SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LUTICASS 250 mcg/10 mcg Inhalation Aerosol, Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per actuation:
Active substance:
Fluticasone propionate……..250 mcg (equivalent to 230 mcg dose delivered to the patient)
Formoterol fumarate dihydrate…...10 mcg (equivalent to 9 mcg dose delivered to the patient)
Excipients:
For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Inhalation aerosol, suspension
Aerosol inhaler in a metal tube with concave bottom and dosing valve with plastic activator attached

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LUTICASS is used to improve and control asthma symptoms. It is given as of the third step in the stepwise treatment of asthma.

50 microgram fluticasone propionate/5 microgram formoterol fumarate dihydrate combination is indicated in adults, adolescents and children aged 5 years and above.

125 microgram fluticasone propionate/5 microgram formoterol fumarate dihydrate combination is indicated in adults, adolescents and children aged 12 years and above.

LUTICASS 250 mcg/10 mcg Inhalation Aerosol, Suspension is indicated only in adults.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
Patients should be trained on the use of the inhaler and the status of their asthma should be regularly evaluated by a doctor, so that the strength of LUTICASS 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. Once control of asthma is achieved with the lowest strength of LUTICASS administered twice daily, treatment should be reviewed and consideration given as to whether patients should be stepped down to an inhaled corticosteroid alone. As a general principle the dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Regular review of patients as treatment is stepped down is extremely important.

There are no data available for use of LUTICASS in patients with COPD. LUTICASS should not be used in patients with COPD.

Patients should be given the strength of LUTICASS containing the appropriate fluticasone propionate dosage for the severity of their disease.

Note: 50 microgram fluticasone propionate/5 microgram formoterol fumarate dihydrate combination is not appropriate in adults and adolescents with severe asthma. Prescribers should be aware that, in patients with asthma, fluticasone propionate is as effective as some other inhaled steroids when administered at approximately half the total daily dose (in microgram). If an individual patient should require doses outside the recommended dose regimens, appropriate doses of the β_2-agonist and the inhaled corticosteroid in separate inhalers, or appropriate doses of the inhaled corticosteroid alone, should be prescribed.

LUTICASS is delivered by a press-and-breathe pressurized metered dose inhaler which also contains an integrated dose indicator. Each inhaler will provide at least 120 actuations.

Inhaled corticosteroids alone are the first line of treatment for most patients. LUTICASS is not intended for the initial treatment of mild asthma. For patients with severe asthma, the inhaled corticosteroid therapy should be established before prescribing a fixed-dose combination product.

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

Patients using LUTICASS should not use additional long-acting β_2-agonists for any reason. If asthma symptoms arise in the period between doses, an inhaled, short-acting β_2-agonist should be taken for immediate relief.

For patients who are currently receiving medium to high doses of inhaled corticosteroid therapy, and whose disease severity clearly warrants treatment with two maintenance therapies, the recommended starting dose is 125 microgram fluticasone propionate/5 microgram formoterol fumarate dihydrate twice daily.

Use of a spacer device with LUTICASS is recommended in patients who find it difficult to synchronize aerosol actuation with inspiration of breath.

Patients should be instructed in the proper use and care of their inhaler and spacer and their technique checked to ensure optimum delivery of the inhaled drug to the lungs.

Re-titration to the lowest effective dose should always follow the introduction of a spacer device.

Recommended dose for adults:
LUTICASS 250 microgram /10 microgram Inhalation Aerosol, Suspension - two inhalations (puffs) twice daily normally taken in the morning and in the evening.

Patients may be transferred to a lower strength of this combination product i.e. 125 microgram fluticasone propionate/5 microgram formoterol fumarate dihydrate combination or ultimately 50 microgram fluticasone propionate/5 microgram formoterol fumarate dihydrate combination if their asthma is adequately controlled. A patient's dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

Method of administration
For inhalation use.

To ensure proper administration of the drug, the patient should be shown how to use the inhaler

correctly by a physician or other health professionals. The correct use of the pressurized metered dose inhaler is essential for successful treatment. The patient should be advised to read the package leaflet carefully and follow the instructions for use and pictograms in the leaflet.

The actuator has an integrated counter which counts down the number of actuations (puffs) remaining. This counter is also color coded. The counter counts down from 120 in intervals of 10. When there are less than 40 doses left it changes to red. When this is getting near to zero, the patient should be advised to contact their prescriber for a replacement inhaler. The inhaler must not be used after the dose indicator reads "0".

Priming the inhaler
Before using the inhaler for the first time, or if the inhaler has not been used for 3 days or more, or after exposure to freezing or refrigerated conditions (see section 6.4) the inhaler must be primed before use:

- Remove the mouthpiece cover and shake the inhaler well.
- Actuate (puff) the inhaler whilst pointing it away from the face. This step must be performed 4 times.
- The inhaler should always be shaken immediately before use.

Whenever possible patients should stand or sit in an upright position when inhaling from the inhaler.

