Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Formoterol 12 micrograms inhalation powder, hard capsule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 12 micrograms of formoterol fumarate (as dihydrate).

Excipients with known effect: Lactose Monohydrate 23.99 mg.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder, hard capsule.

Transparent gelatin capsules containing white powder for inhalation.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prevention of bronchospasm as a result of exertion, symptomatic treatment of bronchial asthma and other chronic obstruction pulmonary diseases with a reversible component.
Symptomatic long-term treatment of bronchial asthma in combination with a long-term antiinflammatory therapy (eg. corticosteroids).

Note:
There are no indications to date that formoterol can replace treatment with corticosteroids. In any case formoterol must be combined with corticosteroids by inhalation in bronchial asthma.

4.2 Posology and method of administration

Capsules are only for inhalation.

Formoterol's bronchodilator effect is still significant 12 hours after inhalation. Administration twice daily will therefore in most cases be adequate to control bronchoconstriction associated with chronic conditions, both during the day and at night.

Posology

Adults:
Symptomatic treatment of bronchial asthma and other chronic obstructive pulmonary diseases with a reversible component.
Normal maintenance dose is 1 inhalation capsule (12 micrograms) twice a day.
If it is necessary to relieve possible symptoms, a further 1-2 capsules per day may be used. The maximum daily dose is 4 capsules (48 micrograms).
The patient should be informed that if the extra dosage is necessary more than twice a week, the doctor should be consulted and treatment reassessed, as it is possible that the condition has deteriorated.

Prophylaxis on exertion-induced bronchospasm or before an unavoidable exposure to a known allergen:
The contents of 1 inhalation capsule (12 micrograms) are inhaled 15 minutes before expected activity or exposure to the allergen. In adult patients with serious asthma, 2 capsules (24 micrograms) may be necessary.

Paediatric population

Children from 6 years:
Symptomatic treatment of bronchial asthma without other chronic obstructive pulmonary diseases with a reversible component:

Normal maintenance dose is 1 inhalation capsule (12 micrograms) twice a day.
If it is necessary to relieve possible symptoms, a further 1-2 capsules per day may be used. The maximum daily dose is 4 capsules (48 micrograms).
The patient should be informed that if the extra dosage is necessary more than twice a week, the doctor should be consulted and treatment reassessed, as it is possible that the condition has deteriorated.

Prevention of bronchospasm as a result of inhaled allergens or exertion:
The contents of 1 inhalation capsule (12 micrograms) are inhaled 15 minutes before expected activity or exposure to the allergen.

Should not be used inchildren under the age of 6 years.

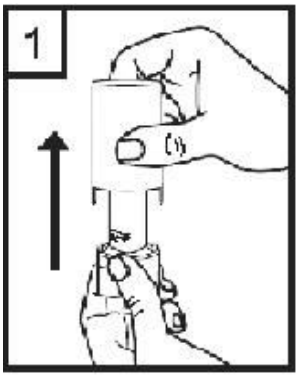
Renal and hepatic impairment:
There is no theoretical reason to suggest that the formoterol dosage requires adjustment in patients with renal or hepatic impairment, however no clinical data have been generated to support its use in these groups.

It should be ensured that the patient is instructed in the use of the inhaler by doctor or pharmacist.

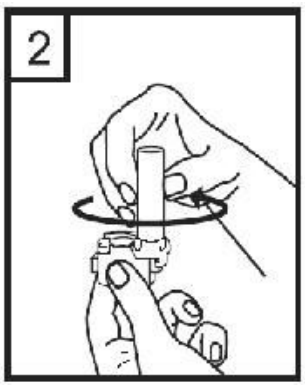
Method of administration

Instructions for use:

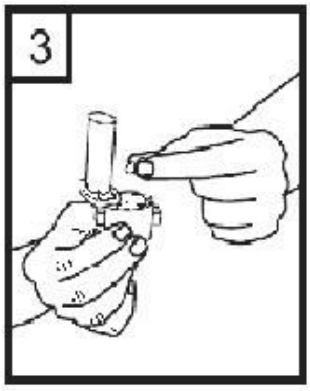
1. Pull off the cap.



