PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-FLUTICASONE HFA

Fluticasone Propionate Inhalation Aerosol

50, 125 and 250 mcg / metered dose

Apotex Standard

Corticosteroid for Oral Inhalation

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RECENT MAJOR LABEL CHANGES

Indications,1.1 Pediatrics	06/2022
Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	06/2022
Warnings and Precautions, 7.1.3 Pediatrics	06/2022

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-FLUTICASONE HFA (fluticasone propionate) is indicated for:

- the prophylactic management of steroid-responsive bronchial asthma in adults and children (12 months of age or older). For children, this includes patients not controlled on currently available prophylactic medication.

APO-FLUTICASONE HFA is **not** indicated for the relief of acute bronchospasm (see 7 WARNINGS AND PRECAUTIONS, general).

1.1 Pediatrics

Pediatrics (12 months of age and older): APO-FLUTICASONE HFA inhalation aerosol is indicated for children 12 months of age and above who require prophylactic medication, including patients not controlled on currently available prophylactic medication.

At present there are insufficient clinical data to recommend the use of APO-FLUTICASONE HFA inhalation aerosol in children younger than 12 months.

1.2 Geriatrics

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

2 CONTRAINDICATIONS

- Patients with a history of hypersensitivity to any of its ingredients (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING) and in patients with untreated fungal, bacterial or tuberculous infections of the respiratory tract.
- Patients with IgE mediated allergic reactions to lactose or milk (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- In the primary treatment of status asthmaticus or other acute episodes of asthma.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The lowest dose of APO-FLUTICASONE HFA (fluticasone propionate**) required to maintain good asthma control should be used. When the patient's asthma is well controlled, a reduction in the dose of APO-FLUTICASONE HFA should be attempted in order to identify the lowest possible dose required to maintain control. Such an attempt at dose reduction should be carried out on a regular basis.**

Patients using inhaled bronchodilators should be advised to use the bronchodilator before APO-FLUTICASONE HFA in order to enhance the penetration of fluticasone propionate into the bronchial tree. Several minutes should lapse between the use of the two inhalers to allow for

some bronchodilation to occur.

In the presence of excessive mucous secretion, the drug may fail to reach the bronchioles. Therefore, if an obvious response is not obtained after ten days, a short course of systemic corticosteroid treatment might be in order. Continuation of treatment with inhaled fluticasone propionate usually maintains the improvement achieved, the systemic steroid being gradually withdrawn.

Treatment with APO-FLUTICASONE HFA should not be stopped abruptly, but tapered off gradually.

Physicians should be aware that, due to the improved potency of fluticasone propionate, the dose may be different than that required with some other inhaled steroids.

It is intended that each prescribed dose of APO-FLUTICASONE HFA be given by a minimum of two inhalations twice daily.

4.2 Recommended Dose and Dosage Adjustment

Adults and adolescents 16 years of age and older

Usual dosage is 100 to 500 mcg twice daily.

Patients should be given a starting dose of APO-FLUTICASONE HFA which is appropriate for the severity of their disease (see 1 INDICATIONS) as follows:

Asthma Severity	APO-FLUTICASONE HFA Dose
Mild	100 to 250 mcg twice daily
Moderate	250 to 500 mcg twice daily
Severe	500 mcg twice daily. Very severe patients requiring higher dosesof corticosteroids such as those patients currently requiring oral steroids may use doses up to 1000 mcg 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 APO-FLUTICASONE HFA may be gauged at half the total daily dose of beclomethasone dipropionate or equivalent as administered by metered-dose inhaler (see 14 CLINICAL TRIALS section).

Onset of effect occurs within 4 to 7 days, although some benefit may be apparent as soon as 24 hours of the start of treatment with APO-FLUTICASONE HFA for patients who have not previously received inhaled steroids. If no improvement is noted in this time frame, an increase in dose should be considered.

Pediatrics

Children 4 to 16 years of age

The usual starting dose is 100 mcg twice daily and many children's asthma will be well controlled with this regimen. Children should be given a starting dose of inhaled fluticasone propionate which is appropriate for the severity of their disease. The recommended dosing is as follows:

APO-FLUTICASONE HFA Dose	Recommended Administration
100 mcg twice daily	Two inhalations of APO-FLUTICASONE HFA 50 mcg twice daily

APO-FLUTICASONE HFA inhalation aerosol is only available in 50, 125 and 250 mcg/metered dose. It is intended that each prescribed dose of APO-FLUTICASONE HFA be given by two inhalations twice daily for children 4 to 16 years of age.

If therapy does not produce a significant improvement or if the patient's condition worsens, medical advice must be sought to determine a new plan of treatment.

Children 12 months to 4 years of age

Younger children should be given 100 mcg of APO-FLUTICASONE HFA twice daily administered via a pediatric spacer device with a face mask.

Clinical trials in 12 month to 4 year old children have shown that the optimal control of asthma symptoms is achieved with 100 mcg twice daily. Higher doses of inhaled drug are required in younger children compared to older children because of reduced efficiency of drug delivery due to smaller airways and increased nasal breathing.

The diagnosis and treatment of asthma should be kept under regular review.

Dosage Adjustment

The dosage of APO-FLUTICASONE HFA should be adjusted according to individual response. For patients whose asthma has been stabilized without the use of a spacer device, continuation of therapy with a spacer may require a dosage adjustment. The use of different spacer devices may result in variable effects on drug delivery (see 10 CLINICAL PHARMACOLOGY, Pharmacokinetics, Use with Spacers).

Special patient groups

There is no need to adjust the dose in elderly patients or those with hepatic or renal impairment.

Patients receiving systemic steroids

The transfer of steroid-dependent patients to APO-FLUTICASONE HFA, and their subsequent management, needs special care mainly because recovery from impaired adrenocortical function, caused by prolonged systemic therapy, is slow. Patients' bronchial asthma should be stable before being given APO-FLUTICASONE HFA in addition to the usual maintenance dose of systemic steroid. After about a week, gradual withdrawal of the systemic steroid is started by reducing the daily dose by 1.0 milligram of prednisone, or its equivalent of other corticosteroid, at not less than weekly intervals, if the patient is under close observation. In children, the usual rate of withdrawal is 1.0 milligram of the daily dose of prednisone every eight days when under close

supervision. If continuous supervision is not feasible, the withdrawal of the systemic steroid should be slower, approximately 1.0 milligram of the daily dose of prednisone (or equivalent) every ten and every twenty days in adults and in children, respectively. A slow rate of withdrawal cannot be over- emphasized.

If withdrawal symptoms appear, the previous dose of the systemic drug should be resumed for a week before any further decrease is attempted. Patients who have been treated with systemic steroids for long periods of time or at a high dose may have adrenocortical suppression. In these patients adrenocortical function should be monitored regularly and their dose of systemic steroid reduced cautiously.

Some patients feel unwell during the withdrawal phase experiencing symptoms such as joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function. Such patients should be encouraged to persevere with APO-FLUTICASONE HFA but should be watched carefully for objective signs of adrenal insufficiency such as hypotension and weight loss. If evidence of adrenal insufficiency occurs, the systemic steroid dosage should be boosted temporarily and thereafter further withdrawal should be continued more slowly.

Transferred patients whose adrenocortical function is impaired should carry a warning card indicating that they need supplementary treatment with systemic steroids during periods of stress, e.g. surgery, chest infection, or severe asthma attack. Consideration should be given to supplying such patients with oral steroids to use in an emergency. The dose of inhaled fluticasone propionate should be increased at this time and then reduced to the maintenance level after the systemic steroid has been discontinued.

