SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLIXON 125 mcg Aerosol Inhaler

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
For each actuation:
Fluticasone propionate……125 microgram

Excipient(s):
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurized, metered dose aerosol.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is used as anti-inflammatory, bronchodilator, symptom controller in all steps of asthma and used to reduce the requirement for oral steroids. Not recommended for use alone in COPD.

4.2 Posology and method of administration

Posology/Frequency and duration of administration:
Patients should be made aware of the prophylactic nature of therapy with inhaled fluticasone propionate and that it should be taken regularly even when they are asymptomatic. FLIXON is for oral inhalation only.

It is intended that each prescribed dose is given by a minimum of 2 inhalations.

- Asthma

The onset of therapeutic effect is 4 to 7 days, although some benefit may be apparent as soon as 24 hours for patients who have not previously received inhaled steroids.

If patients find that relief with short-acting bronchodilator treatment becomes less effective or they need more inhalations than usual, medical attention must be sought.

Adults and children over 16 years of age: 100 to 1000 microgram twice daily.

Patients should be given a starting dose of FLIXON which is appropriate for the severity of their disease:
Mild asthma: 100 to 250 microgram twice daily.
Moderate asthma: 250 to 500 microgram twice daily.
Severe asthma: 500 to 1000 microgram twice daily.

The dose may then be adjusted until control is achieved or reduced to the minimum effective dose, according to the individual response.

Alternatively, the starting dose of fluticasone propionate may be gauged at half the total daily dose of beclomethasone dipropionate or equivalent as administered by metered-dose inhaler.

- Chronic Obstructive Pulmonary Disease (COPD):

500 microgram twice daily.

Not recommended for use alone in COPD.
Patients should be made aware that FLIXON must be used daily for optimum benefit. Benefit is usually seen within 3 to 6 months. However, if there is no improvement after 3 to 6 months then the patient should undergo medical assessment.

Route of administration
FLIXON is for oral inhalation only.
In patients who find co-ordination of a pressurized metered dose inhaler difficult, a spacer (volumatic spacer) may be used with FLIXON.

Additional information on special populations
Renal/Hepatic impairment:
There is no need to adjust the dose in hepatic or renal impairment.

Pediatric population
- Asthma

Children over 4 years of age:
50 – 200 microgram twice daily.
Many children's asthma will be well controlled using the 50 to 100 microgram twice daily dosing regimen. For those patients whose asthma is not sufficiently controlled, additional benefit may be obtained by increasing the dose up to 200 microgram twice daily.

Children should be given a starting dose of FLIXON which is appropriate for the severity of their disease.

The dose may then be adjusted until control is achieved, or reduced to the minimum effective dose, according to the individual response.

Children aged 1 to 4 years:
FLIXON is of benefit to younger children in the control of frequent and persistent asthma symptoms.

Clinical trials in 1 to 4 year old children have shown that the optimal control of asthma symptoms is achieved with 100 microgram twice daily administered via a pediatric spacer device with a face mask. The diagnosis and treatment of asthma should be kept under regular review.

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

4.3 Contraindications

It is contraindicated in patients with hypersensitivity to any of the ingredients of FLIXON (see Pharmaceutical Particulars – List of excipients).

4.4 Special warning and precautions for use

The management of asthma should follow a stepwise program, and patient response should be monitored clinically and by lung function tests.

Increasing use of short-acting inhaled beta$_2$-agonists to control asthma symptoms indicates deterioration of asthma control. Under these conditions, the patient's therapy plan should be reassessed.

Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to increasing corticosteroid dosage. In patients considered at risk, daily peak flow monitoring may be instituted.

FLIXON is not for use in asthma attacks, but for routine long-term management. Patients will require a fast and short-acting inhaled bronchodilator to relieve of acute asthmatic symptoms. Patients should be advised to have such rescue medication available.

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

Lack of response or severe exacerbations of asthma should be treated by increasing the dose of inhaled FLIXON and, if necessary, by giving a systemic steroid and/or an antibiotic if there is an infection.

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 (See Overdose). Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioral effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained (see Undesirable Effects).

