Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Novolizer Formoterol 6 micrograms/dose inhalation powder

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains 6 micrograms formoterol fumarate dihydrate (corresponding to one delivered dose leaving the mouthpiece of 5.1 micrograms formoterol fumarate dihydrate equivalent to 4.18 micrograms formoterol).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Inhalation powder

White powder

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Novolizer Formoterol 6 micrograms is indicated in adults, adolescents and children aged 6 to 12 years.

Novolizer Formoterol 6 micrograms is indicated for the long-term symptomatic treatment of persistent, moderate to severe asthma in patients requiring regular long-acting B_2 agonist therapy in combination with inhaled anti-inflammatory therapy (with or without oral glucocorticoids).

Glucocorticoid therapy should be continued on a regular basis.

Novolizer Formoterol 6 micrograms is also indicated for the relief of broncho-obstructive symptoms in patients with chronic obstructive pulmonary disease (COPD) requiring long-acting bronchodilatory therapy.

4.2 Posology and method of administration

For inhalation use

Use of doses above those normally required by the individual patient on more than 2 days per week is a sign of suboptimal disease control and maintenance treatment should be reassessed.

Novolizer Formoterol 6 micrograms should be taken twice daily.

Asthma

Adults (including older people) and adolescents over 12 years of age

Regular Maintenance Therapy:
2 inhalations (12 micrograms) to be inhaled twice daily. For more severe disease this dose regimen can be increased to 4 inhalations (24 micrograms) to be inhaled twice daily.

The maximum daily dose is 8 inhalations (4 inhalations inhaled twice daily) corresponding to 48 micrograms.

Paediatric population

Children 6 years and older

Regular Maintenance Therapy:

2 inhalations (12 micrograms) to be inhaled twice daily. For more severe disease this dose regimen can be increased to 4 inhalations (24 micrograms) to be inhaled twice daily but only after assessment by a physician.

The regular daily dose should not exceed 4 inhalations (24 micrograms), however, occasionally up to a maximum of 8 inhalations (corresponding to 48 micrograms) may be allowed within a 24-hours period.

Children below 6 years of age
Novolizer Formoterol is not recommended for use in children under the age of 6 years as insufficient experience is available in this age group.

COPD
Adults (including older people) and adolescents over 12 years of age
Regular dosage: 2 inhalations (12 micrograms) twice daily.

The daily dose for regular use should not exceed 4 inhalations (24 micrograms).
If required, additional inhalations above those prescribed for regular therapy may be used for relief of symptoms, up to a maximum total daily dose of 8 inhalations corresponding to 48 micrograms (regular plus as required). More than 4 inhalations should not be taken on any single occasion.

The use of formoterol is indicated for those patients receiving inhaled corticosteroids where further regular symptomatic treatment of asthma is required in addition to inhaled corticosteroids.

Although formoterol has a rapid onset of action, long-acting inhaled bronchodilators (as formoterol) should be used for maintenance bronchodilator therapy only.

Formoterol is not intended to relieve acute asthma attacks. In the event of an acute attack, a short acting β_2-agonist should be used.

Patients should be advised not to stop or change their steroid therapy when Novolizer Formoterol is introduced.

Older people and patients with renal or hepatic impairment
No adjustment of dose should be required in the elderly, or in patients with renal or hepatic impairment at the recommended normal doses. (See section 4.4).

Mode of treatment

In order to ensure that the active substance optimally reaches the intended site of action it is necessary to inhale steadily, deeply and as rapidly as possible (to the maximum inhalation). A clearly audible click and a colour change in the control window indicate that inhalation has been performed correctly. If an audible click is not heard and there is no colour change in the control window, inhalation should be repeated. The inhaler remains locked until inhalation is performed correctly.

Usage and handling of the Novolizer

Refilling

1. Lightly press together the ribbed surfaces on both sides of the lid, move the lid forwards and lift off.

2. Remove the protective aluminium foil from the cartridge box and take out the new cartridge.

3. Insert the cartridge into the Novolizer with the dosage counter facing the mouthpiece.

4. Replace the lid into the side guides from above and push down flat towards the dosage button until it snaps into place. The cartridge can be left in the Novolizer until it has been used up, or for up to 6 months after insertion.

Note: Novolizer Formoterol 6 micrograms cartridges may only be used in the Novolizer powder inhaler.