Steps to follow when using the inhaler:

1. Remove the mouthpiece cover and check that the mouthpiece is clean, and free from dust and dirt.
2. The inhaler should be shaken immediately before releasing each actuation (puff) to ensure that the contents of the inhaler are evenly mixed.
3. Breathe out as far as is comfortable and as slowly and deeply as possible.
4. Hold the canister vertically with its body upwards and put the lips around the mouthpiece. Hold the inhaler upright with the thumb on the base of the mouthpiece and the forefinger/index finger on the top of the inhaler. Do not bite the mouthpiece.
5. Breathe in slowly and deeply through the mouth. After starting to breathe in press down on the top of the inhaler to release one actuation (puff) and continue to breathe in steadily and deeply (optimally for about 2-3 seconds for children and 4-5 seconds in adults)
6. While holding breath, remove the inhaler from mouth. Patients should continue to hold their breath for as long as is comfortable. Do not breathe out into the inhaler.
7. For the second actuation (puff), keep the inhaler in a vertical position then repeat steps 2 to 6.
8. After use, replace the mouthpiece cover.

IMPORTANT: Do not perform steps 2 to 6 too quickly.
Patients may be advised to practise their technique in front of a mirror. If a mist appears following inhalation, either from the inhaler or from the sides of the mouth, the procedure should be repeated from step 2.

For patients with weak hands, it may be easier to hold the inhaler with both hands. Therefore the index fingers should be placed on the top of the inhaler canister and both thumbs on the base of the inhaler.

Patients should rinse their mouth, gargle with water or brush the teeth after inhaling and spit out the residue to minimise the risk of oral candidiasis or dysphonia.

Cleaning:
Patients should be advised to read the Package Leaflet carefully for cleaning instructions:
The inhaler should be cleaned once a week.

- Remove the mouthpiece cover.
- Do not remove the canister from the plastic casing.
- Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue.
- Replace the mouthpiece cover in the correct orientation.
- Do not put the metal canister into water.

If a patient requires a spacer device then they must be advised to read the instructions provided by the manufacturer to ensure they use it and clean and maintain it properly.

Additional information on special populations
Renal/Hepatic impairment
There are no data available for use of fluticasone propionate/formoterol fumarate dihydrate combination in patients with hepatic or renal impairment (see section 5.2). These patients should be regularly monitored by a physician to ensure titration to the lowest dose at which effective control of symptoms is maintained. As the fractions of fluticasone and formoterol which reach systemic circulation are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe hepatic impairment.

Pediatric population
Adolescents under 18 years and children:
No data are available for this strength of LUTICASS in children or adolescents. Experience in children is limited to the lowest strength (50 microgram/5 microgram) (see sections 4.4, 4.8, 5.1 and 5.3). **LUTICASS in this strength (250 microgram/10 microgram) is not recommended for use in adolescents or children; LUTICASS 250 mcg/10 mcg Inhalation Aerosol, Suspension should not be used in this young age group.**

LUTICASS 250 microgram/10 microgram (per actuation) should not be used in adolescents or children. However there are lower strengths available i.e. 50 microgram/5 microgram (per actuation) which may be used in children or adolescents or 125 microgram/5 microgram (per actuation) which may be used in adolescents.

Geriatric population
There is no need to adjust the dose in elderly patients.

4.3 Contraindications

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

4.4 Special warning and precautions for use

Formoterol should not be used alone as monotherapy in patients with asthma.

Rarely, serious and sometimes fatal asthma-related respiratory problems may occur with long-acting beta-agonist preparations.

LUTICASS is not recommended for the initial treatment of asthma.

Long-acting beta-agonists should be used for the shortest period of time that achieves asthma symptom control, and their use should be discontinued, if possible, once asthma control is achieved. Afterwards, patients should be maintained with a control treatment.

In pediatric and adolescent patients using long-acting beta-agonists in addition to inhaled corticosteroids, a combination preparation containing both an inhaled corticosteroid and a long-acting beta-agonist is recommended to ensure compliance with both drugs.

Treatment with long-acting beta-agonists should not be initiated if patients are in exacerbations or have severe or acutely worsening asthma.

Pneumonia in patients with COPD
An increased incidence of pneumonia, including pneumonia requiring hospitalization, has been observed in patients with COPD receiving inhaled corticosteroid-containing drugs. There is evidence of an increased risk of pneumonia with increasing steroid dose, but this has not been conclusively demonstrated in all studies.

There is no conclusive clinical evidence for intra-class difference in the magnitude of the pneumonia risk of inhaled corticosteroid-containing drugs.

Physicians should be alert to the possible development of pneumonia in patients with COPD, as the clinical features of infections may be confused with the exacerbation of COPD symptoms.

Pneumonia risk factors in COPD patients include smoking, advanced age, low body mass index and severe COPD.

When using long-acting β_2 agonists such as salmeterol and formoterol, patients should be closely monitored for the first three months after initiation of this drug, particularly for asthma-related adverse events.