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Children <16 years taking high doses of fluticasone propionate (typically ≥1000 microgram/day) may be at particular risk. 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, decreased level of consciousness, hypoglycemia, and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

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.

Certain individuals can show greater susceptibility to the effects of inhaled corticosteroid than do

most patients.
Treatment with FLIXON should not be stopped abruptly.

Increased blood glucose levels have been reported very rarely in patients with or without a history of diabetes mellitus (see Undesirable Effects) and this should be taken into account when prescribing to patients with a history of diabetes mellitus.

As with all inhaled corticosteroids, special care is necessary in patients with active or quiescent pulmonary tuberculosis.

During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (See section Interaction with other medicinal products and other forms of interaction).

The possibility of impaired adrenal response should always be borne in mind in mind in emergency situations, including surgery, and in elective situations that may cause stress, and appropriate corticosteroid treatment should be considered (see Overdose).

Adrenal function and adrenal reserve usually remain within the normal range on recommended doses of FLIXON therapy. The benefit of inhaled FLIXON treatment is to minimize the need for oral steroids. However, the possibility of adverse effects in patients, resulting from prior or intermittent administration of oral steroids, may persist for some time. The extent of the adrenal impairment may require specialist advice before elective procedures. The possibility of impaired adrenal response should always be borne in mind in mind in emergency situations, including surgery, that may cause stress, and appropriate corticosteroid treatment should be considered.

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

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

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

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

Switching a patient treated with oral corticosteroids to FLIXON treatment:
Caution should be exercised when switching to FLIXON treatment in oral corticosteroid-dependent patients. impaired adrenocortical function caused by prolonged systemic steroid therapy may take time to resolve.

Patients who have been treated with systemic steroids for long periods of time or at a high dose may

have adrenocortical suppression. With these patients adrenocortical function should be monitored regularly and their dose of systemic steroid reduced cautiously.

After approximately a week, gradual withdrawal of the systemic steroid is commenced. Decrements in dosages should be appropriate to the level of maintenance systemic steroid, and introduced at not less than weekly intervals. For maintenance doses of prednisolone (or equivalent) of 10 mg daily or less, the decrements in dose should not be greater than 1 mg per day, at not less than weekly intervals. For maintenance doses of prednisolone in excess of 10 mg daily, it may be appropriate to employ cautiously, larger decrements in dose at weekly intervals.

Because of the possibility of impaired adrenal response, patients transferring from oral steroid therapy to FLIXON therapy should be treated with special care, and adrenocortical function regularly monitored.

Some patients feel unwell in a non-specific way during the withdrawal phase despite improvement of the respiratory function. They should be encouraged to persevere with inhaled fluticasone propionate and to continue withdrawal of systemic steroid, unless there are objective signs of adrenal insufficiency.

Following introduction of inhaled fluticasone propionate, withdrawal of systemic therapy should be gradual and patients encouraged to carry a steroid warning card indicating that they may need additional treatment in times of stress such as worsening of asthma attacks, chest infection, major illness, surgery and trauma.

Similarly replacement of systemic steroid treatment with inhaled therapy may unmask allergies such as allergic rhinitis or eczema previously controlled by the systemic drug. These allergies should be symptomatically treated with antihistamine and/or topical preparations, including topical steroids.

Patients' inhaler technique should be checked to make sure that inhaler actuation is synchronized with inspiration to ensure optimum delivery of the medicine to the lungs.

4.5 Interaction with other medicinal products and other forms of interaction

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.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing’s syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid 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, 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.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category is C.

Women of childbearing potential / Birth control (Contraception)
There is not any reported effect on women of childbearing potential or any interaction with drugs used for birth control (contraception).

Pregnancy
There is inadequate evidence of safety of fluticasone propionate in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of fetal development, including cleft palate and intra-uterine growth retardation. There may therefore be a very small risk of such effects in the human fetus. However, that the fetal changes in animals occur after relatively high systemic exposure. Because FLIXON delivers fluticasone propionate directly to the lungs by the inhaled route it avoids the high level of exposure that occurs when corticosteroids are given by systemic routes. Administration of fluticasone propionate during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Breast-feeding
The excretion of fluticasone propionate into human breast milk has not been investigated. When measurable plasma levels were obtained in lactating laboratory rats following subcutaneous administration there was evidence of fluticasone propionate in the breast milk. However, plasma levels in patients following inhaled application of fluticasone propionate at recommended doses are likely to be low. When fluticasone propionate is used in breast-feeding mothers the therapeutic benefits must be weighed against the potential hazards to mother and baby.

