marketing authorisation holder
AstraZeneca (Israel) Ltd.
1 Atirei Yeda St., Kfar Saba 4464301.

8. Manufacturer
AstraZeneca AB, Sodertalje, Sweden

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