SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLIXOTIDE 250 micrograms/dose, pressurised inhalation, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluticasone propionate ..... 250 micrograms
For one dose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation, suspension.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Continuous anti-inflammatory treatment of persistent asthma*.
*Persistent asthma is defined by daytime symptoms several times per week and/or night-time symptoms more than twice per month.

4.2. Posology and method of administration

Posology

Posology is strictly individual. The initial dose will be determined according to the severity of the disease and will be adjusted according to individual results.

It is best to always search for the lowest effective dose.

For a patient treated with beclomethasone, the recommended dose of fluticasone is usually half of the dose of beclomethasone used.

Adult

- Mild persistent asthma: (daytime symptoms more than once a week and less than once a day, night-time symptoms more than twice a month, PEFR or FEV1 > 80% of the predicted values, variability of the PEFR* between 20 and 30%): 100 to 150 µg twice a day (morning and evening).

- Moderate persistent asthma: (daily daytime symptoms, attack affecting activity and sleep, symptoms of nocturnal asthma more than once a week, daily use of short-acting inhaled beta-2-mimetics, PEFR or FEV1 between 60 and 80% of the predicted values, variability of the PEFR* greater than 30%): 150 to 500 µg twice a day (morning and night).

- Severe persistent asthma: (permanent symptoms, frequent attacks, frequent nocturnal asthma symptoms, physical activity limited by the symptoms of asthma, PEFR or FEV1 less than 60% of the predicted values, variability of the PEFR* greater than 30%): 500 to 1000 µg twice a day (morning and night).

*The variability of the PEFR is evaluated over the course of a day:
(evening PEFR - morning PEFR)
½ (evening PEFR + morning PEFR)

or a week.

Children over 4 years of age

Mild to moderate asthma: 50 to 100 µg twice a day.
Severe asthma: 200 µg twice a day.
The efficacy/safety ratio of higher daily doses has not been studied in children. It is best to always search for the lowest effective dose.
Lower-dose presentations allow for the administration of dosages recommended in children.

Children from 1 to 4 years of age

In children from 1 to 4 years of age, clinical trials have shown that optimal control of asthma symptoms was achieved with 100 µg twice daily, but few data are available with fluticasone for severe asthma in children from 1 to 4 years of age.
It is best to always search for the lowest effective dose and to plan to reduce the dose when the patient is stabilised.

Lower-dose presentations allow for the administration of dosages recommended in children.

Special populations

No dose adjustment is necessary in elderly patients or in patients with hepatic or renal impairment.

Frequency of administration

Warn the patient that this medicinal product is not intended to stop an overt asthma attack, but is a regular maintenance treatment for asthma that must be taken regularly, daily and at the prescribed doses, even when there are no symptoms, and whose effects on asthma symptoms will be felt only after a few days to a few weeks.
The daily dose is generally divided into two doses per day.
In case of unstable asthma, the dose and the number of doses taken can be increased up to administration in 3 to 4 doses per day depending on the patient's clinical condition.
In children over 4 years of age, when asthma is stabilised by a daily dose of 100 µg per day, it may be administered in one dose per day when symptoms have regressed and the asthma is controlled. In the case of asthma destabilisation, the dose and the number of doses taken must be increased again.
If a patient feels that his short-acting bronchodilator treatment becomes less effective or if he has to increase the number of doses normally taken, a medical consultation should be scheduled.

Method of administration

Flixotide is designed for oral inhalation only.
Inhalation by inhaler with mouthpiece.
It is recommended that the physician himself ensures the correct use of the inhalation system by the patient. The patient can also check his technique in a mirror (see section 3 of the leaflet "How to use Flixotide 250 micrograms/dose, pressurised inhalation, suspension").
When it is obvious that there is poor hand/lung synchronisation preventing the coordination of inhalation movements/device triggering, the use of a suitable inhalation chamber is indicated.
Instructions for use:
Patients should be instructed on how to use the dosing inhaler (see leaflet).
During inhalation, it is preferable to remain seated or standing. The inhaler has been designed to be used in a vertical position.
Checking that the device is functioning:
Before first use or if the device has not been used for a week or more, remove the cover from the mouthpiece by pressing on each side, shake the inhaler well, hold the device between fingers, placing the thumb on the base of the device below the mouthpiece, then press on the cartridge and release two puffs of product into the air to check that the device is functioning correctly. The number of doses released is counted each time the device is triggered.

