ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Symbicort, 80 micrograms/2.25 micrograms/actuation pressurised inhalation, suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each actuation delivers: budesonide 80 micrograms and formoterol fumarate dihydrate 2.25 micrograms (delivered, ex-actuator). This is equivalent to budesonide 100 micrograms and formoterol fumarate dihydrate 3 micrograms (metered).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation, suspension.
White suspension in an aluminium canister fitted into a red actuator with a grey dust cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma
Symbicort is indicated in adults and adolescents (12 years and older) for the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β_2 adrenoceptor agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β_2 adrenoceptor agonists.

or

- patients already adequately controlled on both inhaled corticosteroids and long-acting β_2 adrenoceptor agonists.

4.2 Posology and method of administration

Route of administration: Inhalation use

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

The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Patients should be regularly reassessed by their prescriber/healthcare provider so that the dosage of Symbicort remains optimal. When long-term control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

For Symbicort there are two treatment approaches:

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

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

A. <u>Symbicort maintenance therapy</u>
Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

Recommended doses:
Adults (18 years and older): 2-4 actuations twice daily. Some patients may require up to a maximum of 8 actuations twice daily.
Adolescents (12-17 years): 2-4 actuations twice daily.

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

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

Children under 12 years: As only limited data for Symbicort (pressurised inhalation, suspension) 80 micrograms/2.25 micrograms/actuation are available, Symbicort maintenance therapy is not recommended for children.

B. <u>Symbicort maintenance and reliever therapy</u>
Patients take a daily maintenance dose of Symbicort and, in addition, take Symbicort as needed in response to symptoms. Patients should be advised to always have Symbicort available for rescue use.

For patients taking Symbicort as reliever, preventative use of Symbicort for allergen- or exercise-induced bronchoconstriction should be discussed between physician and patient; the recommended use should take into consideration the frequency of need. In case of frequent need of bronchodilation without corresponding need for an increased dose of inhaled corticosteroids, an alternative reliever should be used.

Symbicort maintenance and reliever therapy should especially be considered for patients with:
- inadequate asthma control and in frequent need of reliever medication
- asthma exacerbations in the past requiring medical intervention

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

Recommended doses:
Adults and adolescents (12 years and older): The recommended maintenance dose is 4 actuations per day, given either as 2 actuations in the morning and evening or as 4 actuations in either the morning or evening. For some patients, a maintenance dose of 4 actuations twice daily may be appropriate. Patients should take 2 additional actuations as needed in response to symptoms. If symptoms persist after a few minutes, 2 additional actuations should be taken. Not more than 12 actuations should be taken on any single occasion.

A total daily dose of more than 16 actuations is not normally needed; however, a total daily dose of up to 24 actuations could be used for a limited period. Patients using more than 16 actuations daily should be strongly recommended to seek medical advice. They should be reassessed and their maintenance therapy should be reconsidered.

Children under 12 years: Symbicort maintenance and reliever therapy is not recommended for children.

General information

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

Instructions for correct use of Symbicort
On actuation of Symbicort, a volume of the suspension is expelled from the canister at high velocity. When the patient inhales through the mouthpiece at the same time as actuating the inhaler, the substance will follow the inspired air into the airways.

Use of a spacer device (e.g. ***AeroChamber Plus Flow Vu or AeroChamber Plus***) with Symbicort (pressurised inhalation, suspension) is usually recommended, especially in patients who have, or are likely to have, difficulties to coordinate actuation with inhalation (see section 5.2).

Note: Patients should be instructed on the correct use and care of their inhaler and spacer, and their inhalation technique checked to ensure optimum delivery of inhaled drugs to the lungs. It is important to instruct the patient to:

