

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flamerio 50 microgram/500 microgram/dose, inhalation powder, pre-dispensed

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-dispensed dose of Flamerio contains.

50 micrograms of salmeterol (as salmeterol xinafoate) and 500 micrograms of fluticasone propionate.

Excipient with known effect:
24.427 mg of lactose per dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed.
White powder.

Flamerio contains two medicines packed in the two blisters of the single dose foil strips (double-blisters strips), which are stored in the inhalation device Elpenhaler.
Each dose is pre-dispensed in one double-blisters strip.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Flamerio is indicated in adults only Asthma

Flamerio is indicated in the regular treatment of asthma where use of a combination product (long-acting β_2 -agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting β_2 -agonist

or

- patients already adequately controlled on both inhaled corticosteroid and long-acting β_2 -agonist.

Chronic Obstructive Pulmonary Disease (COPD)

Flamerio 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

Flamerio is for inhalation use only.

Posology

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

Patients should be regularly reassessed by a doctor, so that the strength of Flamerio 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 β_2 -agonist could be titrated to Flamerio 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 Flamerio 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 β_2 -agonist and/or corticosteroid should be prescribed.

Recommended Doses:

Asthma

Adults

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.

A short term trial of Flamerio may be considered as initial maintenance therapy in adults with moderate persistent asthma (defined as patients with daily symptoms, daily rescue use and moderate to severe airflow limitation) for whom rapid control of asthma is essential. In these cases, the recommended initial dose is one inhalation of 50 micrograms salmeterol and 100 micrograms fluticasone propionate twice daily. Once control of asthma is attained treatment should be reviewed and consideration given as to whether patients should be stepped down to an inhaled corticosteroid alone. Regular review of patients as treatment is stepped down is important.

A clear benefit has not been shown as compared to inhaled fluticasone propionate alone used as initial maintenance therapy when one or two of the criteria of severity are missing. In general inhaled corticosteroids remain the first line treatment for most patients. Flamerio is not intended for the initial management of mild asthma. Salmeterol/fluticasone propionate 50 microgram/100 micrograms strength is not appropriate in adults with severe asthma; it is recommended to establish the appropriate dosage of inhaled corticosteroid before any fixed combination can be used in patients with severe asthma.

For dosages, which cannot be achieved with Flamerio, other strengths of salmeterol/fluticasone medicinal products are available.

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 salmeterol/fluticasone propionate in patients with hepatic impairment.

Children and adolescents

Flamerio should not be used in children and adolescents.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Deterioration of disease

Flamerio 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 medicinal product to be used for relief in an acute asthma attack available at all times.

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

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 Flamerio. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Flamerio 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 Flamerio. Treatment with Flamerio 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, Flamerio 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, Flamerio may cause cardiac arrhythmias e.g. supraventricular tachycardia, extrasystoles and atrial fibrillation, and a mild transient reduction in serum potassium at high therapeutic doses. Flamerio 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. Flamerio 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.

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, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). **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 mcg. 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 minimise 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). Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, 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.

Data from a large clinical trial (the Salmeterol Multi-Center Asthma Research Trial, SMART) suggested African-American patients were at increased risk of serious respiratory-related events or deaths when using salmeterol compared with placebo (see section 5.1). It is not known if this was due to pharmacogenetic or other factors. Patients of black African or Afro-Caribbean ancestry should therefore be asked to continue treatment but to seek medical advice if asthma symptoms remained uncontrolled or worsen whilst using Flamio.

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).

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 behavioural 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.

Excipients

Flamario contains lactose. The amount does not normally cause problems in lactose intolerant people. The excipient lactose contains small amounts of milk proteins, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interactions

β adrenergic blockers may weaken or antagonise 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 β_2 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 P450 3A4 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 P450 3A4 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 moderate CYP3A inhibitors, such as erythromycin, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side-effects. Caution is recommended and long-term treatment with such drugs should if possible be avoided.

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 (500mg 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 Fertility, 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 moderate amount of data on pregnant women (between 300 to 1000 pregnancy outcomes) indicates no malformative or foeto/neonatal toxicity of salmeterol and fluticasone propionate. Animal studies have shown reproductive toxicity after administration of β_2 -adrenoreceptor agonists and glucocorticosteroids (see section 5.3).

