

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1473/028/002

Case No: 2054100

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

McDowell Pharmaceuticals

4 Altona Road, Lisburn, N. Ireland, BT27 5QB

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Symbicort Turbohaler 200 micrograms/6 micrograms/inhalation, inhalation powder

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **30/10/2009**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Symbicort Turbohaler 200 micrograms/6 micrograms/inhalation, inhalation powder.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Symbicort Turbohaler 200 micrograms/6 micrograms/inhalation delivers the same amount of budesonide and formoterol as the corresponding Turbohaler monoproducts, .ie.budesonide 200 micrograms/inhalation (metered dose) and formoterol 6 micrograms/inhalation (metered dose) alternatively labelled as 4.5 micrograms/inhalation (delivered dose).

Excipients: Lactose monohydrate 730 micrograms per dose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder

Product imported from the UK:

White powder

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Asthma

Symbicort is indicated in the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting beta₂-agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and “as needed” inhaled short-acting beta₂-agonists.
- or
- patients already adequately controlled on both inhaled corticosteroids and long-acting beta₂-agonists.

COPD

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

4.2 Posology and method of administration

Asthma

Symbicort is not intended for the initial management of asthma. The dosage of the components of Symbicort is individual and should be adjusted to the severity of the disease. This should be considered not only when treatment with combination products is initiated but also when the maintenance dose is adjusted.

If an individual patient should require a combination of doses other than those available in the combination inhaler, appropriate doses of beta₂-agonists and/or corticosteroids by individual inhalers should be prescribed.

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

For Symbicort there are two treatment approaches:

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

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

A. Symbicort maintenance therapy

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

Recommended doses:

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

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

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

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

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

B. Symbicort maintenance and reliever therapy

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

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

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

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

Recommended doses:

Adults (18 years and older): The recommended maintenance dose is 2 inhalations per day, given either as one inhalation in the morning and evening or as 2 inhalations in either the morning or evening. For some patients a maintenance dose of 2 inhalations twice daily may be appropriate. Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion.

A total daily dose of more than 8 inhalations is not normally needed; however, a total daily dose of up to 12 inhalations could be used for a limited period. Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice. They should be reassessed and their maintenance therapy should be reconsidered.

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

COPD

Recommended doses:

Adults: 2 inhalations twice daily.

General information

Special patient groups:

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

Instructions for correct use of Turbohaler:

Turbohaler is inspiratory flow-driven, which means that when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

Note: It is important to instruct the patient

- to carefully read the instructions for use in the patient information leaflet which is packed together with each 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 Turbohaler 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 Turbohaler due to the small amount of drug dispensed.

4.3 Contraindications

Hypersensitivity (allergy) to budesonide, formoterol or lactose (which contains small amounts of milk proteins).

4.4 Special warnings and precautions for use

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

If patients find the treatment ineffective, or exceed the highest recommended dose of Symbicort, medical attention must be sought (see section 4.2 Posology and method of administration). Sudden and progressive deterioration in control of asthma or COPD is potentially life threatening and the patient should undergo urgent medical assessment. In this situation consideration should be given to the need for increased therapy with corticosteroids, e.g. a course of oral corticosteroids, or antibiotic treatment if an infection is present.

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

Patients should be reminded to take their Symbicort maintenance dose as prescribed, even when asymptomatic. The prophylactic use of Symbicort, eg before exercise, has not been studied. The reliever inhalations of Symbicort should be taken in response to asthma symptoms but are not intended for regular prophylactic use, e.g. before exercise. For such use, a separate rapid-acting bronchodilator should be considered.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Symbicort. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Symbicort should be used (see section 4.2 Posology and method of administration).

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

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

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

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition consideration should be given to referring the patient to a paediatric respiratory specialist.

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

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

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

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

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

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

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

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

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

Potentially serious hypokalaemia may result from high doses of beta₂-agonists. Concomitant treatment of beta₂-agonists with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine-derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the beta₂-agonist. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalaemia adverse effects is increased. It is recommended that serum potassium levels are monitored during these circumstances.

As for all beta₂-agonists, additional blood glucose controls should be considered in diabetic patients.

Symbicort Turbohaler contains lactose (<1 mg/inhalation). This amount does not normally cause problems in lactose intolerant people. The excipient lactose contains small amounts of milk proteins, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

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

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), monoamine oxidase inhibitors 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 beta₂-sympathomimetics.