Reproductive ability / Fertility
There is no data.

4.7 Effects on ability to drive and use machines

FLIXON is unlikely to produce such an effect.

4.8 Undesirable effects

Adverse effects are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 and <1/10); uncommon (≥1/1000 and <1/100); rare (≥1/10,000 and <1/1000); very rare (<1/10,000); not known (cannot be estimated from available data).

Very common and common events were generally determined from clinical trial data. Rare and very rare events were generally determined from spontaneous data.

Infections and infestations
Very common: Candidiasis of the mouth and throat
Candidiasis of the mouth and throat (thrush) occurs in some patients. It may be beneficial for such patients to rinse their mouths with water after taking their

medications. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing FLIXON.
Common: Pneumonia (patients with COPD)

Immune system disorders
Uncommon: Cutaneous hypersensitivity reactions
Very rare: Angioedema (mainly facial and oropharyngeal edema), respiratory symptoms (dyspnea and/or bronchospasm) and anaphylactic reactions

Endocrine disorders
Very rare: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation, decreased bone mineral density, cataract, glaucoma.

Metabolism and nutrition disorders
Very rare: Hyperglycemia

Psychiatric disorders
Very rare: Anxiety, sleep disorders and behavioral changes, including hyperactivity and irritability (predominantly in children).
Not known: Depression, aggression (predominantly in children)

Respiratory, thoracic and mediastinal disorders
Common: Hoarseness (In some patients FLIXON may cause hoarseness. It may be helpful to rinse out the mouth with water immediately after inhalation)
Very rare: Paradoxical bronchospasm (As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast and short-acting inhaled bronchodilator. FLIXON should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary).

Gastrointestinal disorders
Very rare: Dyspepsia

Skin and subcutaneous tissue disorders
Common: Contusions

Musculoskeletal and connective tissue disorders
Very rare: Arthralgia

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

Acute: Inhalation of the FLIXON in doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not necessitate emergency action being taken. In these patients treatment with fluticasone propionate by inhalation should be continued at a dose sufficient to control asthma adrenal function recovers in a few days and can be verified by measuring plasma

cortisol.
Chronic: If higher than approved doses are continued over prolonged periods, significant adrenocortical suppression is possible. Monitoring of adrenal reserve may be indicated. Treatment with inhaled fluticasone propionate should be continued at a dose sufficient to control asthma.

Patients receiving higher than approved doses should be managed closely and the dose reduced gradually.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, glucocorticoids
ATC code: R03BA05

FLIXON given by inhalation at recommended doses has a potent glucocorticoid anti-inflammatory action within the lungs which results in reduced symptoms and exacerbations of asthma.
According to clinical studies, there is a significant reduction of symptoms of COPD and an improvement in lung function regardless of patient age, gender, lung base line function, smoking status or atopy status. This can result in a significant improvement in the quality of life.

5.2. Pharmacokinetic properties

General properties
Absorption:
The absolute bioavailability of fluticasone propionate for each of the available inhaler devices has been estimated from within and between study comparisons of inhaled and intravenous pharmacokinetic data. In healthy adult subjects, the absolute bioavailability has been estimated for fluticasone propionate Accuhaler/Diskus (7.8%), fluticasone propionate Diskhaler (9%), fluticasone propionate Evohaler (%10.9), salmeterol-fluticasone propionate Evohaler (%5.3) and salmeterol-fluticasone propionate Accuhaler/Diskus (5.5%) respectively. 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.

Distribution:
The disposition of fluticasone propionate is characterized by a large volume of distribution at steady-state (approximately 300 L). Plasma protein binding is moderately high (91%).