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

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 Flamerio 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 machines

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

4.8 Undesirable effects

As Flamerio 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ 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
	Angioedema (mainly facial and oropharyngeal oedema),	Rare
	Respiratory symptoms (dyspnoea)	Uncommon
	Respiratory symptoms (bronchospasm)	Rare
	Anaphylactic reactions including anaphylactic shock	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	Common ³
	Hyperglycaemia	Uncommon ⁴
Psychiatric Disorders	Anxiety	Uncommon
	Sleep disorders	Uncommon
	Behavioural changes, including psychomotor hyperactivity and irritability (predominantly in children)	Rare
	Depression, aggression (predominantly in children)	Not known
Nervous System Disorders	Headache	Very Common ¹
	Tremor	Uncommon
Eye Disorders	Cataract	Uncommon
	Glaucoma	Rare ⁴
Cardiac Disorders	Palpitations	Uncommon
	Tachycardia	Uncommon
	Cardiac arrhythmias (including supraventricular tachycardia and extrasystoles)	Rare
	Atrial fibrillation	Uncommon
	Angina pectoris	Uncommon
Respiratory, Thoracic & Mediastinal Disorders	Nasopharyngitis	Very Common ^{2,3}
	Throat irritation	Common
	Hoarseness/dysphonia	Common
	Sinusitis	Common ^{1, 3}
	Paradoxical bronchospasm	Rare ⁴
Skin and Subcutaneous Tissue Disorders	Contusions	Common ^{1,3}
Musculoskeletal & Connective Tissue Disorders	Muscle Cramps	Common
	Traumatic fractures	Common ^{1,3}
	Arthralgia	Common
	Myalgia	Common

¹Reported commonly in placebo²Reported very commonly in placebo³Reported over 3 years in a COPD study⁴See section 4.4⁵See section 5.1

Description of selected adverse reactions

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.

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. Flamerio 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 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 Flamerio.

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 behavioural changes, including hyperactivity and irritability.

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 are no data available from clinical trials on overdose with Flamerio, 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 Flamerio 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 stabilised, 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, Flamerio 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

Flamerio 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) β_2 -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 β_2 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.

Clinical efficacy and safety

Asthma clinical trials

A twelve month study (Gaining Optimal Asthma Control, GOAL), in 3416 adult and adolescent patients with persistent asthma, compared the safety and efficacy of Salmeterol/Fluticasone propionate versus inhaled corticosteroid (Fluticasone Propionate) alone to determine whether the goals of asthma management were achievable. Treatment was stepped up every 12 weeks until total control was achieved or the highest dose of study drug was reached. GOAL showed more patients treated with salmeterol/fluticasone propionate achieved asthma control than patients treated with ICS alone and this control was attained at a lower corticosteroid dose.

*Well Controlled asthma was achieved more rapidly with salmeterol/fluticasone propionate than with ICS alone. The time on treatment for 50% of subjects to achieve a first individual well controlled week was 16 days for salmeterol/fluticasone propionate compared to 37 days for the ICS group. In the subset of steroid naive asthmatics the time to an individual well controlled week was 16 days in the salmeterol/fluticasone propionate treatment compared to 23 days following treatment with ICS.

The overall study results showed:

Percentage of Patients Attaining *Well Controlled (WC) and **Totally Controlled (TC) Asthma over 12 months				
Pre-Study Treatment	Salmeterol/Fluticasone propionate		Fluticasone propionate	
	WC	TC	WC	TC
No ICS (SABA alone)	78%	50%	70%	40%
Low dose ICS (≤ 500 micrograms BDP or equivalent/day)	75%	44%	60%	28%
Medium dose ICS (> 500-1000 micrograms BDP or equivalent/day)	62%	29%	47%	16%
Pooled results across the 3 treatment levels	71%	41%	59%	28%

*Well controlled asthma; less than or equal to 2 days with symptom score greater than 1 (symptom score 1 defined as 'symptoms for one short period during the day'), SABA use on less than or equal to 2 days and less than or equal to 4 occasions/week, greater than or equal to 80% predicted morning peak expiratory flow, no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy

**Total control of asthma; no symptoms, no SABA use, greater than or equal to 80% predicted morning peak expiratory flow, no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy

The results of this study suggest that salmeterol/fluticasone propionate 50/100 micrograms bd may be considered as initial maintenance therapy in patients with moderate persistent asthma for whom rapid control of asthma is deemed essential (see section 4.2).