Usage

1. Whenever possible, sit or stand while inhaling. When using the Novolizer always keep it horizontal. First remove the protective cap.

2. Completely depress the coloured dosage button. A loud double click will be heard and the colour of the control window (lower) will change from red to green. Then release the coloured dosage button. The colour green in the window indicates that the Novolizer is ready for use.

3. Exhale as far as possible (but not into the powder inhaler).

4. Put the lips around the mouthpiece. Inhale the powder steadily, deeply and as rapidly as possible (to the maximum inhalation).During this breath a loud click should be heard, indicating correct inhalation. Hold the breath for a few seconds and then continue with normal breathing.

Note: If the patient needs to take more than 1 actuation at a time, steps 2 - 4 should be repeated.

5. Replace the protective cap on the mouthpiece - the inhalation procedure is now complete.

6. The number in the top window indicates the number of inhalations left.

Note: The coloured dosage button should only be pressed immediately before inhalation.

A double inhalation in erroris not possible with the Novolizer. The click sound and the change of colour in the control window indicate that inhalation has been performed correctly. If the colour of the control window does not change, then inhalation should be repeated. If inhalation is not completed correctly after several attempts, then the patient should consult the doctor/physician.

Cleaning

The Novolizer should be cleaned at regular intervals, but at least every time the cartridge is changed. Instructions on how to clean the device can be found in the brochure operating instructions in the carton.

Note: In order to ensure correct use of the inhaler, patients should receive thorough instructions on how to use the device. Children should only use this product under the supervision of an adult.

4.3 Contraindications

Hypersensitivity to the active substance formoterol or to the excipient lactose.

4.4 Special warnings and precautions for use

Novolizer Formoterol 6 micrograms should not be used (and is not sufficient) as the first treatment for asthma.

Asthmatic patients who require therapy with long-acting β_2-agonists, should also receive optimal maintenance anti-inflammatory therapy with corticosteroids. Patients must be advised to continue taking their anti-inflammatory therapy and must be told that the dose of anti-inflammatory therapy should not be decreased following the introduction of formoterol without a medical advice even when symptoms improve. Should symptoms persist or worsen or the number of doses of β_2-agonists required to control symptoms increases, this usually indicates a worsening of the underlying condition and the patients should be told to contact their doctor in order that their asthma and its treatment can be reassessed.

Although Novolizer Formoterol 6 micrograms may be introduced as add-on therapy when inhaled corticosteroids do not provide adequate control of asthma symptoms, patients should not be initiated on Novolizer Formoterol 6 micrograms during an acute severe asthma exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Serious asthma-related adverse events and exacerbations may occur during treatment with Novolizer Formoterol 6

micrograms. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Novolizer Formoterol 6 micrograms.
Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Novolizer Formoterol 6 micrograms. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Novolizer Formoterol 6 micrograms should be used.

Formoterol should only be used in patients requiring treatment with long-acting bronchodilators (see section 4.1) and should not be used as an alternative to short-acting B_2agonists in the event of an acute attack. In the event of an acute attack, a short-acting B_2 agonist must be used.

The maximum daily dose should not be exceeded. The long-term safety of regular treatment at higher doses than 8 inhalations per day in adults with asthma, 4 inhalations per day in children with asthma and 4 inhalations per day in patients with COPD, has not been established.

Frequent need of medication for the prevention of exercise-induced bronchoconstriction (EIB) can be a sign of suboptimal asthma control, and warrants a reassessment of the asthma therapy and an evaluation of compliance. If the patient needs prophylactic treatment for EIB several times every week despite adequate maintenance treatment (e.g. corticosteroids and long-acting β_2-agonists), the total asthma management should be reassessed by a specialist.

Caution should be observed when treating patients with thyrotoxicosis, phaeochromocytoma, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, cardiac arrhythmias, especially third degree atrioventricular block, or severe heart failure. An adjustment of the dose of formoterol may be considered.

Formoterol may induce prolongation of the QT_c-interval. Caution should be observed when treating patients with prolongation of the QT_c-interval (see section 4.5).

Due to the hyperglycaemic effects of β_2-agonists, additional blood glucose monitoring is recommended initially in diabetic patients.