The management of asthma should normally follow a stepwise program and patients' responses should be monitored clinically and by lung function tests.

LUTICASS 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 medicine to be used for relief in an acute asthma attack available at all times.

The prophylactic use of fluticasone propionate/formoterol fumarate dihydrate combination in exercise-induced asthma has not been studied. For such use, a separate rapid-acting bronchodilator should be considered.

Patients should be reminded to take their LUTICASS maintenance dose as prescribed, even when asymptomatic.

Patients should not be initiated on LUTICASS 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 LUTICASS. Patients should be asked to continue treatment but to seek medical advice if asthma

symptoms remain uncontrolled or worsen after initiation on LUTICASS.

LUTICASS should not be used as the first treatment for asthma.

If increasing use of short-acting bronchodilators to relieve asthma is required, if short-acting bronchodilators become less effective, or ineffective or if asthma symptoms persist, the patient should be reviewed by their doctor as soon as possible as any of these may indicate a deterioration in asthma control and their treatment may need to be changed.

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. The patient should also be medically reviewed when the current dosage of LUTICASS has failed to give adequate control of asthma. Consideration should be given to additional corticosteroid therapies.

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

Treatment with LUTICASS should not be stopped abruptly in patients with asthma due to risk of exacerbation. Therapy should be down-titrated under the supervision of a prescriber.

An exacerbation of the clinical symptoms of asthma may be due to an acute respiratory tract bacterial infection and treatment may require appropriate antibiotics, increased inhaled corticosteroids and a short course of oral corticosteroids. A rapid-acting inhaled bronchodilator should be used as rescue medication. As with all inhaled medication containing corticosteroids, LUTICASS should be administered with caution in patients with pulmonary tuberculosis, quiescent tuberculosis or patients with fungal, viral or other infections of the airway. Any such infections must always be adequately treated if inhaler is being used.

LUTICASS should be used with caution in patients with thyrotoxicosis, pheochromocytoma, diabetes mellitus, uncorrected hypokalemia or patients predisposed to low levels of serum potassium, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders (heart disease, cardiac arrhythmias or severe heart failure).

Potentially serious hypokalemia may result from high doses of β_2 agonists. Concomitant treatment of β_2 agonists with drugs which can induce hypokalemia or potentiate a hypokalemic effect (e.g. xanthine derivatives, steroids and diuretics) may add to a possible hypokalemic effect of the β_2 agonist. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma (as the associated risk may be augmented by hypoxia) and in other conditions when the likelihood for hypokalemia adverse effects is increased. It is recommended that serum potassium levels are monitored during these circumstances.

Caution must be observed when treating patients with existing prolongation of the QTc interval. Formoterol itself may induce prolongation of the QTc interval.

As for all β_2-agonists, additional blood sugar controls should be considered in diabetic patients.

Care should be taken when transferring patients to LUTICASS therapy, particularly if there is any

reason to suppose that adrenal function is impaired from previous systemic steroid 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 inhaled bronchodilator and should be treated straight away. LUTICASS should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

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.

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, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma and more rarely, a range of psychological or behavioral effects (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. Children and adolescents <16 years taking high doses of fluticasone propionate (typically ≥1000 mcg/day) may be at particular risk. 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, hypoglycemia, and seizures. Additional systemic corticosteroid treatment 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. 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. In situations of possible impaired adrenal function hypothalamic pituitary adrenocortical (HPA) axis function should be monitored regularly.

There is an increased risk of systemic side effects when combining fluticasone propionate with potent CYP3A4 inhibitors (see section 4.5).

The patient should be made aware that this fixed-dose combination inhaler is a prophylactic therapy and as such has to be used regularly even when asymptomatic for optimum benefit.

Use of a spacer device may lead to a possible increase in pulmonary deposition and a potential

increase in systemic absorption and systemic adverse events.

As the fractions of fluticasone and formoterol which reach systemic circulation are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe hepatic impairment.

Pediatric population
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a pediatric respiratory specialist.

Possible systemic effects as reported for the individual components of fluticasone propionate/formoterol fumarate dihydrate include Cushing's syndrome, Cushingoid features, adrenal suppression and growth retardation in children and adolescents. Children may also experience anxiety, sleep disorders and behavioral changes, including hyperactivity and irritability (see section 4.8)

Limited data are available on the use of fluticasone propionate/formoterol fumarate dihydrate in children under 5 years of age. Fluticasone propionate/formoterol fumarate dihydrate is NOT recommended for use in children under 5 years of age.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed with fluticasone propionate/formoterol fumarate dihydrate combination.

Fluticasone propionate, an individual component of LUTICASS, is a substrate of CYP 3A4. Co-treatment with CYP3A inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nelfinavir, saquinavir, ketoconazole, telithromycin) 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.

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by β-agonists, especially when the recommended dose of the β-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of a β-agonist with non-potassium sparing diuretics. Xanthine derivates and glucocorticosteroids may add to a possible hypokalemic effect of the β-agonists.