Exacerbations of bronchial asthma which occur during the course of treatment with APO-FLUTICASONE HFA should be treated with a short course of systemic steroid which is gradually tapered as these symptoms subside. Under stressful conditions or when the patient has a severe exacerbation of bronchial asthma, after complete withdrawal of the systemic steroid, use of the latter must be resumed in order to avoid relative adrenocortical insufficiency.

There are some patients who cannot completely discontinue the oral corticosteroid. In these cases, a minimum maintenance dosage should be given in addition to APO-FLUTICASONE HFA.

4.4 Administration

APO-FLUTICASONE HFA inhalation aerosol is to be administered by oral inhalation only.

Patients must be instructed, as described in the PATIENT MEDICATION INFORMATION section, in the correct method of using APO-FLUTICASONE HFA inhalation aerosol to ensure that the drug reaches the target areas within the lungs.

Since the effect of APO-FLUTICASONE HFA depends on its regular use and on the proper technique of inhalation, the patient should be made aware of the prophylactic nature of therapy with inhaled fluticasone propionate, and that for optimum benefit APO-FLUTICASONE HFA should be taken regularly even when the patient is asymptomatic.

As a general rule, rinsing the mouth and gargling with water after each inhalation can help in preventing the occurrence of candidiasis. Cleansing dentures has the same effect.

Inhalation Aerosol
Before the first use of APO-FLUTICASONE HFA inhalation aerosol and after periods of greater than seven days without use, the inhaler must be primed before treatment. Patients must remove the mouth piece cover, shake well for 5 seconds and then with the inhaler pointing away from the face, actuate the inhaler. The patient must then shake and actuate the inhaler a second time.

Inhalation aerosol actuation should be synchronised with inspiration to ensure optimum delivery of drug to the lungs.

The use of the open-mouth technique to administer APO-FLUTICASONE HFA inhalation aerosol has not been investigated in clinical trials.

4.5 Missed Dose

If a single dose is missed, instruct the patient to take the next dose when it is due.

5 OVERDOSAGE

Acute inhalation of APO-FLUTICASONE HFA doses in excess of those approved may lead to temporary suppression of the hypothalamic-pituitary-adrenal axis. This does not usually require emergency action, as normal adrenal function typically recovers within a few days.

If higher than approved doses are continued over prolonged periods, significant adrenocortical suppression is possible. There have been very rare reports of acute adrenal crisis occurring in children exposed to higher than approved dosages (typically 1000 mcg daily and above), over prolonged periods (several months or years); observed features included hypoglycemia and sequelae of decreased consciousness and/or convulsions. Situations which could potentially trigger acute adrenal crisis include exposure to trauma, surgery or infection or any rapid reduction in dosage. Patients receiving higher than approved dosages should be managed closely and the dose reduced gradually.

Chronic use of inhaled fluticasone propionate in daily doses in excess of the recommended dosage may lead to some degree of adrenal suppression. Monitoring of adrenal reserve may be indicated. Gradual reduction of the inhaled dose may be required. Treatment with inhaled APO-FLUTICASONE HFA should be continued at a dose sufficient to control asthma.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Route of Administration, Dosage Forms/Strengths, Nonmedical Ingredients.

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients

Oral Inhalation	Inhalation Aerosol / 50, 125 and 250 mcg/metered dose	1,1,1,2-tetrafluoroethane (HFA-134a).

Inhalation Aerosol
APO-FLUTICASONE HFA (fluticasone propionate) inhalation aerosol is a pressurized metered-dose inhaler (MDI) consisting of an aluminium canister fitted with a metering valve. The 50 mcg canister is fitted into the supplied peach actuator/adaptor. The 125 mcg canister is fitted into the supplied orange actuator/adaptor. The 250 mcg canister is fitted into the supplied red/brown actuator/adaptor.
A dust cap is fitted over the actuator's mouthpiece when not in use.

APO-FLUTICASONE HFA inhalation aerosol comprises a suspension of fluticasone propionate in the propellant, 1,1,1,2-tetrafluoroethane (HFA-134a).

APO-FLUTICASONE HFA inhalation aerosol is available in three strengths: 50 mcg/actuation, 125 mcg/actuation or 250 mcg/actuation. The 50 mcg, 125 mcg and 250 mcg strengths of APO-FLUTICASONE HFA inhalation aerosol are available in 120 dose containers.

This product does not contain chlorofluorocarbons (CFCs) as the propellant.

7 WARNINGS AND PRECAUTIONS

General
It is essential that the patients be instructed that APO-FLUTICASONE HFA (fluticasone propionate) is a preventative agent which must be taken daily at the intervals recommended by their doctors and is not to be used as acute treatment for an asthmatic attack.

Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

Discontinuance
Treatment with APO-FLUTICASONE HFA should not be stopped abruptly, but tapered off gradually.

Ear/Nose/Throat
See Immune, Candidiasis.

Endocrine and Metabolism
Systemic Steroid Replacement by Inhaled Steroid
Particular care is needed in asthmatic patients who are transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred during and after transfer. For the transfer of patients being treated with oral corticosteroids, APO-FLUTICASONE HFA should first be added to the existing oral steroid therapy, which is then gradually withdrawn.

Patients with adrenocortical suppression should be monitored regularly and the oral steroid reduced cautiously. Some patients transferred from other inhaled steroids or oral steroids

remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled fluticasone propionate.

After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although APO-FLUTICASONE HFA may provide control of asthmatic symptoms during these episodes, it does not provide the systemic steroid which is necessary for coping with these emergencies. The physician may consider supplying oral steroids for use in times of stress (e.g. worsening asthma attacks, chest infections, surgery) (see 5 OVERDOSAGE).

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning and evening cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal only if it falls at or near the normal mean level.

Transfer of patients from systemic steroid therapy to APO-FLUTICASONE HFA may unmask allergic conditions outside the pulmonary tract that were previously suppressed by the systemic steroid therapy (e.g. rhinitis, conjunctivitis and eczema). These allergies should be symptomatically treated with anti-histamine and/or topical preparations, including topical steroids.

The replacement of a systemic steroid with inhaled steroid must be gradual and carefully supervised by the physician since upon withdrawal, systemic symptoms (e.g. joint and/or muscular pain, lassitude, and depression) may occur despite maintenance or improvement of respiratory function. The guidelines under Dosage and Administration should be followed in all such cases.

Systemic Effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods; these effects are much less likely to occur than with oral corticosteroids (see 5 OVERDOSAGE). 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 central serous chorioretinopathy (CSCR). It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained (see Monitoring and Laboratory Tests).

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if any child's or adolescent's growth appears slowed.

The long-term effects of fluticasone propionate in human subjects are still unknown. The local effects of the drug on developmental or immunologic processes in the mouth, pharynx, trachea, and lungs are unknown. There is also no information about the possible long-term systemic

effects of the agent (see Monitoring and Laboratory Tests).

Long-term use of orally inhaled corticosteroids may affect normal bone metabolism resulting in a loss of bone mineral density. In patients with major risk factors for decreased bone mineral content, such as chronic alcohol use, tobacco use, age, sedentary lifestyle, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), APO-FLUTICASONE HFA may pose an additional risk.

During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of APO-FLUTICASONE HFA and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see 9 DRUG INTERACTIONS).

Metabolic Effects
Certain individuals can show greater susceptibility to the effects of inhaled corticosteroid than do most patients.

There is an enhanced effect of corticosteroids on patients with hypothyroidism.

There have been very rare reports of increases in blood glucose levels (see 8 ADVERSE REACTIONS) and this should be considered when prescribing to patients with a history of diabetes mellitus.

Hematologic
Eosinophilic Conditions
In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established.

Hepatic/Biliary/Pancreatic
There is an enhanced effect of corticosteroids on patients with cirrhosis.