Potentially serious hypokalaemia may result from β_2-agonist therapy. Particular caution is recommended in acute severe asthma as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatment with xanthine-derivatives, steroids and diuretics. The serum potassium levels should therefore be monitored. Special caution is advised if theophylline and formoterol are used concomitantly in patients with pre-existing cardiac disease.

As with other inhalation therapy there is a risk of paradoxical bronchospasm. If this occurs the patient will experience an immediate increase in wheezing and shortness of breath after dosing which should be treated straightaway with a fast-acting inhaled bronchodilator. Novolizer Formoterol should be discontinued immediately, the patient should be assessed and, if necessary, alternative therapy instituted.

Novolizer Formoterol 6 micrograms contains 5.744 mg lactose per single dose. This amount does not normally cause problems in lactose intolerant people.
Lactose may contain small amounts of milk protein.

Children up to the age of 6 years should not be treated with formoterol, as insufficient experience is available for this age group.

The effect of decreased liver or kidney function on the pharmacokinetics of formoterol and the pharmacokinetics in the elderly is not known. As formoterol is primarily eliminated via metabolism, increased exposure can be expected in patients with severe liver cirrhosis.

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed with Novolizer Formoterol.

Concomitant treatment with other sympathomimetic substances such as other β_2-agonists or ephedrine may potentiate the undesirable effects of formoterol and may require titration of the dose.

Concomitant treatment with xanthine derivatives, steroids or diuretics such as thiazides and loop diuretics may potentiate a possible hypokalaemic adverse effect of β_2-agonists. Hypokalaemia may increase the susceptibility to arrhythmias in patients who are treated with digitalis glycosides.

Concomitant use with oral corticosteroids might increase hyperglycaemic effects.

There is a theoretical risk that concomitant treatment with other drugs known to prolong the QTc-interval may give rise to a pharmacodynamic interaction with formoterol and increase the possible risk of ventricular arrhythmias. Examples of such drugs include certain antihistamines (e.g. terfenadine, astemizole, mizolastine), certain antiarrhythmics (e.g. quinidine, disopyramide, procainamide), phenothiazines, erythromycin and tricyclic antidepressants.

Administration of formoterol to patients being treated with monoamine oxidase inhibitors (*or having been treated during the past 14 days*) or tricyclic antidepressants should be performed with caution, since the action of B_2-adrenergic stimulants on the cardiovascular system may be potentiated.

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

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

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

4.6 Fertility, pregnancy and lactation

Fertility
There are only limited data with regard to fertility (see section 5.3). Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 1000 times the recommended daily inhalation dose of 24 µg in human on a mg/m2 basis).

Pregnancy
There are no adequate data from the use of formoterol in pregnant women. In animal studies formoterol has caused implantation losses as well as decreased early postnatal survival and birth weight. The effects appeared at considerably higher systemic exposures than those reached during clinical use of Formoterol. Treatment with Formoterol may be considered at all stages of pregnancy if needed to obtain asthma control, and if the expected benefit to the mother is greater than any possible risk to the fetus. The potential risk for human is unknown.

Lactation
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 Formoterol 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

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

4.8 Undesirable effects

The most commonly reported adverse events of β_2-agonists therapy, such as tremor and palpitations, tend to be mild and disappear within a few days of treatment.

Adverse reactions, which have been associated with formoterol are given below listed by system organ class and frequency. Frequencies are defined as:
Very common ($\geq$ 1/10); Common ($\geq$ 1/100 to < 1/10); Uncommon ($\geq$ 1/1,000 to < 1/100);
Rare ($\geq$ 1/10,000 to < 1/1,000); Very rare (< 1/10,000); Not known (cannot be estimated from the available data)

Organ System	**Frequency**	**Adverse drug reaction**
Immune system disorders	***Rare***	Hypersensitivity reactions, e.g. bronchospasm, exanthema, urticaria, pruritus, angiooedema
Metabolism and nutrition disorders	***Rare***	Hypokalaemia/Hyperkalaemia

Organ System	Frequency	Adverse drug reaction
	Very rare	Hyperglycaemia
Psychiatric disorders	***Uncommon***	Agitation, restlessness, sleep disturbance
Nervous system disorders	***Common***	Headache, tremor
	Rare	Nervousness
	Very rare	Taste disturbance, dizziness
Cardiac disorders	***Common***	Palpitations
	Uncommon	Tachycardia
	Rare	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles
	Very rare	Angina pectoris, p rolongation of QTc-interval
Vascular disorders	***Very rare***	Variations in blood pressure
Respiratory, thoracic and mediastinal disorders	***Uncommon***	oropharyngeal irritation
Gastrointestinal disorders	***Rare***	Nausea
Musculoskeletal and connective tissue disorders	***Uncommon***	Muscle cramps