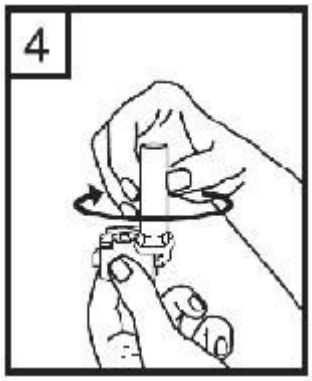
2. Hold the base of the inhaler firmly and turn the mouthpiece in the direction of the arrow to open.



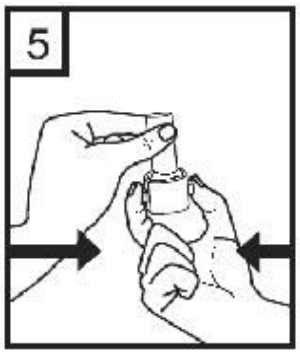
3. Place one capsule with dry hands in the capsule-shaped compartment in the base of the inhaler.



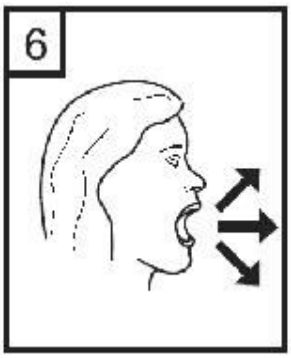
4. Twist the mouthpiece to the closed position.



5. Keeping the inhaler upright (mouthpiece to top), firmly squeeze the two buttons at the same time once only. This will pierce the capsule. Release the buttons.
Note:
It is possible that gelatine capsule fragment and small pieces of gelatin capsule get into mouth and throat during inhalation. Gelatine pieces are harmless and will be digested after swallowing. The risk of fragmentation of gelatine capsule will be minimised if you remove the capsule from the blister pack immediately before use and squeeze the two



6. Breathe out fully.



7. Place the mouthpiece in your mouth and tilt your head slightly backwards. Close your lips around the mouthpiece and breathe in as quickly and as deeply as you can.

8. Hold your breath for as long as you comfortably can while taking the inhaler out of your mouth. Then breathe normally. Open the inhaler to see if any powder is still in the capsule. If there is still powder in the capsule, repeat steps 6 to 8.

9. After use, tip out the empty capsule and close the mouthpiece.

Inhaler cleaning:
In order to remove residual powder, clean mouthpiece and capsule compartment with a dry cloth. Also a clean soft brush can be used.

4.3 Contraindications

Hypersensitivity to the active substance, to beta 2 agonists in general or to lactose (which contains small amount of milk proteins) or to any of the other excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

Ashmatic 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 proved 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 β2-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 QTcinterval (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.

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.

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

Formoterol inhalation powder should not be used therapeutically in the event of premature birth or threatened abortionLike other beta-$_2$ agonists, formoterol may restrict labour pains because of relaxation of the smooth musculature in the uterus.

4.5 Interaction with other medicinal products and other forms of interactions

NospecificinteractionstudieshavebeencarriedoutwithFormoterol.

Concomitanttreatmentwithothersympathomimeticsubstancessuchasotherβ2-agonistsor ephedrinemay potentiatetheundesirableeffectsofFormoterol andmay requiretitrationof thedose.

Concomitanttreatmentwithxanthinederivatives,steroidsordiureticssuchasthiazidesand loopdiureticsmay potentiateararehypokalaemicadverseeffectof β2-agonists. Hypokalaemiamay increasethedispositiontowardsarrhythmiasinpatientswhoaretreated withdigitalisglycosides.

Thereisatheoreticalriskthatconcomitanttreatmentwithotherdrugsknowntoprolongthe QTc-intervalmaygiverisetoa pharmacodynamicinteractionwithformoterolandincrease thepossibleriskofventriculararrhythmias.Examplesofsuchdrugsincludecertain

antihistamines(e.g.terfenadine,astemizole,mizolastine),certainantiarrhythmics(e.g. quinidine,disopyramide,procainamide),erythromycin, phenothiazinesandtricyclicantidepressants.

An increased hyperglycaemic effect of the combination of corticosteroids and formoterol is possible.