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

Concomitant treatment with monoamine oxidase inhibitors, including agents with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions.

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

Concomitant use of other β-adrenergic drugs can have a potentially additive effect.
Hypokalemia may increase the risk of arrhythmias in patients who are treated with digitalis glycosides.
Formoterol fumarate, as with other β_2-agonists, should be administered with caution to patients being treated with tricyclic antidepressants or monoamine oxidase inhibitors, and during the immediate two week period following their discontinuation, or other drugs known to prolong the QTc interval such as antipsychotics (such as phenothiazines), quinidine, disopyramide, procainamide, and antihistamines. Drugs that are known to prolong the QTc interval can increase the risk of ventricular arrhythmias (see section 4.4).

If additional adrenergic drugs are to be administered by any route, they should be used with caution, because the pharmacologically predictable sympathetic effects of formoterol may be potentiated.

β-adrenergic receptor antagonists (β-blockers) and formoterol fumarate may inhibit the effect of each other when administered concurrently. β-blockers may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with β-blockers and this includes β-blockers used as eye drops for treatment of glaucoma. However, under certain circumstances (e.g. as prophylaxis after myocardial infarction), there may be no acceptable alternatives to the use of β-blockers in patients with asthma. In this setting, cardioselective β-blockers could be considered, although they should be administered with caution.

Additional information on special populations
There are no studies on its use in special populations.

Pediatric population
There are no studies on its use in the pediatric population.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category is “C”.

Women of childbearing potential/Contraception
There are no studies on its use in women of childbearing potential.

Pregnancy
There are no adequate data on the use of fluticasone propionate / formoterol fumarate in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

There are limited data on the use of fluticasone propionate and formoterol fumarate, or this fixed-dose combination, in pregnant women, either alone or in combination but with separate inhalers. Studies in animals have shown reproductive toxicity (see section 5.3).

Administration of LUTICASS is not recommended during pregnancy, and should only be considered if expected benefit to the mother is greater than any possible risk to the fetus. If this is the case, then the lowest effective dose needed to maintain adequate asthma control should be used.

Because of the potential for β-agonist interference with uterine contractility, use of LUTICASS for management of asthma during labor should be restricted to those patients in whom the benefit outweighs the risks.

Breast-feeding

It is not known whether fluticasone propionate or formoterol fumarate are excreted in human breast milk. A risk to the suckling child cannot be excluded. Therefore, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from fluticasone propionate and formoterol fumarate therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Reproductive ability / Fertility

There are no data available on effects on fertility following administration of fluticasone propionate and formoterol fumarate. In animal studies, no effects on fertility have been seen following administration of the individual active substances at clinically relevant doses (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Undesirable effects, which have been associated with fluticasone propionate/formoterol fumarate dihydrate combination during clinical development, are given in the table below (listed by system organ class). The following frequency categories form the basis for classification of the undesirable effects as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

Common: Pneumonia (in patients with COPD)
Rare: Oral candidiasis, oral fungal infections, sinusitis

Metabolism and nutrition disorders

Rare: Hyperglycemia

Psychiatric disorders

Uncommon: Sleep disorders including insomnia
Rare: Abnormal dreams, agitation
Not known: Psychomotor hyperactivity, anxiety, depression, aggression, behavioral changes (predominantly in children)

Nervous system disorders

Uncommon: Headache, tremor, dizziness
Rare: Dysgeusia

Eye disorders

Not known: Vision blurred

Ear and labyrinth disorders

Rare: Vertigo

Cardiac disorders
Uncommon: Palpitations, ventricular extrasystoles
Rare: Angina pectoris, tachycardia

Vascular disorders
Rare: Hypertension

Respiratory, thoracic and mediastinal disorders
Uncommon: Exacerbation of asthma, dysphonia, throat irritation
Rare: Dyspnea, cough

Gastrointestinal disorders
Uncommon: Dry mouth
Rare: Diarrhea, dyspepsia

Skin and subcutaneous tissue disorders
Uncommon: Rash
Rare: Pruritus

Musculoskeletal and connective tissue disorders
Rare: Muscle spasms

General disorders and administration site conditions
Rare: Peripheral edema, asthenia

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 inhaled bronchodilator and should be treated straight away. LUTICASS should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Since LUTICASS contains both fluticasone propionate and formoterol fumarate, the same pattern of undesirable effects as reported for these substances may occur. The following undesirable effects are associated with fluticasone propionate and formoterol fumarate, but have not been seen during the clinical development of fluticasone propionate/formoterol fumarate dihydrate combination:

Fluticasone propionate: Hypersensitivity reactions including, urticaria, pruritus, angioedema (mainly facial and oropharyngeal), anaphylactic reactions. Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These may include Cushing's Syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma, contusion, skin atrophy and susceptibility to infections. The ability to adapt to stress may be impaired. The systemic effects described, however, are much less likely to occur with inhaled corticosteroids than with oral corticosteroids. Prolonged treatment with high doses of inhaled corticosteroids may result in clinically significant adrenal suppression and acute adrenal crisis. Additional systemic corticosteroid cover may be required during periods of stress (trauma, surgery, infection).