- Carefully read the instructions for use in the patient information leaflet, which is packed together with each inhaler.
- If a spacer is to be used, carefully read the instructions for use in the instruction leaflet, which is packed with each spacer device.
- If the drying agent, which is inside the wrapper, has leaked out of its packet, do not use the inhaler.
- Shake the inhaler well for at least 5 seconds prior to each use to mix its contents properly.
- Prime the inhaler by actuating it twice into the air when the inhaler is new, has not been used for more than one week or if it has been dropped.
- Remove the mouthpiece cover.
- Hold the inhaler upright.
- Place the mouthpiece in the mouth. While breathing in slowly and deeply, press the device firmly to release the medication. Continue to breathe in and hold the breath for approximately 10 seconds or as long as is comfortable. Inhaling at the same time as actuating the inhaler ensures that active substances reach the lungs.
- Shake the inhaler again and repeat.
- Replace the mouthpiece cover after use.
- Rinse the mouth 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.
- Clean the mouthpiece of the inhaler regularly, at least once a week with a clean dry cloth.
- Do not put the inhaler into water.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

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. 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 rescue inhaler available at all times, either Symbicort (for patients using Symbicort as maintenance and reliever therapy) or a separate rapid-acting bronchodilator (for patients using Symbicort as maintenance therapy only).

Patients should be reminded to take their Symbicort 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 out 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. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of Symbicort.

If patients find the treatment ineffective or exceed the highest recommended dose of Symbicort, medical attention must be sought (see section 4.2). Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy. Sudden and progressive deterioration in control of asthma 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 not be initiated on Symbicort 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 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.

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 administration of the interacting drugs should be as long as possible. In patients using potent CYP3A4 inhibitors, Symbicort maintenance and reliever therapy is not recommended.

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

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

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, 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 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 (see section 4.8).

Paediatric population

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

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 (see section 4.4). In patients using potent CYP3A4 inhibitors, Symbicort maintenance and reliever therapy is not recommended.

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

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

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine) 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.

<u>Paediatric population</u>

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

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

There are no adequate data from use of formoterol in pregnant women. In animal reproduction studies, formoterol has caused adverse effects 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 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 to women who are breast-feeding 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 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Since Symbicort contains both budesonide and formoterol, the same pattern of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side effects of 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. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000) and very rare (<1/10 000).

Table 1

SOC	**Frequency**	**Adverse Drug Reaction**
Infections and infestations	Common	*Candida* infections in the oropharynx
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 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 population

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

An overdose of formoterol would likely lead to effects that are typical for β_2 adrenoceptor 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 of formoterol administered during three hours in patients with acute bronchial obstruction raised no safety concerns.

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

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

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 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, which 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
Clinical performance of Symbicort 80 µg/2.25 µg is documented using a bridging strategy where *in vitro* data is used to show similarity to a higher strength pMDI (160 µg/4.5 µg) and where pharmacokinetic data is used to compare the pMDI to Symbicort Turbuhaler, demonstrating delivery of a comparable amount of active drug to the systemic circulation (see section 5.2).

One randomised, double-blind, parallel-group, multicentre phase-III study compared the efficacy and safety of Symbicort pMDI (160/4.5 µg 2 actuations b.i.d., delivered dose) with that of Pulmicort pMDI (budesonide 200 µg 2 actuations b.i.d., metered dose) and to Symbicort Turbuhaler (budesonide/formoterol 160/4.5 µg 2 inhalations b.i.d., delivered dose) in adolescents and adults with asthma. Symbicort pMDI showed superiority to budesonide pMDI for morning PEF (mean difference 28.6 L/min; 95% CI: 20.9 to 36.4 L/min;

p<0.001). Results were comparable between Symbicort formulations (pMDI and Turbuhaler) with an estimated difference of -2.8 L/min; 95% (CI: -10.4 to 4.9 L/min).

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 (Turbuhaler) was equal to that of the free combination of budesonide and formoterol, and exceeded that of budesonide alone. All treatment arms used a short-acting β_2 adrenoceptor agonist as needed. There was no sign of attenuation of the anti-asthmatic effect over time.

Two clinical studies in 1107 adult and adolescent asthmatics have demonstrated the superior efficacy of Symbicort (80/4.5 and 160/4.5 µg/actuation, pressurised inhalation, suspension) over each of its mono-components in improving lung function (pre-dose FEV_1 and 12-hour FEV_1). Symptom-free days, quality of life and predefined asthma events were significantly improved for Symbicort compared to budesonide and formoterol.