Immune
Candidiasis
Therapeutic dosages frequently cause the appearance of Candida albicans (thrush) in the mouth and throat. The development of pharyngeal and laryngeal candidiasis is a cause for concern because the extent of its penetration into the respiratory tract is unknown. Patients may find it helpful to rinse and gargle with water after using fluticasone propionate. Symptomatic candidiasis can be treated with topical anti-fungal therapy while still continuing to use APO-FLUTICASONE HFA.

Infection
Corticosteroids may mask some signs of infections and new infections may appear. Patients who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with intramuscular pooled immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Monitoring and Laboratory Tests
Increasing use of fast-acting inhaled bronchodilators to control symptoms indicates deterioration of asthma control. Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to increasing corticosteroid dosage. Patients should be instructed to contact their physicians if they find that relief with short-acting bronchodilator treatment becomes less effective or they need more inhalations than usual. During such episodes, patients may require therapy with systemic corticosteroids.

APO-FLUTICASONE HFA is not indicated for rapid relief of bronchospasm but for regular daily treatment of the underlying inflammation. Patients will require a fast and short acting inhaled bronchodilator (e.g. salbutamol) to relieve acute asthmatic symptoms. There is no evidence that control of bronchial asthma can be achieved by the administration of APO-FLUTICASONE HFA in amounts greater than the recommended dosages.

During long-term therapy, HPA axis function and haematological status should be assessed periodically.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored (see 8 ADVERSE REACTIONS).

For patients at risk, monitoring of bone and ocular effects (cataract, glaucoma, and central serous chorioretinopathy) should also be considered in patients receiving maintenance therapy with APO-FLUTICASONE HFA.

Ophthalmologic
Glaucoma, increased intraocular pressure, cataracts and central serous chorioretinopathy (CSCR) have been reported in patients following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, cataracts, and/or CSCR.

Respiratory
As with other inhalation therapy, paradoxical bronchospasm may occur characterized by an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator (e.g. salbutamol) to relieve acute asthmatic symptoms. APO-FLUTICASONE HFA should be discontinued immediately, the patient assessed, and if necessary, alternative therapy instituted (see 8 ADVERSE REACTIONS).

Sexual Health

Fertility

There are no data on human fertility (see 16 NON-CLINICAL TOXICOLOGY, Reproduction and Teratology).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled clinical trials with fluticasone propionate in pregnant women and the safety of fluticasone propionate in pregnancy has not been adequately established. APO-FLUTICASONE HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are limited data from an observational epidemiological study with fluticasone propionate in pregnant women.

Results from a retrospective epidemiological study, based on the UK General Practice Research Database (GPRD), did not find an increased risk of major congenital malformations following exposure to fluticasone propionate when compared to other inhaled corticosteroids, during the first trimester of pregnancy.

Like other glucocorticoids, fluticasone propionate is teratogenic to rodent species (see Toxicology section). Adverse effects typical of potent corticosteroids are only seen at high systemic exposure levels; administration by inhalation ensures minimal systemic exposure. The relevance of these findings to humans has not yet been established since well-controlled trials relating to foetal risk in humans are not available. Infants born of mothers who have received substantial doses of glucocorticoids during pregnancy should be carefully observed for hypoadrenalism.

7.1.2 Breast-feeding

Glucocorticoids are excreted in human milk. 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 fluticasone propionate at recommended doses are likely to be low. The use of fluticasone propionate in nursing mothers requires that the possible benefits of the drug be weighted against the potential risk to the infant.

7.1.3 Pediatrics

APO-FLUTICASONE HFA inhalation aerosol is not presently recommended for children younger than 12 months of age due to limited clinical data in this age group. See 4 DOSAGE AND ADMINISTRATION.

Spacer Devices

Spacer devices may be used in patients, such as young children, who have difficulty coordinating inhalation with the actuation of a metered dose inhaler (MDI). The dosage of APO-FLUTICASONE HFA should be adjusted according to individual response. For patients whose

asthma has been stabilized without the use of a spacer device, continuation of therapy with a spacer may require a dosage adjustment. The use of different spacer devices may result in variable effects on drug delivery. (See 10 CLINICAL PHARMACOLOGY, Pharmacokinetics, Use with Spacers).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In general, inhaled corticosteroid therapy may be associated with dose dependent increases in the incidence of ocular complications, reduced bone density, suppression of HPA axis responsiveness to stress, and inhibition of growth velocity in children. Such events have been reported rarely in clinical trials with fluticasone propionate.

Glaucoma may be exacerbated by inhaled corticosteroid treatment for asthma or rhinitis. In patients with established glaucoma who require long-term inhaled corticosteroid treatment, it is prudent to measure intraocular pressure before commencing the inhaled corticosteroid and to monitor it subsequently. In patients without established glaucoma, but with a potential for developing intraocular hypertension (e.g. the elderly), intraocular pressure should be monitored at appropriate intervals.

In elderly patients treated with inhaled corticosteroids, the prevalence of posterior subcapsular and nuclear cataracts is probably low but increases in relation to the daily and cumulative lifetime dose. Cofactors such as smoking, ultraviolet B exposure, or diabetes may increase the risk. Children may be less susceptible.

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of all children taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if any child's or adolescent's growth appears slowed.

Osteoporosis and fracture are the major complications of long-term asthma treatment with parenteral or oral steroids. Inhaled corticosteroid therapy is also associated with dose-dependent bone loss although the degree of risk is very much less than with oral steroid. This risk may be offset by estrogen replacement in post-menopausal women, and by titrating the daily dose of inhaled steroid to the minimum required to maintain optimal asthma control. It is not yet known whether the peak bone density achieved during youth is adversely affected if substantial amounts of inhaled corticosteroid are administered prior to 30 years of age. Failure to achieve maximal bone density during youth could increase the risk of osteoporotic fracture when those individuals reach 60 years of age and older.

No major side effects attributable to the use of fluticasone propionate have been reported. Adverse reactions in controlled clinical studies with fluticasone propionate have been primarily those normally associated with asthma. Apart from asthma and related events and pharmacologically predicted events (candidiasis and hoarseness), there were no dose-related trends. The adverse reactions reported by patients treated with fluticasone propionate were similar to those reported by patients treated with beclomethasone dipropionate.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Use in Adolescents and Adults (aged 16 years and older)
The following table lists adverse events considered by the investigator to be potentially drug-related that occurred at a rate of 3% or greater in any treatment group during clinical trials comparing fluticasone propionate inhalation aerosol and fluticasone propionate inhalation aerosol (CFC formulation) at a dosage of 500 mcg twice daily for one year.

Table 2 Adverse Experience Incidence (percentage of patients) at a rate of ≥ 3% in Clinical Trials in Adolescent and Adult Patients

Adverse Event	Fluticasone Propionate Inhalation Aerosol 500 mcg bid (n=366) (%)	Fluticasone Propionate Inhalation Aerosol formulated with CFC propellants 500 mcg bid (n=371) (%)
Hoarseness[1]/Dysphonia	7	7
Oral candidiasis[1]	6	7
Asthma & related events	6	5
Sore throat	4	2

[1] Patients may find it helpful to rinse and gargle with water after using fluticasone propionate.

There have been very rare reports of anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children and adolescents).

There have been common reports of contusions (skin bruising).

8.2.1 Clinical Trial Adverse Reactions - Pediatrics

In children 4 to 16 years of age, receiving fluticasone propionate inhalation aerosol versus fluticasone propionate inhalation aerosol (CFC formulation), the incidence and nature of adverse events whether considered by the investigator to be drug-related or not, were similar in each treatment group. The most commonly reported events were upper respiratory tract infection, headache, viral infections, throat irritation and rhinitis.