A double-blind, randomised, parallel group study in 318 patients with persistent asthma aged 18 years evaluated the safety and tolerability of administering two inhalations twice daily (doubledose) of salmeterol/fluticasone propionate for two weeks. The

study showed that doubling the inhalations of each strength of salmeterol/fluticasone propionate for up to 14 days resulted in a small increase in β agonist-related adverse events (tremor; 1 patient [1%] vs 0, palpitations; 6 [3%] vs 1 [<1%], muscle cramps; 6 [3%] vs 1 [<1%]) and a similar incidence of inhaled corticosteroid related adverse events (e.g. oral candidiasis; 6 [6%] vs 16 [8%], hoarseness; 2 [2%] vs 4 [2%]) compared to one inhalation twice daily. The small increase in β agonist-related adverse events should be taken into account if doubling the dose of salmeterol/fluticasone propionate is considered by the physician in adult patients requiring additional short-term (up to 14 days) inhaled corticosteroid therapy.

Salmeterol/Fluticasone propionate COPD clinical trials

TORCH was a 3-year study to assess the effect of treatment with salmeterol/fluticasone propionate 50/500mcg bd, salmeterol 50mcg bd, fluticasone propionate (FP) 500mcg bd or placebo on all-cause mortality in patients with COPD. COPD patients with a baseline (pre-bronchodilator) FEV₁ <60% of predicted normal were randomised to double-blind medication. During the study, patients were permitted usual COPD therapy with the exception of other inhaled corticosteroids, long acting bronchodilators and long-term systemic corticosteroids. Survival status at 3 years was determined for all patients regardless of withdrawal from study medication. The primary endpoint was reduction in all cause mortality at 3 years for salmeterol/fluticasone propionate vs Placebo.

	Placebo N=1524	Salmeterol 50 N=1521	FP 500 N=1534	Salmeterol/FP 50/500 N=1533
All cause mortality at 3 years				
Number of deaths (%)	231 (15.2%)	205 (13.5%)	246 (16.0%)	193 (12.6%)
Hazard Ratio vs Placebo (CIs)	N/A	0.879 (0.73, 1.06)	1.060 (0.89, 1.27)	0.825 (0.68, 1.00)
p value		0.180	0.525	0.0521
Hazard Ratio Salmeterol/FP	N/A	0.932 (0.77, 1.13)	0.774 (0.64, 0.93)	N/A
50/500 vs components (CIs)				
p value		0.481	0.007	
<i>1. Non significant P value after adjustment for 2 interim analyses on the primary efficacy comparison from a log-rank analysis stratified by smoking status</i>				

There was a trend towards improved survival in subjects treated with salmeterol/fluticasone propionate compared with placebo over 3 years however this did not achieve the statistical significance level $p \leq 0.05$.

The percentage of patients who died within 3 years due to COPD-related causes was 6.0% for placebo, 6.1% for salmeterol, 6.9% for FP and 4.7% for salmeterol/fluticasone propionate.

The mean number of moderate to severe exacerbations per year was significantly reduced with salmeterol/fluticasone propionate as compared with treatment with salmeterol, FP and placebo (mean rate in the salmeterol/fluticasone propionate group 0.85 compared with 0.97 in the salmeterol group, 0.93 in the FP group and 1.13 in the placebo). This translates to a reduction in the rate of moderate to severe exacerbations of 25% (95% CI: 19% to 31%; $p < 0.001$) compared with placebo, 12% compared with salmeterol (95% CI: 5% to 19%, $p = 0.002$) and 9% compared with FP (95% CI: 1% to 16%, $p = 0.024$). Salmeterol and FP significantly reduced exacerbation rates compared with placebo by 15% (95% CI: 7% to 22%; $p < 0.001$) and 18% (95% CI: 11% to 24%; $p < 0.001$) respectively.

Health Related Quality of Life, as measured by the St George's Respiratory Questionnaire (SGRQ) was improved by all active treatments in comparison with placebo. The average improvement over three years for Salmeterol/Fluticasone propionate compared with placebo was -3.1 units (95% CI: -4.1 to -2.1; $p < 0.001$), compared with salmeterol was -2.2 units ($p < 0.001$) and compared with FP was -1.2 units ($p = 0.017$). A 4-unit decrease is considered clinically relevant.

