เอกสารกำกับยาภาษาอังกฤษ

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medical Product

Fluterol 250 mcg/50 mcg Inhalation powder, hard capsule

Fluterol 500 mcg/50 mcg Inhalation powder, hard capsule

2. Quality and Quantitative Composition

Fluterol, inhalation powder in hard capsule size no. 3, each capsule contains 250, or 500 mcg of fluticasone propionate and 50 mcg of salmeterol (as salmeterol xinafoate).

One capsule is administered for each dose.

Excipients with known effect:

Each delivered dose contains up to 12.5 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Inhalation powder, hard capsules

4. Clinical Particulars

4.1 Therapeutic indication

Asthma

Fluterol is indicated in the regular treatment of asthma where use of a combination product (long-acting β2 agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β2 agonist or

- patients already adequately controlled on both inhaled corticosteroid and long-acting β2 agonist

Chronic Obstructive Pulmonary Disease (COPD)

Fluterol is indicated for the symptomatic treatment of patients with COPD, with a FEV1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

4.2 Posology and method of administration

Posology

Route of administration: Inhalation use.

Patients should be made aware that Fluterol must be used daily for optimum benefit, even when asymptomatic.

Patients should be regularly reassessed by a doctor, so that the strength of Fluterol they are receiving remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Where the control of symptoms is

maintained with the lowest strength of the combination given twice daily then the next step could include a test of inhaled corticosteroid alone. As an alternative, patients requiring a long- acting β2 agonist could be titrated to Fluterol given once daily if, in the opinion of the prescriber, it would be adequate to maintain disease control. In the event of once daily dosing when the patient has a history of nocturnal symptoms the dose should be given at night and when the patient has a history of mainly daytime symptoms the dose should be given in the morning.

Patients should be given the strength of Fluterol containing the appropriate fluticasone propionate dosage for the severity of their disease. If an individual patient should require dosages outside the recommended regimen, appropriate doses of β2 agonist and/or corticosteroid should be prescribed.

Recommended Doses:

Asthma

Adults and adolescents 12 years and older:

- One inhalation of 50 micrograms salmeterol and 250 micrograms fluticasone propionate twice daily or
- One inhalation of 50 micrograms salmeterol and 500 micrograms fluticasone propionate twice daily.

COPD

Adults:

- One inhalation of 50 micrograms salmeterol and 500 micrograms fluticasone propionate twice daily.

Special patient groups:

There is no need to adjust the dose in elderly patients or in those with renal impairment. There are no data available for use of Fluterol in patients with hepatic impairment.

Mode of administration

Fluterol is administered by oral inhalation. In order to use the drug correctly, these steps should be followed;

- Open the device and place a capsule in the capsule-shaped compartment at the base of the inhaler.
- Exhale as completely as possible. Avoid exhale into the device.
- Place the mouthpiece between lips then inhale quickly and deeply.
- Remove the device from the mouth, close lips, hold breath for a few second, and then exhale slowly.
- Remove the used capsule and close the device.
- Rinse mouth with water after inhalation.

4.3 Contraindication

Fluterol is contraindicated for patients who have history of hypersensitivity to the active ingredients or to any excipients of the product.

4.4 Special warning and precautions for use

Deterioration of disease

Fluterol should not be used to treat acute asthma symptoms for which a fast- and short- acting bronchodilator is required. Patients should be advised to have their inhaler to be used for relief in an acute asthma attack available at all times.

Patients should not be initiated on Fluterol 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 Fluterol. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Fluterol.

Increased requirements for use of reliever medication (short-acting bronchodilators), or decreased response to reliever medication indicate deterioration of control and patients should be reviewed by a physician.

Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should undergo urgent medical assessment. Consideration should be given to increasing corticosteroid therapy.

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

For patients with COPD experiencing exacerbations, treatment with systemic corticosteroids is typically indicated, therefore patients should be instructed to seek medical attention if symptoms deteriorate with Fluterol

Treatment with Fluterol should not be stopped abruptly in patients with asthma due to risk of exacerbation. Therapy should be down-titrated under physician supervision. For patients with COPD cessation of therapy may also be associated with symptomatic decompensation and should be supervised by a physician.

As with all inhaled medication containing corticosteroids, Fluterol should be administered with caution in patients with active or quiescent pulmonary tuberculosis and fungal, viral or other infections of the airway. Appropriate treatment should be promptly instituted, if indicated.

Cardiovascular effects

Rarely, Fluterol may cause cardiac arrhythmias e.g. supraventricular tachycardia, extrasystoles and atrial fibrillation, and a mild transient reduction in serum potassium at high therapeutic doses. Fluterol should be used with caution in patients with severe cardiovascular disorders or heart rhythm abnormalities and in patients with diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.