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

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

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

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

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

4.6 Pregnancy and lactation

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

There are no adequate data from use of formoterol in pregnant women. In animal studies formoterol has caused adverse effects in reproduction studies at very high systemic exposure levels (see section 5.3 Preclinical safety data).

Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies glucocorticosteroids have been shown to induce malformations (see section 5.3 Preclinical safety data). This is not likely to be relevant for humans given recommended doses.

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

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

Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the 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 breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

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 beta₂-agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment. In a 3-year clinical trial with budesonide in COPD, skin bruises and pneumonia occurred at a frequency of 10% and 6%, respectively, compared with 4% and 3% in the placebo group (p<0.001 and p<0.01, respectively).

Adverse reactions, which have been associated with budesonide or formoterol, are given below, listed by system organ class and frequency. Frequency are defined as: very common (≥1/10), common (≥1/100) and <1/10), uncommon (≥1/1 000 and < 1/100), rare (≥1/10 000 and < 1/1000) and very rare <1/10 000).

Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Rare	Cardiac arrhythmias, eg. atrial fibrillation, supraventricular tachycardia, extrasystoles
	Very rare	Angina pectoris
Endocrine disorders	Very rare	Signs or symptoms of systemic glucocorticosteroid effects eg. adrenal suppression, growth retardation, decrease in bone mineral density, cataract and glaucoma
Gastrointestinal disorders	Uncommon	Nausea
Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions, eg. exanthema, urticaria, pruritus,

		dermatitis, angioedema and anaphylactic reaction
Infections and infestations	Common	Candida infections in the oropharynx
Metabolic and nutrition disorders	Rare	Hypokalemia
	Very rare	Hyperglycemia
Musculoskeletal, connective tissue and bone disorders	Uncommon	Muscle cramps
Nervous system disorders	Common	Headache, tremor
	Uncommon	Dizziness
	Very rare	Taste disturbances
Psychiatric disorders	Uncommon	Agitation, restlessness, nervousness, sleep disturbances
	Very rare	Depression, behavioural disturbances (mainly in children)
Respiratory, thoracic and mediastinal disorders	Common	Mild irritation in the throat, coughing, hoarseness
	Rare	Bronchospasm
Skin and subcutaneous tissue disorders	Uncommon	Bruises
Vascular disorders	Very rare	Variations in blood pressure

As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases (see section 4.4 Special warning and precautions for use).

Treatment with beta₂-agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

4.9 Overdose

An overdose of formoterol would likely lead to effects that are typical for beta₂-adrenergic agonists: tremor, headache, palpitations. Symptoms reported from isolated cases are tachycardia, hyperglycaemia, hypokalaemia, prolonged QTc-interval, arrhythmia, nausea and vomiting. Supportive and symptomatic treatment may be indicated. A dose of 90 micrograms administered during three hours in patients with acute bronchial obstruction raised no safety concerns.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergics and other drugs for obstructive airway diseases. ATC-code: R03AK07

Mechanisms of action and pharmacodynamic effects

Symbicort contains formoterol and budesonide, which have different modes of action and show additive effects in terms of reduction of asthma exacerbations. The specific properties of budesonide and formoterol allow the combination to be used both as maintenance and reliever therapy, or as maintenance treatment of asthma.

Budesonide

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

Formoterol

Formoterol is a selective beta₂-adrenergic agonist that when inhaled results in rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose dependant, with an onset of effect within 1-3 minutes. The duration of effect is at least 12 hours after a single dose.

Symbicort Turbohaler

Asthma

Clinical efficacy for Symbicort maintenance therapy

Clinical studies in adults have shown that the addition of formoterol to budesonide improved asthma symptoms and lung function, and reduced exacerbations. In two 12-week studies the effect on lung function of Symbicort was equal to that of the free combination of budesonide and formoterol, and exceeded that of budesonide alone. All treatment arms used a short-acting beta₂-agonist as needed. There was no sign of attenuation of the anti-asthmatic effect over time.

In a 12-week paediatric study, 85 children aged 6-11 years were treated with a maintenance dose of Symbicort (2 inhalations of 80 micrograms /4.5 micrograms/inhalation twice daily), and a short-acting beta₂-agonist as needed. Lung function was improved and the treatment was well tolerated compared to the corresponding dose of budesonide Turbohaler.