The estimated 3-year probability of having pneumonia reported as an adverse event was 12.3% for placebo, 13.3% for salmeterol, 18.3% for FP and 19.6% for salmeterol/fluticasone propionate (Hazard ratio for salmeterol/fluticasone propionate vs placebo: 1.64, 95%CI: 1.33 to 2.01, $p < 0.001$). There was no increase in pneumonia related deaths; deaths while on treatment that were adjudicated as primarily due to pneumonia were 7 for placebo, 9 for salmeterol, 13 for FP and 8 for salmeterol/fluticasone propionate. There was no significant difference in probability of bone fracture (5.1% placebo, 5.1% salmeterol, 5.4% FP and 6.3% salmeterol/fluticasone propionate; Hazard ratio for salmeterol/fluticasone propionate vs placebo: 1.22, 95% CI: 0.87 to 1.72, $p = 0.248$).

Placebo-controlled clinical trials, over 6 and 12 months, have shown that regular use of salmeterol/fluticasone propionate 50/500 micrograms improves lung function and reduces breathlessness and the use of relief medication.

Studies SCO40043 and SCO100250 were randomised, double-blind, parallel-group, replicate studies comparing the effect of salmeterol/fluticasone propionate 50/250 micrograms bd (a dose not licensed for COPD treatment in the European Union) with salmeterol 50 micrograms bd on the annual rate of moderate/severe exacerbations in subjects with COPD with FEV1 less than 50% predicted and a history of exacerbations. Moderate/severe exacerbations were defined as worsening symptoms that required treatment with oral corticosteroids and/or antibiotics or in-patient hospitalisation.

The trials had a 4 week run-in period during which all subjects received open-label salmeterol/FP 50/250 to standardize COPD pharmacotherapy and stabilise disease prior to randomisation to blinded study medication for 52 weeks. Subjects were randomised 1:1 to salmeterol/FP 50/250 (total ITT $n = 776$) or salmeterol (total ITT $n = 778$). Prior to run-in, subjects discontinued use of previous COPD medications except short-acting bronchodilators. The use of concurrent inhaled long-acting bronchodilators (β_2 agonist and anticholinergic), ipratropium/salbutamol combination products, oral β_2 agonists, and theophylline preparations were not allowed during the treatment period. Oral corticosteroids and antibiotics were allowed for the acute treatment of COPD exacerbations with specific guidelines for use. Subjects used salbutamol on an as-needed basis throughout the studies.

The results of both studies showed that treatment with salmeterol/fluticasone propionate 50/250 resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with salmeterol (SCO40043: 1.06 and 1.53 per subject per year, respectively, rate ratio of 0.70, 95% CI: 0.58 to 0.83, $p < 0.001$; SCO100250: 1.10 and 1.59 per subject per year, respectively, rate ratio of 0.70, 95% CI: 0.58 to 0.83, $p < 0.001$). Findings for the secondary efficacy measures (time to first moderate/severe exacerbation, the annual rate of exacerbations requiring oral corticosteroids, and pre-dose morning (AM) FEV1) significantly favoured salmeterol/fluticasone propionate 50/250 micrograms bd over salmeterol. Adverse event profiles were similar with the exception of a higher incidence of pneumonias and known local side effects (candidiasis and dysphonia) in the salmeterol/fluticasone propionate 50/250 micrograms bd group compared with salmeterol. Pneumonia-related events were reported for 55 (7%) subjects in the salmeterol/fluticasone propionate 50/250 micrograms bd group and 25 (3%) in the salmeterol group. The increased incidence of reported pneumonia with salmeterol/fluticasone 50/250 micrograms bd appears to be of similar magnitude to the incidence reported following treatment with salmeterol/fluticasone propionate 50/500 micrograms bd in TORCH.