Hyperglycaemia

There have been very rare reports of increases in blood glucose levels (see section 4.8) and this should be considered when prescribing to patients with a history of diabetes mellitus.

Paradoxical bronchospasm

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and should be treated straightaway. Fluterol should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

The pharmacological side effects of β_2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.

Excipients

Fluterol contains lactose monohydrate up to 12.5 milligram /dose. 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.

Systemic corticosteroid effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) (see Paediatric population sub-heading below for information on the systemic effects of inhaled corticosteroids in children and adolescents). It is important, therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Very rare cases of adrenal suppression and acute adrenal crisis have also been described with doses of fluticasone propionate between 500 and less than 1000 micrograms. Situations, which could potentially trigger acute adrenal crisis include trauma,

surgery, infection or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, hypotension, decreased level of consciousness, hypoglycaemia, and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

The benefits of inhaled fluticasone propionate therapy should minimize the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Therefore these patients should be treated with special care and adrenocortical function regularly monitored. Patients who have required high dose emergency corticosteroid therapy in the past may also be at risk. This possibility of residual impairment should always be borne in mind in emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment must be considered. The extent of the adrenal impairment may require specialist advice before elective procedures.

Ritonavir can greatly increase the concentration of fluticasone propionate in plasma. Therefore, concomitant use should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. There is also an increased risk of systemic side effects when combining fluticasone propionate with other potent CYP3A inhibitors (see section 4.5).

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalization, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Interactions with potent CYP3A4 inhibitors

Concomitant use of systemic ketoconazole significantly increases systemic exposure to salmeterol. This may lead to an increase in the incidence of systemic effects (e.g. prolongation in the QTc interval and palpitations). Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should therefore be avoided unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment (see section 4.5).

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes, which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Paediatric Population

Children and adolescents <16 years taking high doses of fluticasone propionate (typically ≥ 1000 micrograms/day) may be at particular risk. Systemic effects may occur, particularly at high doses prescribed for long periods. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, acute adrenal crisis and growth retardation in children and adolescents and more rarely, a range of psychological or behavioral effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression. Consideration should be given to referring the child or adolescent to a paediatric respiratory specialist.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored. The dose of inhaled corticosteroid should be reduced to the lowest dose at which effective control of asthma is maintained.

4.5 Interaction with other medicinal products and other forms of interactions

β adrenergic blockers may weaken or antagonize the effect of salmeterol. Both non-selective and selective β blockers should be avoided unless there are compelling reasons for their use. Potentially serious hypokalaemia may result from β2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics.

Concomitant use of other β adrenergic containing drugs can have a potentially additive effect.

Fluticasone Propionate

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome CYP3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome CYP3A4 inhibitor) 100 mg b.i.d. increased the fluticasone propionate plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol concentrations. Information about this interaction is lacking for inhaled fluticasone propionate, but a marked increase

in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side effects.

In a small study in healthy volunteers, the slightly less potent CYP3A inhibitor ketoconazole increased the exposure of fluticasone propionate after a single inhalation by 150%. This resulted in a greater reduction of plasma cortisol as compared with fluticasone propionate alone. Co-treatment with other potent CYP3A inhibitors, such as itraconazole and cobicistat-containing products, and moderate CYP3A inhibitors, such as erythromycin, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side effects. Combinations should be avoided unless the benefit outweighs the potential increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Salmeterol

Potent CYP3A4 inhibitors

Co-administration of ketoconazole (400 mg orally once daily) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). This may lead to an increase in the incidence of other systemic effects of salmeterol treatment (e.g. prolongation of QTc interval and palpitations) compared with salmeterol or ketoconazole treatment alone (see section 4.4).

Clinically significant effects were not seen on blood pressure, heart rate, blood glucose and blood potassium levels. Co-administration with ketoconazole did not increase the elimination half-life of salmeterol or increase salmeterol accumulation with repeat dosing.

The concomitant administration of ketoconazole should be avoided, unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment. There is likely to be a similar risk of interaction with other potent CYP3A4 inhibitors (e.g. itraconazole, telithromycin, ritonavir).

Moderate CYP 3A4 inhibitors

Co-administration of erythromycin (500 mg orally three times a day) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 6 days resulted in a small but non-statistically significant increase in salmeterol exposure (1.4-fold C_{max} and 1.2-fold AUC). Co-administration with erythromycin was not associated with any serious adverse effects.

4.6 Pregnancy and lactation

Fertility

There are no data in humans. However, animal studies showed no effects of salmeterol or fluticasone propionate on fertility.

Pregnancy

A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity related to Fluterol. Animal studies have shown reproductive toxicity after administration of β2 adrenoreceptor agonists and glucocorticosteroids (see section 5.3).