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, corticosteroids and xanthine derivatives.

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.

Monoamine oxidase inhibitors:
Formoterol may interact with monoamine oxidase inhibitors and should not be given to patients receiving treatment with these or up to 14 days after discontinuation.

4.6 Fertility, pregnancy and lactation

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 ormoterol . 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.

Breast-feeding
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 ormoterol 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

Formoterolhasnoinfluenceontheabilitytodriveandusemachines.

4.8 Undesirable effects

Themostcommonlyreportedadverseeventsof β2-agonisttherapy,suchastremorand palpitations,tendtobemildanddisappearwithinafew daysoftreatment.

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), now known (cannot be estimated form the available data)

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, oropharingeal irritation
Immune system disorders	Rare	Hypersensitivity reactions, e.g. bronchospasm, exanthema, urticaria, pruritus, severe hypotension, angioedema
	Very rare	Peripheral oedema
Metabolic and nutrition disorders	Rare	Hypokalemia
	Very rare	Hyperglycemia, hyperkalaemia
Musculoskeletal, connective tissue disorders	Uncommon	Muscle cramps, myalgia
Nervous system disorders	Common	Headache, tremor

	Uncommon	Anxiety, nervousness, insomnia, dizziness
	Rare	Taste disturbances
Psychiatric disorders	Uncommon	Agitation, restlessness, sleep disturbances
Vascular disorders	Very rare	Variations in blood pressure
Respiratoy, thoracic and mediastinal disorders	Uncommon	Aggravated bronchospasm

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.

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 HPRA Pharmacovigilance Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie

4.9 Overdose

There is limited clinical experience on the management of overdose. An overdose would likely lead to effects that are typical of β2-agonists: tremor, headache, palpitations, tachycardia, hyperglycaemia, hypokalaemia, prolonged QTc-interval, ventricular arrythmias, somnolence, metabolic acidosis, hypotension, nausea and vomiting. Beta 2 agonists may provoke ischaemic heart disease by acute reduction of the diastolic blood pressure or precipitation of heart arrhythmias.

Treatment:
Surportive and symptomatic.
In serious cases, the patient should be admitted to hospital.
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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: drugs for obstructive airway diseases, adrenergics, inhalants, selective beta-2-adrenoreceptor agonists, ATC code: R03 AC13.
Formoterol is a powerful selective beta-2 adrenergic receptor agonist. Formoterol exhibits a bronchodilator effect in patients with reversible airways obstruction. The effect sets in quickly (within 1-3 minutes) and is still significant 12 hours after inhalation. With therapeutic doses, the cardiovascular effects are small and appear only occasionally.

Formoterol inhibits the release of histamine and leukotrienes from passively sensitised human lung. Certain anti-inflammatory properties, such as inhibition of oedema and inflammatory cell accumulation, are observed in experiments with animals.

In humans, Formoterol has proven to be effective in the prevention of bronchospasm induced by inhaled allergens, physical activity, cold air, histamine and metacholine.

In patients with stable chronic obstructive pulmonary disease with a reversible component, formoterol inhaled via Aerolizer in doses of 12 and 24 micrograms twice daily has proven to have a bronchodilator effect of rapid onset that lasts for at least 12 hours. In addition, the treatment gave rise to a subjective improvement in quality of life evaluated using Saint George's Respiratory Questionnaire.

5.2 Pharmacokinetic properties

Absorption:
It is probable that up to 90% of the administered volume of formoterol is swallowed and absorbed from the gastrointestinal tract. This means that the pharmacokinetic characteristics of an oral formulation to a great degree apply for inhalation powder.

Oral doses of up to 300 micrograms of formoterol fumarate are quickly absorbed from the gastrointestinal tract. Peak plasma concentrations of unaltered substance are achieved 0.5-1 hour after ingestion. Of an oral dose of 80 micrograms, 65% or more is absorbed.

Formoterol's pharmacokinetics are linear in the dose interval studied (20-300 micrograms). Repeated oral administration of 40-160 micrograms/day causes no significant accumulation of the substance.