Use of the device
After removing the cover from the mouthpiece by pressing on each side, the patient should:

- check that there are no foreign bodies on the inside and outside of the inhaler, including in the mouthpiece,

- shake the inhaler well to ensure that there are no foreign bodies and that the contents of the inhaler are properly mixed,

- exhale deeply,

- place the mouthpiece in front of the mouth with the bottom of the metal cartridge pointing up,

- start to inhale while pressing on the metal cartridge while continuing to breathe in slowly and deeply,

- remove the mouthpiece and hold your breath for at least 10 seconds,

- after each use, rinse your mouth with water and spit it out,

- replace the cover on the mouthpiece and press firmly to return it to its position.

Each push on the bottom of the cartridge delivers a precise dose. The duration of the push is therefore not important.
Cleaning:
The inhaler should be cleaned at least once a week.
1. Remove the cover from the mouthpiece.
2. Do not remove the cartridge from its plastic adapter.
3. Wipe the inside and outside of the mouthpiece and plastic adapter with a tissue or clean and dry cloth.
4. Replace the cover on the mouthpiece.
DO NOT IMMERSE THE METAL CARTRIDGE IN WATER.

4.3. Contraindications

- Hypersensitivity to fluticasone propionate or to any of the excipients listed in section 6.1.

- Intolerance to this medicinal product (onset of cough or bronchospasm after inhalation of the product). In this case, this treatment should be discontinued and other forms of administration or other treatments prescribed.

4.4. Special warnings and precautions for use

If a patient develops a rapid increase in their consumption of fast- and short-acting inhaled beta-2-mimetic bronchodilators within a few days (especially if peak flow meter values decrease and/or become irregular), there is a danger of decompensation of their illness and the possibility of progression to severe acute asthma (status asthmaticus). The physician should also warn the patient of the need to seek immediate medical advice in this case.
Therapeutic management will then have to be reassessed.
A sudden, progressive deterioration of asthma control may be life-threatening. Consideration should then be given to increasing corticosteroid therapy. In patients at risk, daily peak flow monitoring is recommended.
The patient should be advised that an improvement in their clinical condition must not lead to a change in treatment, and in particular to the discontinuation of inhaled corticosteroid therapy, without medical advice.
Flixotide treatment must not be stopped abruptly.
As with other corticosteroids for administration via inhalation, Flixotide must be used with caution in patients with pulmonary tuberculosis.

In case of bronchial infection or abundant bronchorrhoea, appropriate treatment is necessary in order to encourage optimal distribution of the product in the respiratory tract.
In the event of asthma destabilisation, or insufficient control of asthma exacerbations despite maximum doses of inhaled corticosteroids, short-term treatment with systemic corticosteroids should be considered. It is then necessary to maintain the inhaled corticosteroid in combination with systemic treatment.
Systemic effects associated with inhaled corticosteroids may appear, particularly if high doses are prescribed over prolonged periods. The risk of systemic effects is, however, less significant with inhaled corticosteroids than with oral corticosteroids (see section 4.9). Potential systemic effects may include Cushing's syndrome or Cushingoid appearance, skin thinning, subcutaneous haematoma, adrenal insufficiency, growth retardation in children and adolescents, loss of bone mineral density, and, more rarely, psychological or behaviour disorders, including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggressiveness (particularly in children). It is therefore always better to search for the lowest effective dose that makes it possible to maintain asthma control (see section 4.8 "Undesirable effects").

Growth in children on long-term inhaled corticosteroid therapy must be regularly monitored.