Formoterol fumarate: Hypersensitivity reactions (including hypotension, urticaria, angioneurotic edema, pruritus, exanthema), QTc interval prolongation, hypokalemia, nausea, myalgia, increased

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

Hypersensitivity reactions have been reported in patients taking sodium cromoglicate as an active ingredient.

In the unlikely event of a hypersensitivity reaction to LUTICASS, treatment should be initiated in accordance with standard treatment for any other hypersensitivity reaction (the use of antihistamines and other treatment as required). LUTICASS may need to be discontinued immediately and an alternative asthma therapy may need to be initiated if necessary.

Dysphonia and candidiasis may be relieved by gargling or rinsing the mouth with water or brushing the teeth after using the product. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst continuing the treatment with LUTICASS.

Pediatric population
Possible systemic effects as reported for the individual components of fluticasone propionate/ formoterol fumarate dihydrate include Cushing's syndrome, Cushingoid features, adrenal suppression and growth retardation in children and adolescents. Children may also experience anxiety, sleep disorders and behavioral changes, including hyperactivity and irritability. Studies conducted with fluticasone propionate/formoterol fumarate dihydrate demonstrated similar safety and tolerability profile as compared to fluticasone monotherapy in children aged 5-12 years and fluticasone/ salmeterol in children aged 4-12. Long-term treatment with fluticasone propionate/formoterol fumarate dihydrate for 24 weeks in 208 children did not show any indication of growth retardation or adrenal suppression. Another pharmacodynamic study conducted in children aged 5-12 years showed similar lower leg growth rate after treatment with fluticasone propionate/formoterol fumarate dihydrate as compared to fluticasone monotherapy for 2 weeks.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 the national reporting system.

4.9 Overdose

There are no data available from clinical trials on overdose with fluticasone propionate/formoterol fumarate dihydrate combination; however, data on overdose with both single drugs are given below:

Symptoms:
Formoterol fumarate:
An overdose of formoterol would likely lead to an exaggeration of effects that are typical for β_2-agonists; in which case the following adverse experiences may occur: angina, hypertension or hypotension, palpitations, tachycardia, arrhythmia, prolonged QTc interval, headache, tremor, nervousness, muscle cramps, dry mouth, insomnia, fatigue, malaise, seizures, metabolic acidosis, hypokalemia, hyperglycemia, nausea and vomiting.

Fluticasone propionate:
Acute overdose with fluticasone propionate usually does not constitute a clinical problem. The only harmful effect after inhalation of a large amount of the drug over a short period is suppression of

hypothalamic pituitary adrenocortical (HPA) axis function. HPA axis function usually recovers in a few days, as verified by plasma cortisol measurements. Treatment with the inhaled corticosteroid should be continued at the recommended dose to control asthma.

There are reports of rare cases of acute adrenal crisis. Children and adolescents <16 years taking high doses of fluticasone propionate: (typically ≥1000 microgram/day) may be at particular risk. Presenting symptoms can be vague (anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting and hypotension). Typical symptoms of an adrenal crisis are decreased level of consciousness, hypoglycemia and/or seizures.

Following chronic use of very high doses a degree of atrophy of the adrenal cortex and HPA axis suppression may occur. Monitoring of adrenal reserve may be necessary. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma (see section 4.4).

Treatment:
Formoterol fumarate:
Treatment of formoterol overdose consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of cardio selective β-receptor blockers may be considered, bearing in mind that such medication can induce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial in cases of formoterol overdose. Cardiac monitoring is recommended.

If LUTICASS 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. Serum potassium levels should be monitored as hypokalemia can occur. Potassium replacement should be considered.

Fluticasone propionate:
In the management of chronic overdose, oral or systemic corticosteroids may be required in situations of stress. All patients deemed to be chronically overdosed should be treated as if steroid dependent with a suitable maintenance dose of a systemic corticosteroid. When stabilized, treatment should be continued with an inhaled corticosteroid at the recommended dose for symptom control.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airways adrenergics in combination with corticosteroids or other drugs excluding anticholinergics
ATC code: R03AK11

Mechanism of Action
LUTICASS contains both fluticasone propionate and formoterol fumarate. The mechanisms of action are described below for the individual components. These drugs represent two classes of medications (a synthetic corticosteroid and a selective, long-acting β_2-adrenergic receptor agonist) and as with other inhaled corticosteroid and long-acting β_2-adrenergic agonist combinations additive effects are seen in terms of a reduction in asthma exacerbations.

Fluticasone propionate
Fluticasone propionate is a synthetic, trifluorinated glucocorticoid with potent anti-inflammatory activity in the lungs when given by inhalation. Fluticasone propionate reduces symptoms and

exacerbations of asthma with less adverse effects than when corticosteroids are administered systemically.