The Salmeterol Multi-center Asthma Research Trial (SMART)

SMART was a multi-centre, randomised, double-blind, placebo-controlled, parallel group 28-week study in the US which randomised 13,176 patients to salmeterol (50 micrograms twice daily) and 13,179 patients to placebo in addition to the patients' usual asthma therapy. Patients were enrolled if ≥ 12 years of age, with asthma and if currently using asthma medication (but not a LABA). Baseline ICS use at study entry was recorded, but not required in the study. The primary endpoint in SMART was the combined number of respiratory-related deaths and respiratory-related life-threatening experiences.

Key findings from SMART: primary endpoint

Patient group	Number of primary endpoint events/number of patients		Relative Risk (95% confidence intervals)
	salmeterol	placebo	
All patients	50/13,176	36/13,179	1.40 (0.91, 2.14)
Patients using inhaled steroids	23/6,127	19/6,138	1.21 (0.66, 2.23)
Patients not using inhaled steroids	27/7,049	17/7,041	1.60 (0.87, 2.93)

African-American patients	20/2,366	5/2,319	4.10 (1.54, 10.90)
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(Risk in bold is statistically significant at the 95% level.)

Key findings from SMART by inhaled steroid use at baseline: secondary endpoints

	Number of secondary endpoint events/number of patients		Relative Risk (95% confidence intervals)
	salmeterol	placebo	
Respiratory-related death			
Patients using inhaled steroids	10/6127	5/6138	2.01 (0.69, 5.86)
Patients not using inhaled steroids	14/7049	6/7041	2.28 (0.88, 5.94)
Combined asthma-related death or life-threatening experience			
Patients using inhaled steroids	16/6127	13/6138	1.24, (0.60, 2.58)
Patients not using inhaled steroids	21/7049	9/7041	2.39 (1.10, 5.22)
Asthma-related death			
Patients using inhaled steroids	4/6127	3/6138	1.35 (0.30, 6.04)
Patients not using inhaled steroids	9/7049	0/7041	*

(* = could not be calculated because of no events in placebo group. Risk in bold figures is statistically significant at the 95% level. The secondary endpoints in the table above reached statistical significance in the whole population.) The secondary endpoints of combined all cause death or life-threatening experience, all cause death, or all cause hospitalisation did not reach statistical significance in the whole population.

5.2 Pharmacokinetic properties

For pharmacokinetic purposes each component can be considered separately.

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 pre-systemic 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 characterised 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 faeces.

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 faeces 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 embryo-fetal 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

Flamario contains two medicines packed in the two alu-alu blisters of the single dose foil strips (double-blisters), which are stored in the inhalation device Elpenhaler.

The foil protects the powder for inhalation from the effects of the atmosphere.

Each dose is pre-dispensed in one double-blisters strip.

Each carton box contains one inhalation device Elpenhaler with 60 double blister strips. 60 doses per pack.

Each carton box contains one inhalation device Elpenhaler with 30 alu-alu double blister strips and one spare storage compartment with 30 additional alu-alu double blister strips. 60 doses per pack.

Each carton box contains one inhalation device Elpenhaler with 30 alu-alu double blister strips. 30 doses per pack (sample pack).

Each carton box contains three inhalation devices Elpenhaler with 60 alu-alu double blister strips each. 180 doses per pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

To ensure proper administration of the drug, the patient should be shown how to use the inhaler by a physician or other health professional.

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

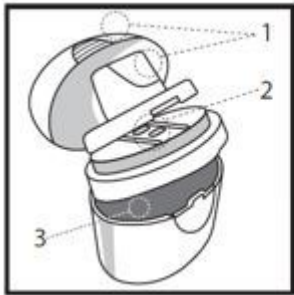
INSTRUCTIONS FOR USE AND HANDLING OF THE ELPENHALER

The following are instructions to the patient for the proper inhalation of the two medicines packed in the two blisters of the single dose strips (double-blister strips), which are stored in the Elpenhaler.

DESCRIPTION

The Elpenhaler is a device for inhaling at the same time two medicines which are in the form of powder. The two medicines form in one medicinal combination. Each medicine is packed separately from the other in one of the two blisters of the specially designed double-blister strip.

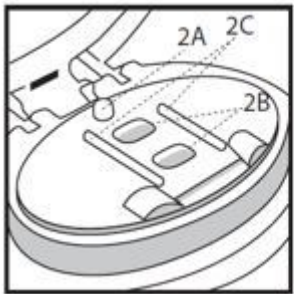
The double-blister strip contains one (1) dose of the medicinal combination.