The long-term safety and efficacy of Symbicort (80/4.5 and 160/4.5 µg/actuation, pressurised inhalation, suspension) compared to budesonide (80 and 160 µg/actuation) was evaluated in a 26-week safety and efficacy study on 11,963 adults and adolescents with asthma. The hazard ratio comparing risk of serious asthma-related events between Symbicort and budesonide, as assessed by the composite endpoint of asthma-related deaths, intubations and hospitalisations, was 1.07 (95% CI: 0.70 to 1.70). Statistical non-inferiority was demonstrated based on the upper limit of the 95% CI for the hazard ratio being <2. Symbicort was statistically superior to budesonide, as assessed by time to first severe asthma exacerbation and measures of symptom control.

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, of which 4447 were randomised to budesonide/formoterol (Turbuhaler) maintenance and reliever therapy for 6 or 12 months. Patients were required to be symptomatic despite use of inhaled glucocorticosteroids.

Budesonide/formoterol (Turbuhaler) 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 (Turbuhaler) at a higher maintenance dose with terbutaline as reliever (study 735) and budesonide/formoterol (Turbuhaler) at the same maintenance dose with either formoterol or terbutaline as reliever (study 734) (Table 2). 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 (Turbuhaler) 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 2 Overview of severe exacerbations in clinical studies

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 (Turbuhaler) provided rapid and effective relief of bronchoconstriction similar to salbutamol and formoterol.

See 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption
In a single-dose study, 8 inhalations of Symbicort (pressurised inhalation, suspension) 160 micrograms/4.5 micrograms (total dose 1280/36 micrograms) were administered to healthy volunteers. Budesonide and formoterol were rapidly absorbed with maximum plasma concentrations reached at 15 and 6 minutes after inhalation, respectively. Symbicort (pressurised inhalation, suspension) delivered a comparable amount of active drug to the systemic circulation as Symbicort Turbuhaler (total dose 1280/36 micrograms). The AUC for the budesonide component in Symbicort (pressurised inhalation, suspension) was 90% of the Turbuhaler comparator. The AUC for the formoterol component in Symbicort (pressurised inhalation, suspension) was 116% of the Turbuhaler comparator.

The systemic exposure to budesonide and formoterol from Symbicort (pressurised inhalation, suspension) 160 micrograms/4.5 micrograms, with and without the ***AeroChamber Plus Flow Vu*** spacer device, was evaluated in a study conducted in healthy volunteers.

The total systemic exposure of Symbicort (pressurised inhalation, suspension) 160 micrograms/4.5 micrograms administered through the ***AeroChamber Plus Flow Vu*** spacer was increased compared to no spacer, with mean AUC being 68% and 77% higher for budesonide and formoterol, respectively. However, the highest increases in exposure with spacer were observed in subjects showing low exposure without spacer (most probably due to poor inhalation technique).

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

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% to 13% of the delivered dose of formoterol is excreted unmetabolised in the urine. Formoterol has a high systemic clearance (approximately 1.4 l/min) and the terminal elimination half-life averages 17 hours.

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

budesonide have been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 l/min) and the plasma elimination half-life after i.v. dosing averages 4 hours.

The pharmacokinetics of budesonide or formoterol in patients with renal failure are 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

Apaflurane (HFA 227)
Povidone
Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life for Symbicort as packaged for sale is 2 years. The shelf life after first opening is 3 months.

6.4 Special precautions for storage

For best results, this medicine should be at room temperature before use. Do not refrigerate or freeze. Protect from frost and direct sunlight.

Replace the mouthpiece cover firmly and snap into position after use.

As with most inhaled medicinal products in pressurised containers, the therapeutic effect of this medicinal product decreases when the container is cold. This medicine should be at room temperature before use. The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister. The canister should not be broken, punctured or burnt, even when it seems empty.

6.5 Nature and contents of container

A pressurised container comprising an internally coated aluminium can, sealed with a metering valve and attached to a dose indicator. The can is fitted into a red plastic actuator incorporating a white plastic mouthpiece and integrated grey plastic dust cap. Each inhaler delivers 60 or 120 actuations of budesonide/formoterol fumarate dihydrate 80/2.25 micrograms after initial priming. Each inhaler is individually wrapped in a foil laminate pouch containing a desiccant.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

For Sweden (RMS):
AstraZeneca AB
151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2021-02-26