Formoterol fumarate
Formoterol fumarate is a long-acting selective β_2-adrenergic receptor agonist. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. The onset of bronchodilating effect is rapid (within 1 - 3 minutes), and the duration of effect is at least 12 hours after a single dose.

Pharmacodynamic effects
In 12-week clinical trials in adults and adolescents, the addition of formoterol to fluticasone propionate improved asthma symptoms and lung function and reduced exacerbations. Therapeutic effect of fluticasone propionate/formoterol fumarate dihydrate combination exceeded that of fluticasone propionate alone. There are no long-term data comparing fluticasone propionate/ formoterol fumarate dihydrate combination with fluticasone propionate.

In an 8-week clinical trial, the effect on lung function with fluticasone propionate/formoterol fumarate dihydrate combination was at least equal to that of the combination of fluticasone propionate and formoterol fumarate when administered as separate inhalers. Long-term comparative data of fluticasone propionate/formoterol fumarate dihydrate combination versus fluticasone propionate and formoterol fumarate are not available. There were no signs of attenuation of therapeutic effects of fluticasone propionate/formoterol fumarate dihydrate combination in trials lasting up to 12 months including adult and adolescent patients.

Dose-response trends for fluticasone propionate/formoterol fumarate dihydrate combination were evident for symptom-based endpoints (with incremental benefits from high versus low dose fluticasone propionate/formoterol fumarate dihydrate being most likely in patients with more severe asthma).

Pediatric population
In a 12-week double-blind study 512 children aged 5-11 years were randomized to fluticasone propionate/formoterol fumarate dihydrate (2 inhalations of 50/5 microgram twice daily), fluticasone/salmeterol or fluticasone monotherapy. Fluticasone propionate/formoterol fumarate dihydrate (2 inhalations of 50/5 microgram twice daily) was superior to fluticasone monotherapy and non-inferior to fluticasone/salmeterol with regards to change from baseline in pre-dose (FEV_1) to post dose FEV1 over 12 weeks and 4-hour FEV_1 area under the curve (AUC) at Week 12. Fluticasone propionate/formoterol fumarate dihydrate combination (2 inhalations of 50/5 microgram twice daily) was not superior to fluticasone monotherapy in change in pre-dose FEV_1 over the 12-week treatment but was non-inferior to fluticasone/salmeterol on this endpoint.

In a second 12-week pediatric study including a 6-month extension phase 210 children aged 4-12 years were treated with a maintenance dose of fluticasone propionate/formoterol fumarate dihydrate combination (2 inhalations of 50/5 mcg twice daily) or with fluticasone/salmeterol. Fluticasone propionate/formoterol fumarate dihydrate combination (2 inhalations of 50/5 microgram twice daily) was non-inferior to fluticasone/salmeterol. 205 patients subsequently completed the 6-month extension phase during which they received fluticasone propionate/formoterol fumarate dihydrate combination (2 inhalations of 50/5 microgram twice daily). Fluticasone propionate/formoterol fumarate dihydrate combination was safe and well tolerated.

5.2 Pharmacokinetic properties

Fluticasone propionate

Absorption:

Following inhalation, systemic absorption of fluticasone propionate occurs mainly through the lungs and has been shown to be linearly related to dose over the dose range 500 to 2000 mcg. Absorption is initially rapid then prolonged.

Published studies using oral dosing of labelled and unlabeled drug have demonstrated that the absolute oral systemic bioavailability of fluticasone propionate is negligible (<1%) due to a combination of incomplete absorption from the GI tract and extensive first-pass metabolism.

Distribution:

Following intravenous administration, fluticasone propionate is extensively distributed in the body. The initial disposition phase for fluticasone propionate is rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averages 4.2 L/kg. The percentage of fluticasone propionate bound to human plasma proteins averages 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Biotransformation:

The total clearance of fluticasone propionate is high (average, 1,093 ml/min), with renal clearance accounting for less than 0.02% of the total. The very high clearance rate indicates extensive hepatic clearance. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 isoform subfamily (CYP 3A4) pathway. This metabolite has less affinity (approximately 1/2000) than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro*. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

Elimination:

87 - 100% of an oral dose is excreted in the feces (up to 75% as parent compound). There is also a non-active major metabolite.

Following intravenous dosing, fluticasone propionate shows polyexponential kinetics and has a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled dose is excreted in the urine as metabolites, and the remainder is excreted in the feces as parent drug and metabolites.

Formoterol fumarate

Data on the plasma pharmacokinetics of formoterol were collected in healthy volunteers after inhalation of doses higher than the recommended range and in COPD patients after inhalation of therapeutic doses.

Absorption:

Following inhalation of a single 120-microgram dose of formoterol fumarate by healthy volunteers, formoterol was rapidly absorbed into plasma, reaching a maximum concentration of 91.6 pg/ml within 5 minutes of inhalation. In COPD patients treated for 12 weeks with formoterol fumarate 12 or 24 mcg twice daily, the plasma concentrations of formoterol ranged between 4 and 8.9 pg/ml and 8 and 17.3 pg/ml respectively at 10 minutes, 2 hours and 6 hours post inhalation.