The Elpenhaler is comprised of 3 parts:

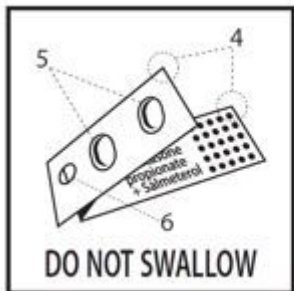
- The mouthpiece and its cap (1).
- The surface (2) on which the double-blister strip is placed (drug supporting surface).
- The storage case (3) which houses the double-blister strips.

The three parts are connected to each other and can be opened separately.



The drug supporting surface contains:

- An attachment point (2A) where the double-blister strip is attached.
- Two cavities (2B) which accommodate the two blisters of the strip.
- Two strip guides (2C) which firmly secure the double-blister strip in the correct position on the drug supporting surface.

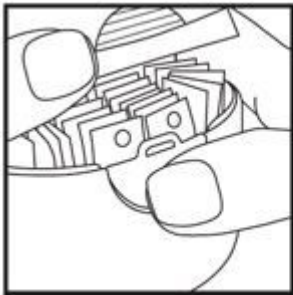


The double-blister strip contains:

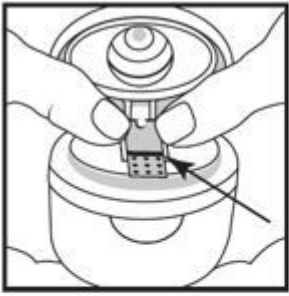
- Two aluminium sheets (4).
- Two blisters (5), one containing salmeterol and the other fluticasone propionate.
- A hole (6).

USE OF THE ELPENHALER

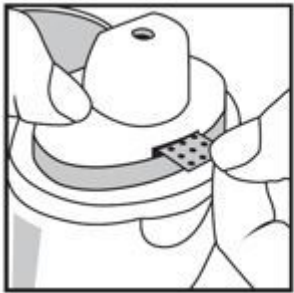
A. Preparing the device



Open the storage case by pressing as in the figure, take a strip and close the storage case again.



Uncover the mouthpiece completely by applying light pressure on the stripped area.
 Unlock and push the mouthpiece backwards so as to reveal the drug supporting surface.
 Hold the double-blister strip with its shiny surface upwards, so as to see the blue line, as shown by the arrow in the figure. The labeled surface of the strip should face downwards.
 Place the hole of the strip on the attachment point of the drug supporting surface. By applying light pressure make sure the strip is securely attached on the attachment point.
 The two blisters of the strip will fit in the cavities of the drug supporting surface and the guides will secure the strip in the correct position.



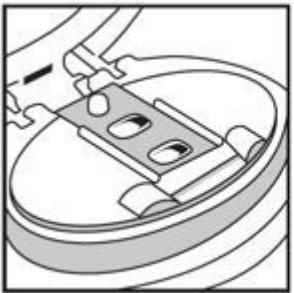
Close the mouthpiece and pull away horizontally the embossed protruding end of the strip to be detached.
 The dose is now ready to be inhaled.

B. Inhalation of the dose

Hold the device away from your mouth. Exhale completely. Be careful not to exhale on the mouthpiece of the device. Bring the Elpenhalerto your mouth and place your lips tightly around the mouthpiece.



Breathe in slowly and deeply from your mouth (and not from your nose) until your lungs are full.
 Hold in your breath approximately 5 seconds or as long as you comfortably can and at the same time remove the device from your mouth.
 Exhale and continue to breathe normally.



Open the mouthpiece.
 You will notice that you have inhaled all the powder and that the blisters of the strip are empty.
 Remove the empty strip and proceed to step C.

C. Cleaning the device

Following each use, wipe the mouthpiece and the drug supporting surface with a dry cloth or dry paper tissue. Do not use water to clean the device.
 Close the mouthpiece and place its cap.

7 MARKETING AUTHORISATION HOLDER

Elpen Pharmaceutical Co. Inc.
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 Attica
 Greece
 31 January 2020

8 MARKETING AUTHORISATION NUMBER

PA1879/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 3rd May 2013

Date of Renewal: 27th April 2018

10 DATE OF REVISION OF THE TEXT

January 2020