Concomitant administration of inhaled corticosteroids in asthmatics on long-term oral corticosteroid treatment (corticodependent patients) does not mean that the necessary precautions can be disregarded when decreasing doses of oral corticosteroids. These will be decreased very gradually and weaning should be performed under careful medical supervision (looking for the appearance of signs of acute or subacute adrenal failure) extending beyond the discontinuation of the systemic corticosteroid therapy.
Likewise, the replacement of oral inhaled corticosteroid therapy may sometimes reveal allergies, such as allergic rhinitis or eczema, previously controlled with the systemic treatment.
The risk of having an inappropriate adrenal function response to emergency situations and/or situations likely to be stressful (including surgical procedures) must always be taken into account, especially in patients taking high doses in the long term. Appropriate corticosteroid replacement therapy should be considered (see section 4.9). A specialist opinion may be required.
At the recommended doses, Flixotide generally has no impact on adrenal function. Administration of inhaled fluticasone propionate helps reduce reliance on oral corticosteroids, but it does not prevent the risk of developing adrenal insufficiency resulting from previous or intermittent administration of oral corticosteroids. A specialist opinion may be required.
A number of post-marketing reports of clinically significant drug interactions have been reported in patients who received fluticasone propionate in the inhaled or intranasal form and ritonavir, resulting in systemic effects linked to corticosteroids, including Cushing's syndrome and inhibition of adrenal function. As a result, the concomitant administration of fluticasone propionate and ritonavir should be avoided, unless the potential benefits for the patient outweigh the risk of systemic undesirable effects associated with corticosteroids (see section 4.5).
As with any other inhaled treatment, paradoxical bronchospasm may occur, characterised by a sudden increase in wheezing after use. It must be treated immediately with a fast- and short-acting inhaled bronchodilator. Administration of fluticasone propionate should be discontinued immediately, the patient evaluated, and, if necessary, alternative therapy should be instituted (See section 4.8 "Undesirable effects").
Increases in blood glucose levels have been very rarely reported (see section 4.8). This should be considered when prescribing this medicinal product to patients with a history of diabetes.
The patient's inhalation technique must be checked to ensure that the activation of the patient's inhaler is synchronised with inspiration for optimal delivery of the product to the lung.
Sportspeople should be aware that this proprietary medicinal product contains an active ingredient that can induce a positive reaction during doping tests.
Visual disturbance may occur with systemic and topical corticosteroid use. In case of blurred vision or any other visual symptom appearing during the corticosteroid therapy, an ophthalmologist examination is required to seek possible causes, in particular, cataract, glaucoma or rare diseases such as central serous chorioretinopathy, which have been reported while using corticosteroids systemically and topically.

4.5. Interaction with other medicinal products and other forms of interaction

Under normal conditions of use, plasma concentrations of fluticasone propionate reached after inhaled administration are low due to a significant first pass effect (hepatic and intestinal) and high plasma clearance via a significant metabolism mediated by cytochrome P450 3A4. Consequently, the risk of clinically significant interactions with fluticasone propionate seems low.
However, a study on the interaction in healthy volunteers receiving fluticasone propionate administered nasally has shown that ritonavir (a very powerful inhibitor of cytochrome P450 3A4) at a dose of 100 mg twice daily increased plasma concentrations of fluticasone propionate by a factor of several hundred, triggering a marked decrease in plasma cortisol concentrations. A number of post-marketing reports of clinically significant drug interactions have been reported in patients who received fluticasone propionate in the inhaled or intranasal form and ritonavir, resulting in systemic effects linked to corticosteroids, including Cushing's syndrome and inhibition of adrenal function. As a result, the concomitant administration of fluticasone propionate and ritonavir should be avoided, unless the potential benefits for the patient outweigh the risk of systemic undesirable effects associated with corticosteroids.
The concomitant administration of CYP3A inhibitors, including products containing cobicistat, increases the risk of systemic side effects. A number of studies have shown that other cytochrome P450 3A4 inhibitors cause negligible (erythromycin) and minor (ketoconazole) increases in systematic exposure to fluticasone propionate without a significant reduction of cortisol serum concentrations. These combinations must be avoided, except if the benefits outweigh the increased risk of systemic side effects of corticosteroids; in this case, patients must be monitored to detect any systemic side effects of corticosteroids.

4.6. Fertility, pregnancy and lactation

Pregnancy

Fluticasone propionate

The data available for pregnant women are limited. The administration of fluticasone propionate during pregnancy should only be considered if the expected benefit for the mother outweighs any potential risk for the foetus.
The results of a retrospective epidemiological study have not shown an increase in the risk of Major Congenital Malformations (MCM) following exposure to fluticasone propionate compared with exposure to other inhaled corticosteroids, during the first trimester of pregnancy (see section "5.1. Pharmacodynamic properties").
In animals, experiments highlight a variable teratogenic effect of corticosteroids depending on the species. The reproduction studies performed have only shown effects characteristic of corticosteroids for systemic exposures much higher than those observed at recommended inhaled doses.
Epidemiological studies did not detect any malformative risk linked with the use of corticosteroids in the first trimester although there is transplacental passage.
In chronic diseases requiring treatment throughout pregnancy, slight intrauterine growth retardation is possible. Neonatal adrenal insufficiency was exceptionally observed after systemic, high-dose corticosteroid therapy.
The implementation of a period of clinical (weight, urine output) and laboratory monitoring of the newborn seems justified.

Norflurane (Tetrafluoroethane or HFA 134a): propellant

The study of reproductive functions in animals did not reveal any harmful effect of the administration of norflurane (tetrafluoroethane or HFA 134a) contained in this medicinal product.
In the absence of teratogenic effects in animals, no malformative effect in humans is expected.
However, there is currently no relevant or sufficient data to assess any malformative effect or foetal toxicity of norflurane when administered during pregnancy.