In children 12 months to 4 years of age, receiving fluticasone propionate inhalation aerosol, the nature of adverse events were as expected for this subject population. The majority of the adverse events reported were primarily from the ear, nose and throat and lower respiratory body systems. The most commonly reported adverse events, whether considered by the investigator to be drug-related or not, were upper respiratory tract infection, cough, fever, asthma and rhinitis.

Overall, the incidence and nature of the adverse events reported for fluticasone propionate

inhalation aerosol CFC formulation were similar.

There have been very rare reports of anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children and adolescents).

8.5 Post-Market Adverse Reactions

In addition to adverse events reported from clinical trials, the following events have been identified during worldwide use of any formulation of fluticasone propionate and salmeterol, regardless of indication. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate or salmeterol a combination of these factors.

Endocrine Disorders

Rare: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation (in children and adolescents), decreased bone mineral density, cataract, glaucoma.

Infections and Infestations

Rare: Esophageal candidiasis

Immune System Disorders

Uncommon: Cutaneous hypersensitivity reactions.

Very rare: Hypersensitivity reactions manifesting as angioedema (mainly facial and oropharyngeal edema), respiratory symptoms (dyspnea and/or bronchospasm) and anaphylactic reactions.

Metabolism and Nutrition Disorders

Very rare: Hyperglycemia.

Musculoskeletal and Connective Tissue Disorders

Very Rare: Osteonecrosis [particularly with previous or concurrent use of systemic steroids(e.g., IV or oral)].

Psychiatric Disorders

Very rare: Anxiety, sleep disorders and behavioural changes, including hyperactivity andirritability (predominantly in children and adolescents).

Respiratory, Thoracic and Mediastinal Disorders

Very rare: Paradoxical bronchospasm (see 7 WARNINGS AND PRECAUTIONS).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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 involving fluticasone propionate are unlikely.

A drug interaction study of intranasal fluticasone propionate 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 intranasal or inhaled 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.

This study has shown that other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. However, there have been a few case reports during worldwide post-market use of adrenal cortisol suppression associated with concomitant use of azole anti-fungals and inhaled fluticasone propionate. Therefore, care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole) as there is potential for increased systemic exposure to fluticasone propionate.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 Established or Potential Drug-Drug Interactions

Drug type	Ref	Effect	Clinical comment
Ritonavir	CT, PM	Systemic effects including Cushing's syndrome and adrenal suppression.	Concomitant use of fluticasone propionate and ritonavir should be avoided. (See "9 DRUG INTERACTIONS, Overview")
Other inhibitors of cytochrome P450 3A4	CT	Increased systemic exposure to fluticasone propionate.	Care is advised when co-administering potent cytochrome P450 3A4 inhibitors. (See "9 DRUG INTERACTIONS, Overview")
Acetylsalicylic acid	T		Use with caution in conjunction with corticosteroids in hypoprothrombinemia.

Legend: CT = Clinical Trial; PM = Post-marketing; T = Theoretical

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Fluticasone propionate is a highly potent glucocorticoid anti-inflammatory steroid. When administered by inhalation at therapeutic dosages it has direct potent anti-inflammatory action within the lungs, resulting is reduced symptoms and exacerbations of asthma and less adverse effects than systemically administered corticosteroids.

10.2 Pharmacodynamics

Fluticasone propionate has many pharmacokinetic and pharmacodynamic features similar to those of other inhaled glucocorticoids used for the treatment of asthma. However, in contrast to these other steroids, a combination of incomplete gastrointestinal absorption and high first pass metabolic extraction ensures that virtually no fluticasone propionate swallowed after oral inhalation reaches the systemic circulation.

Fluticasone propionate was screened for a wide range of steroid hormonal or anti-hormonal activity. To ensure significant systemic exposure, fluticasone propionate was administered subcutaneously to rats and mice and was found to be devoid of androgenic, anabolic, oestrogenic, and anti-gonadotrophic activity. Fluticasone propionate had some progestational activity in oestrogen-primed weanling rabbits, and also showed some anti-androgenic and anti-oestrogenic activity. Weak anti-anabolic activity, another characteristic of potent glucocorticoids, was observed in the castrated rat. Fluticasone propionate lacked mineralocorticoid activity but caused significant diuresis and urinary excretion of sodium and potassium.

10.3 Pharmacokinetics

Following intravenous administration, the pharmacokinetics of fluticasone propionate are proportional to dose.

Absorption: The absolute bioavailability of fluticasone propionate has been estimated from within and between study comparisons of inhaled and intravenous pharmacokinetic data. In healthy adult subjects the absolute systemic bioavailability of fluticasone propionate from fluticasone propionate inhalation aerosol was 10.9%. Systemic absorption of fluticasone propionate occurs mainly through the lungs, and is initially rapid then prolonged. Since the bioavailability of the swallowed portion of an inhaled dose that reaches the gastrointestinal tract is virtually zero, due to incomplete absorption and extensive first-pass metabolism, the systemic absorption would be a reflection of the amount of drug reaching the lungs.

Distribution: Fluticasone propionate is extensively distributed within the body. The volume of distribution at steady state is 4.2 L/kg. The percentage of fluticasone propionate bound to human plasma proteins averages 99%.

Metabolism: Fluticasone propionate is extensively metabolised by the CYP3A4 enzyme to an inactive carboxylic acid derivative.

Elimination: Following single intravenous doses in healthy volunteers, clearance of fluticasone propionate was 900 ml/min, with renal clearance (0.11 mL/min) accounting for less than 1%. Peak plasma fluticasone propionate concentrations are reduced by approximately 98% within 3-

4 hours and only low plasma concentrations are associated with the terminal half-life, which is approximately 8 hours. Studies with radiolabelled and unlabelled fluticasone propionate administered orally to human volunteers indicate that the majority of the dose (87-100%) is excreted in the feces, with up to 75% as unchanged drug, depending on the dose administered. Between 1% and 5% of the dose is excreted as metabolites in urine.

In animals and humans, propellant HFA-134a was eliminated rapidly in the breath, with no evidence of metabolism or accumulation in the body. Time to maximum plasma concentration (T_{max}) and mean residence time are both extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

Use with Spacers

Spacer devices may be used in patients, such as young children, who have difficulty coordinating inhalation with the actuation of the APO-FLUTICASONE HFA metered dose inhaler (MDI). Several small-scale studies have investigated spacer device performance and the systemic exposure of fluticasone propionate.

A cross over study was conducted to compare the use of the BABYHALER spacer device versus the AEROCHAMBER PLUS valved holding chamber (VHC) in children aged 1 < 4 years. Systemic exposure following treatment with 100 mcg of fluticasone propionate twice daily with the BABYHALER spacer device was approximately 50% lower compared to treatment with 100 mcg fluticasone propionate twice daily with the AEROCHAMBER PLUS VHC with facemask [52 pg•h/mL (34, 64) versus 97 pg•h/mL (85, 113), respectively]. Overall exposure to fluticasone propionate with use of either spacer was low.

A separate population pharmacokinetic analysis was also performed for fluticasone propionate using steady state data from 4 controlled clinical trials and additional data from one separate single- dose cross-over study. This combined cohort analysis included both pediatric and adult patients (n = 269), of whom 268 received treatment with fluticasone propionate. Fluticasone propionate was delivered to patients aged < 4 years using an AEROCHAMBER PLUS VHC with facemask.

Of those 268 that were treated, steady state data was obtained from 197 patients aged 1 year or older who received fluticasone propionate 50 mcg given as 100 mcg twice daily. Single-dose exposure data from an additional 22 children with asthma aged 4 to 11 years was derived from the cross-over study in which subjects received 6 inhalations of fluticasone propionate 50 mcg (i.e. 300 mcg) with or without AEROCHAMBER PLUS VHC.