Administration of Fluterol to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

The lowest effective dose of fluticasone propionate needed to maintain adequate asthma control should be used in the treatment of pregnant women.

Breastfeeding

It is unknown whether salmeterol and fluticasone propionate/metabolites are excreted in human milk. Studies have shown that salmeterol and fluticasone propionate, and their metabolites, are excreted into the milk of lactating rats.

A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue Fluterol therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machine

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

4.8 Undesirable effects

As Fluterol contains salmeterol and fluticasone propionate, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.

Adverse events which have been associated with salmeterol/fluticasone propionate are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and not known (cannot be estimated from the available data). Frequencies were derived from clinical trial data. The incidence in placebo was not taken into account.

System Organ Class	Adverse Event	Frequency
Infections & Infestations	Candidiasis of the mouth and throat	Common
	Pneumonia (in COPD patients)	Common[1,3,5]
	Bronchitis	Common[1,3]
	Oesophageal candidiasis	Rare
Immune System Disorders	Hypersensitivity reactions with the following manifestations:	
	Cutaneous hypersensitivity reactions	Uncommon

System Organ Class	Adverse Event	Frequency
	Angioedema (mainly facial and oropharyngeal oedema) Respiratory symptoms (dyspnoea) Respiratory symptoms (bronchospasm) Anaphylactic reactions including anaphylactic shock	Rare Uncommon Rare Rare
Endocrine Disorders	Cushing's syndrome, Cushingoid features, Adrenal suppression, Growth retardation in children and adolescents, Decreased bone mineral density	Rare[4]
Metabolism & Nutrition Disorders	Hypokalaemia Hyperglycaemia	Common[3] Uncommon[4]
Psychiatric Disorders	Anxiety Sleep disorders Behavioural changes, including psychomotor hyperactivity and irritability (predominantly in children) Depression, aggression (predominantly in children)	Uncommon Uncommon Rare Not Known
Nervous System Disorders	Headache Tremor	Very Common[1] Uncommon
Eye Disorders	Cataract Glaucoma Vision, blurred	Uncommon Rare[4] Not Known[4]
Cardiac Disorders	Palpitations Tachycardia Cardiac arrhythmias (including supraventricular tachycardia and extrasystoles). Atrial fibrillation Angina pectoris	Uncommon Uncommon Rare Uncommon Uncommon
Respiratory, Thoracic & Mediastinal Disorders	Nasopharyngitis Throat irritation Hoarseness/dysphonia Sinusitis Paradoxical bronchospasm	Very Common[2, 3] Common Common Common[1, 3] Rare[4]
Skin and subcutaneous tissue disorders	Contusions	Common[1, 3]
Musculoskeletal & Connective Tissue Disorders	Muscle cramps Traumatic fractures Arthralgia Myalgia	Common Common[1, 3] Common Common

[1]Reported commonly in placebo

[2]Reported very commonly in placebo

[3]Reported over 3 years in a COPD study

[4]See section 4.4

[5]See section 5.1.

Description of selected adverse reactions

The pharmacological side effects of β2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and should be treated straightaway. Fluterol should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Due to the fluticasone propionate component, hoarseness and candidiasis (thrush) of the mouth and throat and, rarely, of the oesophagus can occur in some patients. Both hoarseness and incidence of mouth and throat candidiasis may be relieved by rinsing the mouth with water and/or brushing the teeth after using the product. Symptomatic mouth and throat candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the Fluterol.

Paediatric population

Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression and growth retardation in children and adolescents (see section 4.4). Children may also experience anxiety, sleep disorders and behavioral changes, including hyperactivity and irritability.

4.9 Overdose

There are no data available from clinical trials on overdose with Fluterol, however data on overdose with both drugs are given below:

The signs and symptoms of salmeterol overdose are dizziness, increases in systolic blood pressure, tremor, headache and tachycardia. If Fluterol therapy has to be withdrawn due to overdose of the β agonist component of the drug, provision of appropriate replacement steroid therapy should be considered. Additionally, hypokalaemia can occur and therefore serum potassium levels should be monitored. Potassium replacement should be considered.

Acute: Acute inhalation of fluticasone propionate doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function is recovered in a few days, as verified by plasma cortisol measurements.

Chronic overdose of inhaled fluticasone propionate: Adrenal reserve should be monitored and treatment with a systemic corticosteroid may be necessary. When stabilized, treatment should be

continued with an inhaled corticosteroid at the recommended dose. Refer to section 4.4: risk of adrenal suppression.

In cases of both acute and chronic fluticasone propionate overdose Fluterol therapy should be continued at a suitable dosage for symptom control.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic Group: Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics.