Biotransformation:
Fluticasone propionate is cleared very rapidly from the systemic circulation, principally by metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Care should be taken when co-administering known CYP3A4 inhibitors, as there is potential for increased systemic exposure to fluticasone propionate.

Elimination:
The disposition of fluticasone propionate is characterized by high plasma clearance (1150 ml/min) and a terminal half-life of approximately 8 hours. The renal clearance of fluticasone propionate is negligible (<0.2%) and less than 5% as the metabolite.

Linearity/Non-linearity:
There is no data.

5.3 Preclinical safety data

Toxicology has shown only those class effects typical of potent corticosteroids, and these only at doses in excess of those proposed for therapeutic use. No novel effects were identified in repeat dose toxicity tests, reproductive studies or teratology studies.

Fluticasone propionate is devoid of mutagenic activity *in-vitro* and *in-vivo* and showed no tumorigenic potential in rodents. It is both non-irritant and non-sensitizing in animal models.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

HFA 134a (A propellant that does not contain chlorofluorocarbons (CFCs))

6.2 Incompatibilities

No incompatibilities have been reported.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at room temperature below 25°C and in a dry place. Protect from frost and direct sunlight.

As with most inhaled medications in pressurized canisters, the therapeutic effect of this medication may decrease when the canister is cold.

The canister should not be punctured, broken or burnt even when apparently empty.

6.5 Nature and contents of container

FLIXON is a metered dose inhaler with a specially designed actuator that allows you to spray 125 micrograms per each actuation. Each canister supplies 120 inhalations. FLIXON contains HFA 134a, which is a propellant that does not contain chlorofluorocarbons (CFCs). It does not damage the ozone layer.

6.6 Special precautions for disposal and other handling

Instructions for use of FLIXON:

Testing your inhaler:
If you are using your inhaler for the first time or if you have not used it for 1 week or more, remove the mouthpiece cover by gently squeezing it from both sides, shake the inhaler well, and release two puffs into the air to make sure that it works.

Using inhaler

1. Remove the mouthpiece cover by gently squeezing the sides.

2. Check inside and outside of the inhaler, including the mouthpiece to make sure that it is clean and free of objects.

3. Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.

4. Hold the inhaler upright with your thumb on the base, below the mouthpiece.

5. Breathe out as far as is comfortable, place the mouthpiece in your mouth between your teeth. Close your lips around it. Do not bite the mouthpiece.

6. As soon as you start breathing through your mouth, press the top of the inhaler down and spray FLIXON while breathing regularly and deeply.

7. Hold your breath, take the inhaler from your mouth and your finger from the top of the inhaler. Continue holding your breath as long as you comfortably can.

8. If you are going to take a larger dose, continue to hold the inhaler upright and wait half a minute before repeating steps 2 to 6.

9. Afterwards, rinse your mouth with water and spit it out.

10. Close the mouthpiece cover by firmly pushing it into place.

IMPORTANT:
Do not rush stages 4, 5 and 6. It is important that you start to breathe in as slowly as possible just before using your inhaler. Practice in front of a mirror for the first few times. If you see "mist" coming from the top of your inhaler or the sides of your mouth you should start again from stage 2.

If your doctor has given you different instructions for using your inhaler, please follow them carefully. Tell your doctor if you have any difficulties.

Children:
Young children may need assistance and adults may need to help them use the inhaler. Encourage the child to breathe out and spray the inhaler just after the child starts to breathe in. Practice the technique together. Older children or people with weak hands can hold the inhaler with both hands. Put the two

forefingers on top of the inhaler and both thumbs on the base below the mouthpiece.
Some young children may need to use a pediatric spacer device.
Your doctor or nurse will help you about this.

Cleaning:
Your inhaler should be cleaned at least once a week.
1. Remove the mouthpiece cover.
2. Do not remove the canister from the plastic casing.
3. Wipe the inside and outside of the mouthpiece with a dry cloth or tissue.
4. Replace the mouthpiece cover.

DO NOT PUT THE METAL CANISTER INTO WATER.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

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

8. MARKETING AUTHORIZATION NUMBER

2014/650

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 29.08.2014
Date of last renewal :

10. DATE OF REVISION OF THE TEXT

07.07.2021