Formoterol

Core Safety Profile

4.2 Posology and method of administration

Capsules are for inhalation only. (*This statement is only applicable to products using capsules*).

4.3 Contraindications

Hypersensitivity to formoterol or to lactose (which contains small amount of milk proteins). *(The statement regarding lactose is only applicable to products which contain lactose as an excipient)*

4.4 Special warnings and special precautions for use

Formoterol 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 after the introduction of Formoterol even when symptoms decrease. Should symptoms persist, or treatment with β_2-agonists need to be increased, this indicates a worsening of the underlying condition and warrants a reassessment of the maintenance therapy.

Although Formoterol may be introduced as add-on therapy when inhaled corticosteroids do not provide adequate control of asthma symptoms, patients should not be initiated on Formoterol 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 Formoterol . Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Formoterol . Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Formoterol . Regular review of patients as treatment is stepped down is important. The lowest effective dose of Formoterol should be used.

The maximum daily dose should not be exceeded. The long term safety of regular treatment at higher doses than 36 micrograms per day in adults with asthma, 18 micrograms per day in children with asthma and 18 micrograms per day in patients with COPD has not been established.

Frequent need of medication (i.e. prophylactic treatment e.g. corticosteroids and long-acting β_2-agonists) for the prevention of exercise-induced bronchoconstriction several times every week, despite an adequate maintenance

treatment, can be a sign of suboptimal asthma control, and warrants a reassessment of the asthma therapy and an evaluation of the compliance.

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, tachyarrhythmias or severe heart failure.

Formoterol may induce prolongation of the QTc-interval. Caution should be observed when treating patients with prolongation of the QTc-interval and in patients treated with drugs affecting the QTc-interval (see 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.

As with other inhalation therapy, the potential for paradoxial bronchospasm should be considered. If it occurs, the treatment should be discontinued immediately and alternative therapy started (see section 4.8).

Formoterol contains lactose monohydrate (less than 500 micrograms per delivered dose). This amount does not normally cause problems in lactose intolerant people. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. *(The statement regarding lactose is only applicable to products which contain lactose as an excipient).*

Children up to the age of 6 years should not be treated with Formoterol , as no sufficient experience is available for this group.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been carried out with 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 rare hypokalaemic adverse effect of β_2-agonists. Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

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), erythromycin and tricyclic antidepressants.

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

The bronchodilating effects of formoterol can be enhanced by anticholinergic drugs.

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 Pregnancy and lactation

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.

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 influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported adverse events of β_2-agonist 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. 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, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles.
	Very rare	Angina pectoris, Prolongation of QTc interval
Gastrointestinal disorders	Rare	Nausea
Immune system disorders	Rare	Hypersensitivity reactions, e.g. bronchospasm, exanthema, urticaria, pruritus
Metabolic and nutrition disorders	Rare	Hypokalemia
	Very rare	Hyperglycemia
Musculoskeletal, connective tissue and bone disorders	Uncommon	Muscle cramps
Nervous system disorders	Common	Headache, tremor
	Very rare	Taste disturbances, dizziness
Psychiatric disorders	Uncommon	Agitation, restlessness, sleep disturbances
Vascular disorders	Very rare	Variations in blood pressure

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

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

The excipient lactose contains small amounts of milk proteins. These may cause allergic reactions.

4.9 Overdose

There is limited clinical experience on 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 QTc-interval, arrythmia, 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 should be monitored.