ATC Code: R03AK06

Mechanism of action and pharmacodynamic effects:

Fluterol contains salmeterol and fluticasone propionate which have differing modes of action. The respective mechanisms of action of both drugs are discussed below.

Salmeterol:

Salmeterol is a selective long-acting (12 hour) β2 adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.

Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting β2 agonists.

Fluticasone propionate:

Fluticasone propionate 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.

5.2 Pharmacokinetic Properties

Salmeterol

Salmeterol acts locally in the lung therefore plasma levels are not an indication of therapeutic effects. In addition there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the drug in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picogram /mL or less) achieved after inhaled dosing.

Fluticasone propionate

The absolute bioavailability of a single dose of inhaled fluticasone propionate in healthy subjects varies between approximately 5 to 11% of the nominal dose depending on the inhalation device used. In patients with asthma or COPD a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed.

Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose may be swallowed but contributes minimally to systemic exposure due

to the low aqueous solubility and presystemic metabolism, resulting in oral availability of less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose.

The disposition of fluticasone propionate is characterized by high plasma clearance (1150 mL/min), a large volume of distribution at steady-state (approximately 300 L) and a terminal half-life of approximately 8 hours.

Plasma protein binding is 91%.

Fluticasone propionate is cleared very rapidly from the systemic circulation. The main pathway is metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Other unidentified metabolites are also found in the feces.

The renal clearance of fluticasone propionate is negligible. Less than 5% of the dose is excreted in urine, mainly as metabolites. The main part of the dose is excreted in feces as metabolites and unchanged drug.

5.3 Preclinical Safety data

The only safety concerns for human use derived from animal studies of salmeterol and fluticasone propionate given separately were effects associated with exaggerated pharmacological actions.

In animal reproduction studies, glucocorticosteroids have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant for man given recommended doses. Animal studies with salmeterol have shown embryofetal toxicity only at high exposure levels. Following co-administration, increased incidences of transposed umbilical artery and incomplete ossification of occipital bone were found in rats at doses associated with known glucocorticoid-induced abnormalities. Neither salmeterol xinafoate or fluticasone propionate have shown any potential for genetic toxicity.

6. Pharmaceutical Particulars

6.1 List of excipient

Lactose monohydrate (which contains milk proteins)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life of the drug is 2 years.

After first opening, Fluterol 250/50 mcg can be used up to 30 days or 60 days for Fluterol 500/50 mcg.

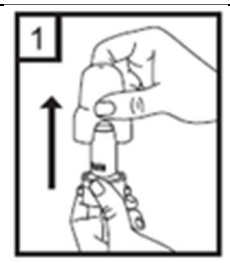
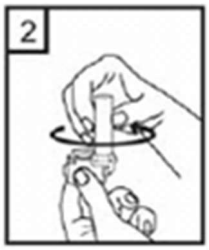
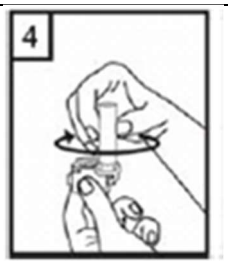
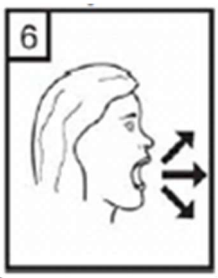
6.4 Special precautions for storage

Store in the original package, at room temperature.

6.5 Nature and contents of container

HDPE bottles contain 60 capsules. Bottles are packed in an aluminium bag together with the plastic device and desiccant. The aluminium bag is then packed in a cardboard box.

6.6 Instructions for using device

	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. Take one of today's capsules. Place it in the capsule-shaped compartment in the base of the inhaler. It is important that you remove the capsule from the pack only immediately before you use it.
	4. Twist the mouthpiece to the closed position until it clicks.
	5. Keeping the inhaler upright, firmly squeeze the two buttons once only. This will pierce the capsule. Release the buttons. Although the capsule is now pierced, the powder will not be released until you inhale it.
	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. As you breathe in, you will inhale the medicine into your lungs.

You should hear the capsule spinning in the inhaler. If you do not hear this whirring noise, the capsule may be stuck in the compartment. If this occurs, open the inhaler and loosen the capsule by prising it out of the compartment. Do not try to loosen the capsule by repeatedly pressing the buttons.

8. If you have heard the whirring noise, 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.

10. Replace the cap.

11. If you need to clean the inhaler, wipe the mouthpiece and capsule compartment with a dry cloth or a clean soft brush.

7. Marketing Authorization Holder

Manufactured by: Laboratorios Liconsa S.A., Guadalajara, Spain

Imported by: Exeltis (Thailand) Co., Ltd, Bangkok, Thailand

8. Marketing Authorization Numbers

On process of registration

9. Date of authorization

Draft version

10. Date of revision of the text

Draft version