As shown in Table 4, stratification of exposure data by age indicated that systemic exposure to fluticasone propionate at steady state, given as fluticasone propionate 100 mcg twice daily, was similar between children aged 1 to < 4 years and adolescents and adults aged ≥ 12 years. Exposure was lower in children aged 4 to 11 years who did not use a VHC.

Table 4 Systemic Exposure to Fluticasone Propionate 100 mcg Twice Daily

Age	Valved Holding Chamber	N	$AUC_{0-\tau}$, pg•hr/mL (95% CI)	C_{max}, pg/mL (95% CI)
1 to < 4 Years	Yes	164	141 (129, 155)	20.0 (19, 22)
4 to 11 Years	No	13	68 (48, 97)	11.4 (8, 16)
≥ 12 Years	No	20	122 (82, 180)	17.9 (13, 25)

The lower exposure to fluticasone propionate in children aged 4 to 11 years who did not use a VHC may reflect the inability to coordinate actuation and inhalation of the MDI.

The impact of the use of a VHC on exposure to fluticasone propionate was evaluated in a single-dose crossover study of patients aged 4 to 11 years treated with 6 inhalations of fluticasone propionate 50 mcg (i.e. 300 mcg total). In this study, use of a VHC increased the systemic exposure to fluticasone propionate (Table 5), possibly correcting for pediatric patient's inability to coordinate actuation and inhalation.

Table 5 Systemic Exposure to Fluticasone Propionate Following a Single Dose of 300 mcg

Age	Valved Holding Chamber	N	$AUC_{(0-\infty)}$, pg•hr/mL (95% CI)	C_{max}, pg/mL (95% CI)
4 to 11 Years	Yes	22	367 (296, 454)	60.9 (51.7, 71.7)
4 to 11 Years	No	21	138 (111, 172)	23.1 (19.5, 27.4)

Overall, the population pharmacokinetic analysis for fluticasone propionate showed no clinically relevant effects of age, gender, race, or body weight on apparent clearance and apparent volume of distribution.

In vitro Testing of Spacer Device Dose Delivery in Pediatrics

In vitro dose characterization studies were performed to evaluate the delivery of fluticasone propionate via VHCs with attached facemasks. The studies were conducted with two different VHCs and two different facemasks (small and medium size) at inspiratory flow rates of 8.0 and 12.0 L/min in combination with holding times of 0, 2, 5, and 10 seconds. The flow rates were selected to be representative of inspiratory flow rates of children aged 2 to 5 years and over 5 years, respectively. The mean delivered dose of fluticasone propionate through the VHCs with facemasks was lower than the 50 mcg of fluticasone propionate delivered directly from the actuator mouthpiece. The results were similar for the two different VHCs (see Table 6 for data on the AEROCHAMBER PLUS VHC). The fine particle fraction (approximately 1 to 5 mcm) across the flow rates used in these studies was 78% to 84% of the delivered dose, consistent with the removal of the coarser fraction by the VHC. In contrast, the fine particle fraction for FLOVENT HFA delivered without a VHC typically represents 42% to 55% of the delivered dose measured at the standard flow rate of 28.3 L/min. These data suggest that even at low flow rates and extended holding times potentially experienced in realistic situations with young children, an adequate amount of fluticasone propionate can be delivered to pediatric patients via a VHC and facemask at the recommended doses.

Table 6 In Vitro Medication Delivery Through AEROCHAMBER PLUS Valved Holding Chamber with a Facemask

Age	Facemask	Flow Rate (L/min)	Holding Time (seconds)	Mean Medication Delivery Through AEROCHAMBER PLUS VHC (mcg/actuation)	Body Weight 50th Percentile (kg)*	Medication Delivered per Actuation (mcg/kg)†
2 to 5 Years	Small	8.0	0	7.3	12.3-18.0	0.4-0.6
			2	6.8		0.4-0.6
			5	6.7		0.4-0.5
			10	7.7		0.4-0.6
2 to 5 Years	Medium	8.0	0	7.8	12.3-18.0	0.4-0.6
			2	7.7		0.4-0.6
			5	8.1		0.5-0.7
			10	9.0		0.5-0.7
> 5 Years	Medium	12.0	0	12.3	18.0	0.7
			2	11.8		0.7
			5	12.0		0.7
			10	10.1		0.6

* Centers for Disease Control growth charts, developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). Ranges correspond to the average of the 50th percentile weight for boys and girls at the ages indicated.
† A single inhalation of fluticasone propionate in a 70-kg adult without use of a VHC and facemask delivers approximately 50 mcg, or 0.6 mcg/kg.

11 STORAGE, STABILITY AND DISPOSAL

Inhalation Aerosol
Replace the mouthpiece cover firmly and snap it into position. Store at room temperature (15°C to 30°C) with the mouthpiece pointing down. Protect from frost and direct sunlight.

12 SPECIAL HANDLING INSTRUCTIONS

Inhalation Aerosol

Contents under pressure. Container may explode if heated. Do not place in hot water or near radiators, stoves, or other sources of heat. Even when apparently empty, do not puncture or incinerate container or store at temperatures over 30°C.

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

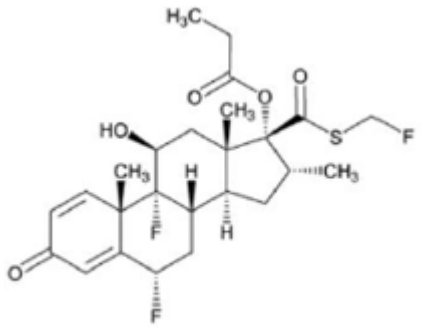
Drug Substance

Proper name: fluticasone propionate

Chemical name: Androsta-1,4-diene-17-carbothionic acid, 6, 9-difluro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)-, (6α, 11β, 16α, 17α)-S-(fluromethyl) ester, s-fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate

Molecular formula and molecular mass: $C_{25}H_{31}F_3O_5S$ 500.57 g/mol

Structural formula:



Physicochemical properties:

Description: Fluticasone propionate is a white or almost white powder. It is practically insoluble in water, sparingly soluble in methylene Chloride, slightly soluble in alcohol.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Adults and Adolescents (aged 15 years and older)

Table 7 – Summary of patient demographics for clinical trials in asthma.

Study #	Trial Design	Dosage, route of administration and duration	Study Subjects (n)	Mean age (Range)	Sex M/F
FLIT35	Multicentre, International, Double Blind, Randomized, Parallel Group	Oral inhalation FP (MDI) 500 mcg BID BDP (MDI) 1000 mcg BID 6 weeks	 82 72	 50 (18-78 years) 52 (20-75 years)	 44/38 41/31
FLIT14	Multicentre, International, Double Blind, Randomized, Parallel Group	Oral inhalation FP (MDI) 100 mcg BID BDP (MDI) 200 mcg BID 4 weeks	 129 132	 46 (19-80 years) 46 (18-74 years)	 70/59 69/63
FLIT72	Multicentre, International, Double Blind, Randomized, Parallel Group	Oral inhalation FP (MDI) 250 mcg BID FP (DPI) 250 mcg BID BDP (MDI) 500 mcg BID 6 weeks	 193 198 194	 46 (18 to 78 years) 45 (16 to 91 years) 46 (15 to 90 years)	 100/93 108/90 98/96
FLIT26	Multicentre, International, Double Blind, Randomized, Parallel Group	Oral inhalation FP (MDI) 750 mcg BID BDP (MDI) 750 mcg BID 3 months (primary efficacy assessment) with 9 months long term extension	 142 132	 48 (17-77 years) 52 (19-80 years)	 91/51 64/68
FLIP04	Randomized, Multicentre, International, Double Blind, Parallel Group	Oral inhalation FP (MDI) 750 - 1500 mcg daily BDP (MDI) 750 - 1500 mcg daily 4 weeks	 49 48	 47.0 (17 to 72 years) 48.9 (25 to 69 years)	 28/21 24/24

BDP= beclomethasone dipropionate; FP= fluticasone propionate; BID= twice daily; MDI= metered-dose inhaler; DPI= dry powder inhaler.

