

IRISH MEDICINES BOARD ACT 1995
MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998
(S.I. No.142 of 1998)

PPA1328/038/001

Case No: 2034068

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

B & S Healthcare

Unit 4, Bradfield Road, Ruislip, Middlesex, HA4 0NU, United Kingdom

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

Symbicort Turbohaler 100/6 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 **26/03/2007** until **28/09/2011**.

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 100/6 Inhalation powder.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Symbicort Turbohaler 100/6 delivers the same amount of budesonide and formoterol as the corresponding Turbohaler monoproducs i.e. budesonide 100 micrograms/inhalation (metered dose) and formoterol 6 micrograms/inhalation (metered dose) alternatively labeled as 4.5 micrograms/inhalation (delivered dose).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Inhalation powder.

Product imported from Spain:
White powder

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Asthma

Symbicort Turbohaler is indicated in the regular treatment of asthma where use of a combination (inhaled corticosteroid and long acting beta-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.

Symbicort Turbohaler 100/6 only

Note: Symbicort Turbohaler (100/6 micrograms/inhalation) is not appropriate for patients with severe asthma.

4.2 Posology and method of administration

Asthma

Symbicort Turbohaler is not intended for the initial management of asthma. The dosage of the components of Symbicort Turbohaler 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 dose is adjusted. If an individual patient should require a combination of doses other than those available in the combination inhaler, appropriate doses of beta-agonist and/or corticosteroids by individual inhalers should be prescribed.

Patients should be regularly reassessed by a doctor, so that the dosage of Symbicort Turbohaler remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

When control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

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

Special patient groups: There is no need to adjust the dose in elderly patients. There are no data available for use of Symbicort Turbohaler 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.

Adults: 1 inhalation twice daily.

Symbicort Turbohaler 100/6

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): 2 inhalations twice daily

Children under 6 years: Symbicort is not recommended for children under 6 years of age.

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 rinse the mouth out with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush

The patient may not taste or feel any medication when using Symbicort Turbohaler due to the small amount of drug dispensed.

4.3 Contraindications

Hypersensitivity (allergy) to budesonide, formoterol or inhaled lactose.

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 current dose of the fixed combination, medical attention must be sought. 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 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 or addition of systemic anti-inflammatory therapy, such as a course of oral corticosteroids, or antibiotic treatment if an infection is present.

There are no data available on the use of Symbicort Turbohaler in the treatment of an acute asthma attack. Patients should be advised to have their rapid acting bronchodilator available at all times. Patients should be reminded to take Symbicort Turbohaler daily as prescribed even when asymptomatic.

Therapy should not be initiated during an exacerbation.

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. Symbicort Turbohaler 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 1cm) 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 growth is slowed, and to minimise the risk of possible systemic effects, it is important that therapy is reviewed and the dose of inhaled corticosteroid is adjusted to the lowest dose at which effective control is maintained.

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 Turbohaler 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 the mouth with water after each dosing occasion.

Concomitant treatment with ketoconazole 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.

Symbicort Turbohaler 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 400/12 Turbohaler contains lactose (<1 mg/inhalation). This amount does not normally cause problems in lactose intolerant people.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Ketoconazole 200 mg once daily increased plasma levels of concomitantly administered oral budesonide (single dose of 3 mg) on average six-fold. When ketoconazole was administered 12 hours after budesonide, the concentration was on average increased three-fold. Information about this interaction is lacking for inhaled budesonide, but marked increases in plasma levels could be expected. Since data to give dosage recommendations are lacking, the combination should be avoided. If this is not possible the time interval between administration of ketoconazole and budesonide should be as long as possible. A reduction in the dose of budesonide should also be considered. Other potent inhibitors of CYP3A4 are also likely to markedly increase plasma levels of budesonide.

Pharmacodynamic interactions

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

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), monoamine oxidase inhibitors and tricyclic anti-depressants can prolong the QTc-

interval and increase the risk of ventricular arrhythmias.

In addition L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards 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 can have a potentially additive effect.

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

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

4.6 Pregnancy and lactation

For Symbicort Turbohaler or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Animal studies with respect to reproductive toxicity of the combination have not been performed.

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 Turbohaler 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.

It is not known whether formoterol or budesonide passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of Symbicort Turbohaler 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.

4.7 Effects on ability to drive and use machines

Symbicort Turbohaler has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Since Symbicort Turbohaler 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 -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.

Common

(>1/100, <1/10) Central nervous system: Headache.
Cardiovascular system: Palpitations.
Musculoskeletal system: Tremor.
Respiratory tract: Candida infections in the oropharynx, mild irritation in the throat, coughing, hoarseness.

Uncommon

(>1/1,000, <1/100) Cardiovascular system: Tachycardia.
Musculoskeletal system: Muscle cramps.
Central nervous system: Agitation, restlessness, nervousness, nausea, dizziness, sleep disturbances.
Skin: Bruises.

Rare

(>1/10,000, <1/1000) Skin: Exanthema, urticaria, pruritus, dermatitis, angioedema.
Respiratory tract: Bronchospasm
Metabolic: Hypokalaemia
Cardiovascular disorders: Atrial fibrillation, supraventricular tachycardia, extrasystoles

Very rare (<1/10,000) Metabolic: Hyperglycaemia, signs or symptoms of systemic glucocorticosteroid effects (including hypofunction of the adrenal gland).
Psychiatric disorders: Depression, behavioural disturbances (mainly in children)

Central nervous system: Taste disturbances

Cardiovascular system: Angina pectoris, variations in blood pressure

As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases (see section 4.4).

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods, see also 4.4.

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

Symbicort Turbohaler 400/12 only

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).

4.9 Overdose

An overdose of formoterol would likely lead to effects that are typical for β_2 -adrenergic agonists: tremor, headache, palpitations. Symptoms reported from isolated cases and 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 Turbohaler contains formoterol and budesonide, which have different modes of action and show additive effects in terms of reduction of asthma exacerbations. The mechanisms of action of the two substances, respectively are discussed below.

Budesonide

Budesonide given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma with less adverse effects than when corticosteroids are administered systemically. The exact mechanism responsible for this anti-inflammatory effect is unknown.

Formoterol

Formoterol is a selective β_2 -adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation, and has a duration of 12 hours after a single dose.

Symbicort Turbohaler

Asthma

In clinical trials, 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 Turbohaler in asthma was equal to that of the free combination of budesonide and formoterol, and exceeded that of budesonide alone. 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 for asthma with Symbicort Turbohaler (2 inhalations of 80/4.5 micrograms/inhalation twice daily), which improved lung function and was well tolerated.

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 Turbohaler compared with 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 28-49% 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 (approx. 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.

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 shall be the date shown on the 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 powder inhaler. 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

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8 Parallel Product Authorisation Number

PPA1328/38/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 29th September 2006

10 DATE OF REVISION OF THE TEXT

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