Clinical efficacy for Symbicort maintenance and reliever therapy

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

Symbicort maintenance and reliever therapy provided statistically significant and clinically meaningful reductions in severe exacerbations for all comparisons in all 5 studies. This included a comparison with Symbicort at a higher maintenance dose with terbutaline as reliever (study 735) and Symbicort at the same maintenance dose with either formoterol or terbutaline as reliever (study 734) (Table 1). In Study 735, lung function, symptom control, and reliever use were similar in all treatment groups. In Study 734, symptoms and reliever use were reduced and lung function improved, compared with both comparator treatments. In the 5 studies combined, patients receiving Symbicort maintenance and reliever therapy used, on average, no reliever inhalations on 57% of treatment days. There was no sign of development of tolerance over time.

Study No. Duration	Treatment groups	N	Severe exacerbations ^a	
			Events	Events/ patient-year
Study 735 6 months	Symbicort 160/4.5 µg bd + as needed	1103	125	0.23 ^b
	Symbicort 320/9 µg bd + terbutaline 0.4 mg as needed	1099	173	0.32
	Salmeterol/fluticasone 2 x 25/125 µg bd + terbutaline 0.4 mg as needed	1119	208	0.38
Study 734 12 months	Symbicort 160/4.5 µg bd + as needed	1107	194	0.19 ^b
	Symbicort 160/4.5 µg bd + formoterol 4.5 µg as needed	1137	296	

				0.29
	Symbicort 160/4.5 µg bd + terbutaline 0.4 mg as needed	1138	377	0.37

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

In 2 other studies with patients seeking medical attention due to acute asthma symptoms, Symbicort provided rapid and effective relief of bronchoconstriction similar to salbutamol and formoterol.

COPD

In two 12-month studies, the effect on lung function and the rate of exacerbation (defined as courses of oral steroids and/or course of antibiotics and/or hospitalisations) in patients with severe COPD was evaluated. Median FEV1 at inclusion in the trials was 36% of predicted normal. The mean number of exacerbations per year (as defined above) was significantly reduced with Symbicort as compared with treatment with formoterol alone or placebo (mean rate 1.4 compared with 1.8-1.9 in the placebo/formoterol group). The mean number of days on oral corticosteroids/patient during the 12 months was slightly reduced in the Symbicort group (7-8 days/patient/year compared with 11-12 and 9-12 days in the placebo and formoterol groups, respectively). For changes in lung-function parameters, such as FEV1, Symbicort was not superior to treatment with formoterol alone.

5.2 Pharmacokinetic properties

Absorption

Symbicort Turbohaler and the corresponding monoproducts have been shown to be bioequivalent with regard to systemic exposure of budesonide and formoterol, respectively.

In spite of this, a small increase in cortisol suppression was seen after administration of Symbicort compared to the monoproducts. The difference is considered not to have an impact on clinical safety.

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

Pharmacokinetic parameters for the respective substances were comparable after the administration of budesonide and formoterol as monoproducts or as Symbicort Turbohaler. 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 Turbohaler ranged from 32% to 44% of the delivered dose. The systemic bioavailability is approximately 49% of the delivered dose.

Inhaled formoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation. In studies the mean lung deposition of formoterol after inhalation via Turbohaler ranged from 28% to 49% of the delivered dose. The systemic bioavailability is about 61% of the delivered dose.

Distribution and metabolism

Plasma protein binding is approximately 50% for formoterol and 90% for budesonide. Volume of distribution is about 4 L/kg for formoterol and 3 L/kg for budesonide. Formoterol is inactivated via conjugation reactions (active O-demethylated and deformedylated metabolites are formed, but they are seen mainly as inactivated conjugates). Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6-beta-hydroxy-budesonide and 16-alfa-hydroxy-prednisolone, is less than 1% of that of budesonide. There are no indications of any metabolic interactions or any displacement reactions between formoterol and budesonide.

Elimination

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

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

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

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 shelf-life expiry date of this product is the date shown on the over-labelled container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Symbicort Turbohaler is an inspiratory flow-driven, multidose. The inhaler is white with a red turning grip. The inhaler is made of different plastic materials (PP, PC, HDPE, LDPE, LLDPE, PBT). Each inhaler contains 120 doses.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 Parallel Product Authorisation Holder

McDowell Pharmaceuticals
4 Altona Road
Lisburn
BT27 5QB
United Kingdom

8 Parallel Product Authorisation Number

PPA1473/028/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th October 2009

10 DATE OF REVISION OF THE TEXT