Key Inclusion/Exclusion criteria:

Study FLIT14: Subjects entered if they had (a) asthma symptoms on at least 4 days or 4 nights during the last 14 days of the run-in period, AND (b) either a diurnal variation in PEFR of 20% or more at least once a week during the last 14 days of the run-in period, OR had demonstrated reversibility of 15% or more to an inhaled bronchodilator during the 12 months prior to the study. Subjects were excluded if: took more than 400 mcg BDP or budesonide daily before the run-in period; were unable to stop taking their inhaled bronchodilator on a regular basis and replace it with salbutamol on an as-required basis; had taken oral corticosteroids within one month or on two or more occasions within six months of the Pre-trial visit.

Study FLIT72: Subjects receiving 400-600 mcg daily inhaled steroid were included in the study if they demonstrated asthma symptoms on at least 4 of the last 14 days of the run-in or, had reversibility of FEV_1 of at least 15% following a bronchodilator dose of salbutamol. Patients receiving 600-1000 mcg daily inhaled steroid were included in the study if their symptoms were stable during the run-in period. Subjects were excluded if they had been treated with systemic corticosteroids within the month preceding the run-in period or within the previous 6 months on 3 or more occasions.

Study FLIT35: Subjects receiving treatment >1500 mcg/day but ≤2000 mcg/day of BDP or budesonide, and 2-agonist therapy, and that met at least two of the following: mean morning PEFR during the previous 7 days of 70% or less of the predicted normal; reversibility of FEV_1 of at least 15%; diurnal variation in PEFR of at least 20% on at least 4 of the previous 7 days; asthma symptoms (day and night combined) on at least 4 of the previous 7 days. Subjects were excluded if: took systemic corticosteroids on four or more occasions during the six months before the run-in period or during the four weeks before the run-in period, or during the run-in period; were required a change in their prophylactic asthma medication, had been hospitalized due to asthma or had had an upper or lower respiratory tract infection during the month prior to entry/run-in period.

Study FLIT26: Subjects receiving ≥1000 mcg/day of BDP or budesonide, and that met at least two of the following: mean morning PEFR during the previous 7 days of 70% or less of the predicted normal; reversibility of FEV_1 of at least 15%; diurnal variation in PEFR of at least 20% on at least 4 of the previous 7 days; asthma symptoms during a minimum of four 24-hour periods in the previous 7 days. Subjects were excluded if they: required systemic corticosteroids during the four weeks before the run-in or during the run-in period; had received systemic corticosteroids on more than three occasions during the previous six months; were currently taking 2000 mcg daily or more of BDP or budesonide.

Study FLIP04: Subjects receiving BDP (600-1500 mcg/day) or budesonide (600-1200 mcg/day) in the previous 4 weeks, and that had incomplete control of their asthma at the end of the run-in period. Subjects were excluded if they had been treated with systemic corticosteroids within the past month.

Pediatrics (12 months to 19 years of age)

Table 8 Summary of patient demographics for clinical trials in children 12 months to 19 years of age with asthma.

Study #	Trial Design	Dosage, route of administration and duration	Study Subjects (n)	Mean age (Range)	Sex M/F
FLIT40	Multinational, Multicentre, Randomized, Double Blind, Parallel Group	Oral inhalation FP (MDI) 100 mcg BID BDP (MDI) 200 mcg BID 6 weeks	 197 201	 10.4 (4 to 19 years) 10.6 (4 to 18 years)	 111/86 114/87

Study #	Trial Design	Dosage, route of administration and duration	Study Subjects (n)	Mean age (Range)	Sex M/F
FLTB3047	Multicentre, Multinational, Randomized, Double Blind, Parallel Group	Oral inhalation FP (HFA MDI) 100 mcg BID FP (CFC MDI) 100 mcg BID 4 weeks	158 157	9.3 (4 to 16 years) 9.3 (4 to 15 years)	103/55 93/64
FAS30007	Multicentre, Randomized, Double Blind, Placebo Controlled, Parallel Group	Oral inhalation administered with pediatric spacer device FP (HFA MDI) 100 mcg BID Placebo BID 12 weeks	79 81	28.0 months (12 to 47 months) 27.6 months (12 to 47 months)	57/22 52/29
FAS30009	Multicentre, Randomized, Open Label, Parallel Group	Oral inhalation administered with pediatric spacer device FP (HFA MDI) 100 mcg BID SCG 5 mg QID 52 weeks	471 154	31.1 months (11 to 47 months) 30.7 months (11 to 47 months)	171/300 44/110
FLUPD/AH 90/N081	Randomized Multicenter Open Label Parallel Group	Oral Inhalation FP (DPI) 50 mcg BID SCG 20 mg QID 8 weeks	110 115	8.5 (4.1-12.7 years) 7.9 (4.1-12.9 years)	64/46 66/49

BDP= beclomethasone dipropionate; FP= fluticasone propionate; BID= twice daily; SCG= sodium cromoglycate; MDI= metered-dose inhaler; QID= four times a day; DPI= dry powder inhaler.

Key Inclusion/Exclusion criteria:

Study FLIT40: Subjects with clinical history of childhood asthma, including bronchoconstriction or cough and who had not changed their asthma medication or been admitted to hospital for their asthma during the previous 4 weeks. Subjects receiving ≤400 mcg of inhaled corticosteroid (ICS) daily, or not receiving any ICS but considered by the investigator to be inadequately controlled following treatment with beta$_2$-agonist, sodium cromoglycate, ketotifen or xanthine derivative therapy. Subjects who were not receiving ICS or were receiving <400 mcg ICS daily were required to show one or more of the following: ≥15% reversibility in FEV$_1$/ PEFR or, during 7 consecutive days of the run-in period, ≥1 waking during the night/early morning, PEFR≤ 80% on at least 3 occasions or asthma symptoms on at least 3 occasions. Subjects already receiving 400 mcg ICS were required to have stable asthma. Subjects were excluded if they: had received systemic corticosteroids in the previous 4 weeks/during the run-in period or on >3

times in the last 6 months.
FLTB3047: Subjects with clinical history of asthma, and who were currently steroid naïve or receiving ≤ 500 mcg/day of BDP/ budesonide/ flunisolide or ≤ 250 mcg/day of FP. Subjects were required to have an FEV_1 of between 70 and 100% of predicted normal values and a mean morning PEF during the last 7 days of the run-in period of ≤ 90% of the response following inhaled salbutamol (maximum cumulative dose of 800 mcg). Subjects were excluded if, in the preceding 4 weeks, they had changed their regular asthma medication, had a respiratory tract infection requiring antibiotics or hospital admission, or received oral/parenteral corticosteroids or if they had received oral/parenteral corticosteroids on ≥ 2 occasions or depot corticosteroids in the preceding 3 months.
Study FAS30007: Subjects with a documented history of persistent or recurrent cough, wheeze, or asthma-like symptoms. Subjects had to demonstrate symptoms on at least 21 of the 28 days, symptoms on at least 3 days of each of the 4 weeks, and a total score for wheeze of 2 or more over the 28 days. Subjects were excluded if they received treatment with corticosteroids within the previous 4 weeks, had life threatening asthma, were admitted to an ICU for treatment of an acute asthma exacerbation within the previous 12 months, or were unable to change from regularly scheduled $beta_2$-agonists to 'as-required' use only.
FAS3009: Subjects with a history of persistent or recurrent cough, wheeze or asthma-like symptoms. Subjects were excluded if they: received systemic corticosteroid therapy for >5 days within the previous 8 weeks, ICS of 200 mcg/day BDP or equivalent within the previous 4 weeks; had been hospitalized within 4 weeks; had been hospitalized more than twice for their asthma within the previous 12 months; had antibiotic therapy for chest infection; or had alteration to their asthma medication within the previous 4 weeks.
FLUPD/AH90/N081: Asthmatic children who previously received only intermittent bronchodilator therapy and had never been treated with inhaled SCG or an inhaled corticosteroid. Subjects were excluded if they received oral corticosteroids in the previous 6 weeks or were given more than 3 short courses of systemic corticosteroid therapy in the previous 6 months.