After inhalation of therapeutic doses, formoterol could not be detected in plasma using previous normal methods of analysis. Analyses of urinary excretion rates suggest that inhaled formoterol is absorbed quickly. The maximum excretion rate after administration of 12- 96 micrograms is achieved 1-2 hours after inhalation. On giving a higher dose than the therapeutic (120 micrograms single dose), peak plasma concentration (266 picomol/l) was observed 5 minutes after inhalation. In patients with chronic obstructive pulmonary disease with a reversible component who were treated for 12 weeks with formoterol fumarate 12 or 24 micrograms twice daily, formoterol concentrations varied between 11.5 and 25.7 picomol/l and 23.3 and 50.3 picomol/l, respectively, 10 minutes, 2 hours and 6 hours after inhalation.

Cumulative urinary excretion of formoterol, after administration of inhalation powder (12-24 micrograms), and two different aerosol formulations (12-96 micrograms), shows a dose-proportional increase in the volume of formoterol accessible in the circulation.

Distribution
61-64% of formoterol is bound to plasma proteins (34% primary to albumin).

No saturation of “binding sites” occurs in the concentration area for therapeutic doses.

Biotransformation
Formoterol is eliminated primarily by glucuronidation. A considerable proportion is metabolised by O-demethylation followed by glucuronidation.
Multiple CYP450 isozymes catalyze the transformation (2D6, 2C19, 2C9, and 2A6) and so consequently the potential for metabolic drug-drug interaction is low. The kinetics of formoterol are similar after single and repeated administration, indicating no auto-induction or inhibition of metabolism.

Elimination
The elimination of formoterol seems to be multiphasic; the apparent half-life depends on the time interval considered. Based on plasma or blood concentrations up to 6, 8 or 12 hours after oral administration, the elimination half-life is 2-3 hours. On the basis of urinary excretion rates between 3 and 16 hours after inhalation, the half-life is measured at 5 hours.

Formoterol and metabolites are completely eliminated by the body, 2/3 (of oral dose) via the urine and 1/3 via faeces. After inhalation, 6-9% of the dose is excreted unaltered in the urine. The renal clearance of formoterol from the blood is 150 ml/min.

5.3 Preclinical safety data

Mutagenicity:
Mutagenicity experiments have been conducted with a wide range of experimental end-points. No genotoxic effect has been found in any of the in-vitro or in-vivo experiments conducted.

Carcinogenicity:
2-year studies with rats and mice show no carcinogenic potential.

Male mice treated with very high doses of formoterol have a slightly greater probability of developing benign adrenal subcapsular cell tumours. This is presumably due to changes in the physiological ageing process.

Two studies with rats, covering two different dose areas showed an increase in the number of cases of mesovarial leiomyoma. These benign neoplasms were typically associated with prolonged treatment of rats, with high concentrations of beta-2 adrenergic medications. Similarly, a great number of cases of ovarian cysts and benign granulomas/thecal cell tumours were observed; beta-agonists are known to affect the rat's ovaries, and this is probably specific to rodents. Few other tumour types were observed at higher doses, but they appear within the frequency in the historical control population and are not seen in experiments with low doses.

None of the tumour cases are increased to a statistically significant degree with the lowest dose; a dose that provides 10 times greater systemic effect than that expected from the maximum recommended dose of formoterol.

On the basis of these findings, as well as the lack of mutagenic potential, it is concluded that formoterol exhibits no carcinogenic risk at therapeutic doses.

Reproductive toxicity:
Experiments with animals have not shown any teratogenic effect. After oral administration, formoterol is secreted in the milk of nursing rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content: Lactose monohydrate.
Capsule shell: Gelatine

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

PCV/PVDC blister packing.

Pack sizes:
1 inhaler + 10, 20, 30, 50, 60, 100, 120, 180 or 200 capsules
2 inhalers + 100 capsules
4 inhalers + 200 capsules
50 inhalers + 500 capsules
50 or 60 capsules without inhaler.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Laboratorios Liconsa, S.A.
C/ Dulcinea s/n, Alcalá de Henares
28805 Madrid, Spain

8 MARKETING AUTHORISATION NUMBER

PA1239/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th March 2008
Date of last renewal: 5th February 2009

10 DATE OF REVISION OF THE TEXT

December 2020