Breastfeeding

Fluticasone propionate

Corticosteroids pass into breastmilk.
The passage of fluticasone propionate into breastmilk has not been studied in humans.
In breastfeeding rats, when measurable plasma concentrations are obtained after subcutaneous administration, the presence of fluticasone propionate is detectable in their milk. However, in patients who received inhaled fluticasone propionate at the recommended doses, the plasma concentrations obtained are likely to be low.
Administration during breastfeeding should only be considered if the expected benefit for the mother outweighs any potential risk for the child.

Fertility

No data on the effect of fluticasone propionate on human fertility are available. Studies conducted in animals have shown no effects of fluticasone propionate on fertility, regardless of sex.

Norflurane (Tetrafluoroethane or HFA 134a): propellant

The passage of HFA 134a and its metabolites into breastmilk is not known.

4.7. Effects on the ability to drive and operate machines

The effect of fluticasone propionate on the ability to drive or use machines is unlikely.

4.8. Undesirable effects

The side effects are cited below, listed by organ class and frequency.
Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000) including isolated cases and frequency undetermined (cannot be estimated on the basis of the available data). Very common, common and uncommon events were generally determined from clinical trial data.
Rare and very rare events are generally determined from spontaneous reports.
Infections and Infestations
Very common: Oropharyngeal candidiasis
More often than not, oropharyngeal candidiasis resolves spontaneously or with appropriate treatment. It rarely requires discontinuation of inhaled corticosteroid therapy. Its risk of occurrence increases with the dose used and the doses taken per day. It can be prevented by rinsing the mouth with water after inhalation.
Rare: Oesophageal candidiasis
Immune system disorders
Skin hypersensitivity reactions have been reported, as follows:
Uncommon: Skin hypersensitivity reactions
Very rare: Angioedema (mostly facial and oropharyngeal oedema), respiratory symptoms (dyspnoea and/or bronchospasm) and anaphylactic reactions.

Eye disorder

Not known frequency: Blurred vision (see section 4.4)

Endocrine disorders
Possible onset of systemic effects (see section 4.4).
Very rare: Cushing's syndrome, Cushingoid appearance, inhibition of adrenal function, decreased bone mineral density, growth retardation in children and adolescents, cataract and glaucoma.
The risk of the occurrence of systemic effects linked to inhaled corticosteroid therapy is minimal but cannot be excluded at high doses. Observations of thinning of the skin, subcutaneous haematoma,

suppression of biological adrenal functions (decrease in plasma cortisol and 24-hour urine free cortisol) have been described with inhaled corticosteroids.
Long-term administration of high doses may therefore require monitoring, especially in children and the elderly.
It should always be recommended to search for the lowest effective dose, taking into account the risk of insufficient asthma control that will have to be weighed against that of the systemic impact.
Metabolism and nutrition disorders
Very rare: Hyperglycaemia
Psychiatric disorders
Very rare: Anxiety, sleep disorders and behavioural changes, including psychomotor hyperactivity and irritability (especially in children).
Unknown frequency: depression and aggressiveness (mainly in children).
Respiratory, thoracic and mediastinal disorders
Common: Hoarseness
Possibility of onset of pharyngeal discomfort, dysphonia and hoarseness, which can be prevented by rinsing the mouth immediately after inhalation.
Very rare: Paradoxical bronchospasm (see section 4.4)
Not known: Epistaxis
Skin and subcutaneous tissue disorders
Common: Contusions

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 the national reporting system: French National Agency for Medicines and Health Products Safety (ANSM) and the network of Regional Pharmacovigilance Centres – Website: www.ansm.sante.fr.

4.9. Overdose

Signs and symptoms

The use of this medicinal product at doses that are much higher than the recommended doses is indicative of the worsening of the respiratory condition, requiring prompt consultation for therapeutic reassessment.
Acute overdose: Administration of inhaled fluticasone propionate at doses higher than those recommended may lead to temporary inhibition of adrenal function. There is no need to take any emergency measures, as adrenal function is restored within several days, as shown by plasma cortisol measurements.
If higher than recommended doses continue to be administered over prolonged periods, the inhibition of adrenal function may be more significant.
Very rare cases of acute adrenal crisis have been reported in children who received doses higher than recommended (generally higher than or equal to 1,000 µg per day), over prolonged periods (several months or years); the signs observed include hypoglycaemia, decrease in consciousness and/or convulsions.
Acute crises of adrenal insufficiency may be triggered by a trauma, surgical procedure, infection or rapid dose reduction.