Studies investigating the cumulative urinary excretion of formoterol and/or its (RR) and (SS)-enantiomers, after inhalation of dry powder (12 - 96 mcg) or aerosol formulations (12-96 mcg), showed that absorption increased linearly with the dose.

After 12 weeks administration of 12 mcg or 24 microgram formoterol twice daily, the urinary excretion of unchanged formoterol increased by 63-73% in adult patients with asthma, by 19-38% in adult patients with COPD and by 18-84% in children, suggesting a modest and self-limiting

accumulation of formoterol in plasma after repeated dosing.

Distribution:
The plasma protein binding of formoterol is 61-64% (34% primarily to albumin).

There is no saturation of binding sites in the concentration range reached with therapeutic doses. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 120-microgram dose.

Biotransformation:
Formoterol is eliminated primarily by metabolism, direct glucuronidation being the major pathway of biotransformation (with O-demethylation followed by further glucuronidation being another pathway). Minor pathways involve sulphate conjugation of formoterol and deformylation followed by sulphate conjugation. Multiple isozymes catalyze the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP 2D6, 2C19, 2C9 and 2A6) of formoterol, and so consequently, the potential for metabolic drug-drug interaction is low. Formoterol did not inhibit cytochrome P450 isozymes at therapeutically relevant concentrations. The kinetics of formoterol is similar after single and repeated administration (indicating no auto-induction or inhibition of metabolism).

Elimination
In asthmatic and COPD patients treated for 12 weeks with 12 or 24 microgram formoterol fumarate twice daily, approximately 10% and 7% of the dose, respectively, were recovered in the urine as unchanged formoterol. In asthmatic children, approximately 6% of the dose was recovered in the urine as unchanged formoterol after multiple dosing of 12 and 24 microgram. The (R,R) and (S,S)-enantiomers accounted for 40% and 60% respectively of urinary recovery of unchanged formoterol, after single doses (12 to 120 microgram) in healthy volunteers and after single and repeated doses in asthma patients.

After a single oral dose of ^{3}H-formoterol, 59-62% of the dose was recovered in the urine and 32-34% in the feces. Renal clearance of formoterol is 150 ml/min.

After inhalation, plasma formoterol kinetics and urinary excretion rate data in healthy volunteers indicate a biphasic elimination, with the terminal elimination half-lives of the (R, R) - and (S, S)-enantiomers being 13.9 and 12.3 hours, respectively. Peak excretion occurs rapidly, within 1.5 hours. Approximately 6.4 - 8% of the dose was recovered in the urine as unchanged formoterol, (with the (R, R) - and (S, S)-enantiomers contributing 40% and 60%, respectively).

Fluticasone propionate/formoterol fumarate combination:
A number of studies have examined the pharmacokinetic characteristics of fluticasone propionate and formoterol fumarate from fluticasone propionate/formoterol fumarate dihydrate combination compared with the individual components, given both together and separately.

There is a high variability both within and between the pharmacokinetic studies however, in general there is a trend for the systemic exposure of fluticasone and formoterol to be less from this fixed combination of fluticasone propionate and formoterol fumarate than from the individual components given together.

Pharmacokinetic equivalence between fluticasone propionate/formoterol fumarate dihydrate

combination and the constituent mono products has not been demonstrated. Long-term comparative data of fluticasone propionate/formoterol fumarate dihydrate combination versus fluticasone propionate and formoterol fumarate are not available (see section 5.1).

Absorption

Fluticasone propionate/formoterol fumarate dihydrate combination – fluticasone propionate

Following inhalation of a single 250 micrograms of fluticasone propionate from 2 actuations of 125 microgram fluticasone propionate/5 microgram formoterol fumarate inhaler by healthy volunteers, fluticasone propionate was rapidly absorbed into the plasma, reaching a mean maximum plasma fluticasone concentration of 32.8 pg/ml within 45 minutes of inhalation. In asthma patients who received single doses of fluticasone propionate from fluticasone propionate/formoterol fumarate dihydrate combination, mean maximum plasma concentrations of 15.4 pg/ml and 27.4 pg/ml were achieved within 20 minutes and 30 minutes for 100 microgram/10 microgram (2 actuations of 50 microgram fluticasone propionate/5 microgram formoterol fumarate inhaler) and 250 microgram/ 10 microgram (2 actuations of 125 microgram fluticasone propionate/5 microgram formoterol fumarate inhaler) doses respectively.

In multiple dose studies in healthy volunteers, fluticasone propionate/formoterol fumarate dihydrate combination doses of 100 microgram/10 microgram, 250 microgram/10 microgram and 500 microgram /20 microgram resulted in mean maximum plasma fluticasone concentrations of 21.4, 25.9 to 34.2 and 178 pg/ml respectively. The data for the 100 microgram/10 microgram and 250 microgram/10 microgram doses were generated by use of a device without a spacer and the data for the 500 microgram/20 microgram dose were generated by use of a device with a spacer. Use of a spacer device increases mean systemic (which equates to pulmonary absorption) bioavailability of fluticasone by 35% in healthy volunteers compared to administration of fluticasone propionate/ formoterol fumarate dihydrate combination via a metered dose inhaler alone.