As with all inhalation therapy, paradoxical bronchospasm may occur in rare cases.
Treatment with β_2-agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

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 IMB Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.imb.ie; e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

There is limited clinical experience in the management of overdose. An overdose would likely lead to effects that are typical of β_2-agonists: tremor, headache, palpitations. Symptoms reported from isolated cases are tachycardia, hyperglycaemia, hypokalaemia, prolonged QT_c -interval, arrhythmia, nausea and vomiting. Supportive and symptomatic treatment is indicated.

Use of cardioselective beta blockers may be considered, but only subject to extreme caution since the use of β-adrenergic blocker medication may provoke bronchospasm. Serum potassium levels should be monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective β_2-agonist**,** formoterol
ATC code: R03AC13

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

5.2 Pharmacokinetic properties

Absorption

Inhaled formoterol is rapidly absorbed. Peak plasma concentration is reached about 10 minutes after inhalation.

Clinical studies indicated that the lung deposition of formoterol after inhalation via the Novolizer is within the range of other inhaler products containing formoterol.

Distribution and metabolism

Plasma protein binding is approximately 50%.

Formoterol is metabolised via direct glucuronidation and O-demethylation. The enzyme responsible for O-demethylation has not been identified. Total plasma clearance and volume of distribution have not been determined.

Elimination

The major part of the dose of formoterol is eliminated via metabolism. After inhalation with a similar powder inhaler device 8-13% of the delivered dose of formoterol was excreted unmetabolised in the urine. About 20% of an intravenous dose is excreted unchanged in the urine. The terminal half-life after inhalation is estimated to be 8 hours.

5.3 Preclinical safety data

The effects of formoterol seen in toxicity studies in rats and dogs were mainly on the cardiovascular system and consisted of hyperaemia, tachycardia, arrhythmias and myocardial lesions. These effects are known pharmacological manifestations seen after the administration of high doses of β_2-agonists.

In animal studies formoterol has caused implantation losses as well as decreased early postnatal survival and birth weight. The effects appeared at considerably higher systemic exposures than those reached during clinical use of formoterol. A somewhat reduced fertility in male rats was observed at high systemic exposure to formoterol.

No genotoxic effects of formoterol have been observed in in-vitro or in-vivo tests. In rats and mice a slight increase in the incidence of benign uterine leiomyomas has been observed. This effect is looked upon as a class-effect observed in rodents after long exposure to high doses of β_2-agonists.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

- **Novolizer Formoterol 6 micrograms**

Shelf life of the medicinal product as packaged for sale: 3 years
Shelf life after first opening the cartridge container: 6 months

- **Novolizer device**

Shelf life before first use: 4 years
In-use shelf life: 1 year

Note: The functioning of the Novolizer has been demonstrated in tests for 2000 metered doses.
This amount of metered doses is not expected to be exceeded during one year of normal dosage.

6.4 Special precautions for storage

Store in the original package.
After first opening the cartridge cylinder: Store below 25 °C. Store protected from moisture.

6.5 Nature and contents of container

The inhaler (mouth- piece) is made of polyethylene and the cartridge is made of acrylonitrile-butadiene-styrene (ABS)/polypropylene.

Pack sizes:
1 powder inhaler and 1 cartridge (ABS / polypropylene)with at least 60 actuations.
1 powder inhaler and 2 cartridges (ABS / polypropylene)with at least 60 actuations each.

Refill packs:
1 cartridge (ABS / polypropylene)with at least 60 actuations
2 cartridges (ABS / polypropylene) with at least 60 actuations each
3 cartridges (ABS / polypropylene)with at least 60 actuations each

Hospital packs:
Pack with 10 x (1 powder inhaler and 1 cartridge (ABS / polypropylene) with at least 60 actuations)
"Not all pack sizes may be marketed"

6.6 Special precautions for disposal

No special requirement.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA2010/051/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th October 2008
Date of last renewal: 23rd November 2009

10 DATE OF REVISION OF THE TEXT

November 2018