Treatment

Patients receiving doses higher than recommended should be monitored regularly and the dose should be gradually reduced.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: INHALED GLUCOCORTICOID - ANTI-ASTHMATIC, ATC code: R03BA05.
Inhaled fluticasone propionate has marked anti-inflammatory action on the bronchial mucosa.
In adults, the inhibitory effect of fluticasone propionate on the adrenocortical system only manifests at a dosage greater than 1,500 µg per 24 hours.

Clinical efficacy and safety

Asthma medications containing fluticasone propionate (FP) used during pregnancy

A retrospective epidemiological observational study using data from an electronic database of patients in the United Kingdom has been conducted to evaluate the risk of Major Congenital Malformations (MCM) resulting from exposure to inhaled fluticasone propionate alone or in combination with fluticasone propionate-salmeterol during the first trimester of pregnancy, compared with exposure to inhaled corticosteroids not containing fluticasone propionate. No placebo comparator was included in this study.
Of the cohort of 5,362 asthmatic patients exposed to inhaled corticosteroids during the first trimester of pregnancy, 131 diagnosed MCMs were identified; of the 1,612 (30%) patients exposed to fluticasone propionate alone or in combination with fluticasone propionate-salmeterol, 42 diagnosed MCMs were identified. The adjusted odds ratios for the MCMs diagnosed at 1 year were 1.1 (95% CI: 0.5-2.3) for women exposed to fluticasone propionate compared with women exposed to corticosteroids not containing fluticasone propionate with moderate asthma, and 1.2 (95% CI: 0.7-2.0) for women suffering from significant to severe asthma. No difference on the risk of MCMs was identified following exposure to fluticasone propionate alone or in combination with fluticasone propionate-salmeterol during the first trimester of pregnancy. The absolute risks of MCMs according to the degree of severity of asthma varied from 2.0 to 2.9 for 100 pregnancies exposed to fluticasone propionate, which is comparable to the results of a study of 15,840 pregnancies not exposed to medicinal products used in the treatment of asthma in the General Practice Research Database (2.8 MCMs in 100 pregnancies).

5.2. Pharmacokinetic properties

Fluticasone propionate

After inhalation, part of the dose is swallowed, while the other part penetrates the bronchi, where it exerts its effects. The absolute bioavailability of fluticasone propionate for each of the devices available was estimated starting from a comparison of the results obtained between different pharmacokinetic studies after administration of the product by inhalation and intravenously.
In healthy adults, the absolute bioavailability of fluticasone propionate was estimated at 7.8% for the Diskus form and 10.9% for the pressurised bottle form. After inhalation, minimal systemic exposure to fluticasone propionate was observed in asthmatic patients. Its oral bioavailability is virtually zero.
After oral administration of fluticasone, 87 to 100% of the dose is excreted in the faeces, including a portion in unchanged form (20% for a 1 mg dose, up to 75% for a dose of 16 mg).
There is a significant hepatic first pass effect. 98% of the dose administered by IV is eliminated within 3 to 4 hours and the terminal plasma elimination half-life is approximately 8 hours.
The volume of distribution is close to 300 litres.
The plasma protein binding rate is 91%. Fluticasone propionate is primarily metabolised by the cytochrome P450 isoenzyme CYP3A4 in the form of metabolites with no corticosteroid effect.

Norflurane (Tetrafluoroethane or HFA 134a): propellant

After inhalation of a puff, HFA 134a absorption is very low and fast, and the maximum concentration is reached in less than 6 minutes.
Very mild hepatic metabolism with formation of trifluoroacetic acid and trifluoroacetaldehyde was found in animals (mice and rats).
However, kinetic studies performed in patients after administration of HFA 134a in a pathological situation, did not highlight the formation of trifluoroacetic acid.

5.3. Preclinical safety data

Not reported.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Propellant: Norflurane (tetrafluoroethane or HFA 134a).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Replace the cover on the mouthpiece and press firmly to return it to its position.
Do not store above 30°C.
Pressurised container: Do not expose to temperatures greater than 50°C, or to the sun, do not pierce, do not incinerate, even empty.

6.5. Nature and contents of container

Pressurised bottle (aluminium) with 60 doses or 120 doses with dosing valve and mouthpiece;
box of 1.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Laboratoire GLAXOSMITHKLINE

23, rue François Jacob

92500 Rueil-Malmaison

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 336 707 2 6: 1 pressurised aluminium bottle with 60 doses with dosing valve and mouthpiece; box of 1.

- 34009 336 708 9 4: 1 pressurised aluminium bottle with 120 doses with dosing valve and mouthpiece; box of 1.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation: 02 November 1993
Date of latest renewal: 28 October 2012

10. DATE OF REVISION OF THE TEXT

25 May 2018

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR THE PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I