14.2 Study Results

Fluticasone Propionate in Adults, Adolescents and Children

Studies in adults and children have compared the effect of fluticasone propionate and beclomethasone dipropionate and sodium cromoglycate over the whole range of asthma severity (see Table 9, Table 10 and Table 11 below).

Table 9 Result Summary for Asthma Studies in Adults (Studies FLIT14, FLIT72, FLIT35, FLIT26, and FLIP04)

	FLIT14		FLIT72			FLIT35		FLIT26		FLIP04	
	Study Product and Dosage										
	FP 100 mcg BID	BDP 200 mcg BID	FP MDI 250 mcg BID	FP DPI 250 mcg BID	BDP MDI 500 mcg BID	FP 500 mcg BID	BDP 1000 mcg BID	FP 750 mcg BID	BDP 750 mcg BID	FP 750 - 1500 mcg daily	BDP 750 - 1500 mcg daily
Morning PEFR (L/min)											
Mean at Study Endpoint*	392	388	378	402	390	315	318	363	348	357	341
Adjusted Mean Change from Baseline			15	16	12						
Mean Difference, FP - BDP (95% CI)	4 (-4, 12)		3 (N/A[3]) (FP MDI - BDP) 5 (-2, 12) (FP DPI - BDP)			-3 (-16, 9)		15 (6, 25)		-16 (-34, 2)	
p-value	0.368		0.339 (FP MDI - BDP) 0.193 (FP DPI - BDP)			0.614		0.002		0.086	
Evening PEFR (L/min)											
Mean at Study Endpoint*	406	404	395	415	406	333	343	374	365	382	368
Adjusted Mean Change from Baseline			7	10	10						

	FLIT14		FLIT72			FLIT35		FLIT26		FLIP04	
	Study Product and Dosage										
	FP 100 mcg BID	BDP 200 mcg BID	FP MDI 250 mcg BID	FP DPI 250 mcg BID	BDP MDI 500 mcg BID	FP 500 mcg BID	BDP 1000 mcg BID	FP 750 mcg BID	BDP 750 mcg BID	FP 750 - 1500 mcg daily	BDP 750 - 1500 mcg daily
Mean Difference, FP - BDP (95% CI)	2 (-6, 10)		-2 (-9, 4) (FP MDI - BDP) 0 (-6, 7) (FP DPI - BDP)			-10 (-22, 3)		10 (0, 19)		-14 (-31, 4)	
p-value	0.605		0.460 (FP MDI - BDP) 0.926 (FP DPI - BDP)			0.128		0.042		0.126	
Overall Efficacy	**FP = BDP**		**FP = BDP**			**FP = BDP**		**FP > BDP**		**FP = BDP**	

*Adjusted mean Days 1-28 used for FLIT14; Mean during Weeks 1-6 used for FLIT72; Adjusted mean at Days 1-42 used for FLIT35; Adjusted mean Weeks 1-12 for FLIT26; and Adjusted mean at Weeks 3-4 for FLIP04.
§N/A: Not available

Table 10 Result Summary for Asthma Studies in Children Between 12 Months and 16 Years of Age (Studies FLIT40, FLTB3047 and FLUPD/AH90/N081)

	FLIT40		FLTB3047		FLUPD/AH90/N081	
	Study Product and Dosage					
	FP 100 mcg BID	BDP 200 mcg BID	FP HFA 100 mcg BID	FP CFC 100 mcg BID	FP 50 mcg BID	SCG 20 mg QID
Morning PEFR (L/min)						
Mean at Study Endpoint*	336	342	288	289	258.4	228.7
Adjusted Mean change at Weeks 1-6	18	15				
Mean Difference, FP - BDP (95% CI)	3 (-3, 9)					
Adjusted Mean Difference FP HFA - FP CFC (90% CI)			-2 (-6, 3)			
Estimate of True Mean Difference FP-SCG (95% CI)					19.5 (9.8, 29.2)	
p-value	0.282		0.589		0.0001	
Evening PEFR (L/min)						
Mean at Weeks 1-6	343	350				
Adjusted Mean change at Weeks 1-6	16	12				
Mean Difference, FP- BDP (95% CI)	4 (-2, 10)					
Estimate of True Mean Difference FP-SCG (95% CI)						
p-value	0.167					
Overall Efficacy	**FP>BDP**		**FP HFA = FP CFC**		**FP>SCG**	

*Mean at Weeks 1-6 for FLIT40; Adjusted mean at weeks 1-4 for FLTB3047; and Mean at Weeks 6-8 for FLUPD/AH90/N081.

Four studies in adults and children have compared the effect of fluticasone propionate at half the daily dose of beclomethasone dipropionate over the whole range of asthma severity (see Table 9 and Table 10 above). Throughout dose range 200-1000 mcg daily, fluticasone propionate at half the dose of beclomethasone dipropionate resulted in at least as great or greater increase in morning PEF, the primary efficacy parameter, as well as at least equal or greater reduction in secondary efficacy parameters such as symptom scores and rescue bronchodilator use. In the pediatric study (FLIT40), the increase in mean percent predicted PEF

was significantly greater with fluticasone propionate 200 mcg daily than with beclomethasone dipropionate 400 mcg.

These data demonstrate at least equal efficacy with fluticasone propionate compared with twice the dose of beclomethasone dipropionate over the whole range of asthma severity. Moreover, in these four studies comparing fluticasone propionate with beclomethasone dipropionate, both the basal and stimulated mean plasma cortisol levels were either the same or significantly higher after fluticasone propionate, indicating less HPA-axis suppression and suggesting an improved therapeutic ratio. In all studies in symptomatic patients, fluticasone propionate improved PEF compared with baseline or placebo.

In 2 clinical trials using a 1:1 dose ratio in 373 severe asthmatic patients, fluticasone propionate was significantly more effective than beclomethasone dipropionate at equal doses. In addition, the improvement in lung function was maintained over 12 months (see Table 9 above).

In clinical trials in over 1300 asthmatic children, fluticasone propionate 50 mcg bid (100 mcg/day) and 100 mcg bid (200 mcg/day) and fluticasone propionate inhaler 100 mcg bid (200 mcg/day) are effective in the treatment of childhood asthma. In one of these clinical studies (study FLUPD/AH90/N081) with 225 asthmatic children, daily doses of fluticasone propionate at 100 mcg/day demonstrated significantly greater efficacy than sodium cromoglycate given at 80 mg/day (see study FLUPD/AH90/N081 results in Table 10 above). In another clinical trial in 398 asthmatic children, doses of 200 mcg/day fluticasone propionate were equal to or more effective than beclomethasone dipropionate given at 400 mcg/day (see study FLIT40 results in Table 10 above).

Onset of improvement occurred within 4 to 7 days of the start of treatment with fluticasone propionate. In a 12-week study in 274 adult patients with severe asthma, those receiving fluticasone propionate demonstrated an improvement in morning PEF of over 20 L/min above baseline by day 7. An equivalent increase of 20 L/min was achieved after at least 4 weeks in patients receiving beclomethasone dipropionate.