Fluticasone propionate/formoterol fumarate dihydrate combination – formoterol fumarate

Following a single dose of fluticasone propionate/formoterol fumarate dihydrate combination in healthy volunteers, a dose of 20 mcg of formoterol fumarate from 2 actuations of 250 microgram fluticasone propionate/10 microgram formoterol fumarate inhaler resulted in a mean maximum plasma formoterol concentration of 9.92 pg/ml within 6 minutes of inhalation. Following multiple doses, 20 micrograms of fluticasone propionate/formoterol fumarate dihydrate combination from 2 actuations of 250 microgram/10 microgram inhaler resulted in a mean maximum plasma formoterol concentration of 34.4 pg/ml.

Use of a spacer device decreases mean systemic bioavailability of formoterol by 25% in healthy volunteers compared to administration of fluticasone propionate/formoterol fumarate dihydrate combination via a metered dose inhaler alone. This is likely to be due to a reduction in absorption from the gastrointestinal tract when the spacer is used, offsetting the expected corresponding increase in pulmonary absorption.

Distribution

There is currently no plasma protein binding information specific to fluticasone propionate or formoterol fumarate from fluticasone propionate/formoterol fumarate inhaler.

Biotransformation

There are currently no data relating to the metabolism of fluticasone propionate or formoterol fumarate specifically from the inhalation of formoterol fumarate from fluticasone propionate/formoterol fumarate inhaler.

Elimination
Fluticasone propionate
Following inhalation of fluticasone propionate from 2 actuations of 250 microgram fluticasone propionate/10 microgram formoterol fumarate combination, fluticasone propionate has a terminal elimination half-life of approximately 14.2 h.

Formoterol fumarate
Following inhalation of formoterol fumarate from 2 actuations of 250 microgram fluticasone propionate/10 microgram formoterol fumarate combination, formoterol fumarate has a terminal elimination half-life of approximately 6.5 h. Less than 2% of a single dose of formoterol fumarate from fluticasone propionate/formoterol fumarate is excreted in the urine.

5.3 Preclinical safety data

The toxicity observed in animal studies with formoterol fumarate and fluticasone propionate, given in combination or separately consisted mainly of effects associated with exaggerated pharmacological activity. Effects on the cardiovascular system are related to formoterol administration and included hyperemia, tachycardia, arrhythmias and myocardial lesions. Neither increase in toxicity nor occurrence of unexpected findings was observed upon administration of the combination.

Reproduction studies in rats and rabbits with fluticasone propionate/formoterol fumarate dihydrate combination confirmed the known embryo-fetal effects of the two individual components (fetal growth retardation, incomplete ossification, embryo lethality, cleft palate, edema and skeletal variations). These effects were seen at lower exposures than those expected by using the clinical maximum recommended dose. A somewhat reduced fertility in male rats was observed at very high systemic exposure to formoterol.

Neither formoterol fumarate nor fluticasone propionate were found to be genotoxic in standard *in vitro* and *in vivo* tests, when tested individually. No carcinogenicity studies have been performed with the combination. No carcinogenic potential has been identified for fluticasone propionate. A slight increase in the incidence of benign tumors was observed in the reproductive tract of female mice and rats following administration of formoterol. This effect is looked upon as a class effect in rodents after long exposure to high doses of β_2-agonists and does not suggest any potential risk of carcinogenicity in man.

Pre-clinical studies with HFA 227 reveal no special hazard for man (based on studies of repeated-dose toxicity, genotoxicity, carcinogenicity and toxicity to reproduction).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone (PVP) K 25
Polyethylene glycol (PEG) 1000
HFA 227 ea pharma grade

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Keep at room temperature below 25°C and its original package.

Do not refrigerate or freeze. If the inhaler is exposed to freezing conditions then the patient must be advised to allow the inhaler to warm at room temperature for 30 minutes then re-prime the inhaler (see section 4.2).

The canister contains a pressurized liquid. Do not expose to temperatures higher than 50°C. Do not puncture, break or burn, even when apparently empty.

6.5 Nature and contents of container

LUTICASS 250 mcg/10 mcg Inhalation Aerosol, Suspension is available in 14 ml aluminum canisters with metering valve for 120 doses. Each canister (tube and valve) is placed inside a plastic actuator fitted with a dust cap to deliver the required spray in accordance with the purpose of inhaler use. The device is placed with a package leaflet in a cardboard box.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. 34303 No.:1
Küçükçekmece / İSTANBUL / TURKEY

8. MARKETING AUTHORIZATION NUMBER

2019/546

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 25.10.2019
Date of last renewal :

10. DATE OF REVISION OF THE TEXT