The rapid onset of efficacy of fluticasone propionate was reflected in a reduced incidence of asthma exacerbations when fluticasone propionate was given at half the dose of beclomethasone dipropionate in 3 short-term (4- to 6-week) clinical trials in 1000 mild, moderate and severe asthmatics. The rate of asthma exacerbations was low for both treatments and similar on each treatment, although the ratio of doses (fluticasone propionate: beclomethasone dipropionate) was 1:2. The number of patients with at least one exacerbation of asthma remained constant over 12 months of treatment in two high dose studies in severe asthma. Approximately 70 to 75% of patients with severe asthma from these 2 studies were exacerbation- free after 12 months of treatment with high-dose fluticasone propionate.

Throughout the clinical trial programme, mean serum cortisol levels for both adults and children remained within the normal range for up to 12 months across the dosage range.

After 12 months treatment at 2000 mcg/day, suppression of HPA-axis occurred in approximately 7% of asthma patients.

Clinical trials were conducted to investigate the use of fluticasone propionate 200 mcg twice daily in children aged 4 years and over, whose asthma is not sufficiently controlled. More than 1,800 asthmatic children aged 4 to 16 years were studied in controlled trials. Results have

shown statistically significant increases in lung function for fluticasone propionate 200 mcg twice daily compared with the study comparator.

A long term study (52 weeks) conducted in children aged 4 to 9 showed that treatment with fluticasone propionate 200 mcg twice daily was associated with significantly higher growth rate compared with budesonide dipropionate 200 mcg twice daily. Assessments of HPA-axis function, although variable, gave no clinical evidence of significant adrenal suppression or reduction in cortisol levels during any treatment and therefore were not considered by the investigators to be of clinical relevance or cause for concern.

There was no evidence to suggest that long-term exposure of fluticasone propionate 200 mcg twice daily for up to 12 months caused any unfavourable effects in terms of adverse events.

Clinical Trials conducted with Fluticasone Propionate Inhalation Aerosol
A multicentre, randomized, double-blind study (FLTB3047) was conducted in children 4 to 16 years of age to assess the efficacy and safety of fluticasone propionate inhalation aerosol compared to the CFC formulation of fluticasone propionate. The results of the study demonstrated comparable efficacy between fluticasone propionate inhalation aerosol and the CFC formulation over a 4-week period (90% confidence limits for the difference between treatments were contained within ± 15L/min for mean morning PEF) (see results for study FLTB3047 in Table 10 above). The results from Clinic Visit FEV_1, percentage predicted Clinic Visit FEV_1, Clinic Visit PEF and percentage predicted PEF were similar between treatments, showing improvement from baseline. The adverse event profile was similar for both treatment groups and no new or unexpected adverse events were observed.

In a randomized, multicentre, double-blind, placebo-controlled trial (study FAS30007) involving 160 pre-school children aged 12 months to 4 years of age, who exhibited persistent chronic asthma symptoms, treatment with fluticasone propionate 100 mcg twice daily via a pediatric spacer device demonstrated a statistically significant difference between treatment groups in favour of fluticasone propionate in the percentage of symptom-free 24-hour periods (including cough and wheeze) (p=0.035) over the 12-week treatment period. In addition, fluticasone propionate inhalation aerosol showed similar tolerability and adverse event profile compared to placebo (See study FAS30007 results in Table 11 below).

Table 11 Result Summary for Study FAS30007 (Proportional odds analysis of percentage of symptom-free 24 hour periods)

Numbers of subjects whose percentage symptom-free 24-hour periods over weeks 1-12 fell into each percentage category	**FP N=79 n (%)**	**Placebo N=81 n (%)**
> 0 and ≤ 25%	30 (38)	42 (52)
> 25 and ≤ 50%	23 (29)	20 (25)
> 50 and ≤ 75%	18 (23)	13 (16)
> 75 and 100%	8 (10)	6 (7)
Odds ratio and 95%CI	0.53 (0.29, 0.95) p=0.035	

A long-term study (52 weeks) conducted in preschool children aged 12 months to 4 years of age showed that treatment with fluticasone propionate inhalation aerosol 100 mcg twice daily via a pediatric spacer device was associated with a statistically significant difference in the

percentage of symptom-free days ($p<0.001$) and percentage of days with no rescue medication ($p=0.023$) compared to sodium cromoglycate. Growth rate was not affected over the 52-week treatment period by fluticasone propionate treatment compared to sodium cromoglycate treatment. No differences were apparent for the height velocities when analyzed according to sex or age. A reduction in cortisol levels was observed in subjects treated with fluticasone propionate; however, this was not considered by the investigators to be of clinical significance. The nature and incidence of adverse events were similar in both treatment groups.

A three-month, prospective, post-marketing, observational cohort study was carried out to actively monitor the safety of the introduction of fluticasone propionate inhalation aerosol, into general practice in England, during the transition period from fluticasone propionate CFC to fluticasone propionate inhalation aerosol. The primary comparison was of event rates, as recorded by the prescribing GP, in the three months before and the three months after first exposure to fluticasone propionate inhalation aerosol. The final cohort consisted of 13,413 patients. Of these, 1381 (10.3%) received fluticasone propionate inhalation aerosol 50 mcg per inhalation; 5992 (44.7%) 125 mcg per inhalation and 6040 (45.0%) 250 mcg per inhalation. 2683 patients (20%) were age 16 years and under. There were no statistically significant differences in event reported pre-exposure compared to post-exposure. Less than 10% of the total cohort stopped using fluticasone propionate inhalation aerosol within the 3 month study period. The most common reasons for stopping were “condition improved” and “other drug substituted”. Overall, the results suggest that the transition to fluticasone propionate inhalation aerosol was well tolerated.

14.3 Comparative Bioavailability Studies

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy male volunteers. The results obtained from 50 volunteers who completed the study with evaluable data are summarized in the following table. The rate and extent of absorption of fluticasone propionate were measured and compared following a single oral inhalation dose (2 x 250 mcg metered dose inhaler) of APO-FLUTICASONE HFA (fluticasone propionate) pMDI 250 mcg per metered dose (Cipla Ltd., India.) and FLOVENT® HFA 250 mcg per metered dose (GlaxoSmithKline Inc.).

Fluticasone propionate (A single 500 mcg dose: 2 x 250 mcg) From Measured Data Geometric Mean[#] Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_T (pg•h/mL)	519.11 600.23 (61.46)	456.28 528.12 (62.50)	113.77	104.52- 123.84
AUC_I (pg•h/mL)	561.16 641.55 (59.64)	492.08 564.63 (60.84)	114.04	105.17-123.65
C_{max} (pg/mL)	63.62	61.15	104.03	96.95-111.63

Fluticasone propionate (A single 500 mcg dose: 2 x 250 mcg) From Measured Data Geometric Mean# Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	Ratio of Geometric Means (%)	90% Confidence Interval (%)
	69.32 (43.69)	67.22 (49.53)		
T_{max}[3] (h)	1.70 (48.24)	1.56 (48.70)		
$T_{1/2}$[3] (h)	7.59 (35.13)	6.92 (25.87)		

[1] APO-FLUTICASONE HFA pMDI 250 mcg per metered dose (Cipla Ltd., India)

[2] FLOVENT® HFA 250 mcg per metered dose (GlaxoSmithKline Inc.) was purchased in Canada.

[3] Expressed as arithmetic means (CV%) only.

[#] Based on Geometric Least Squares Means.

16 NON-CLINICAL TOXICOLOGY

Pharmacology-Related Effects in Animals

Studies in rodents were conducted to quantify and compare anti-inflammatory activity after topical administration of fluticasone propionate, and the ability to produce specific systemic steroid-related effects after topical, oral or parenteral administration.

Relative therapeutic index was determined from relative anti-inflammatory and hypothalamic-pituitary-adrenal (HPA) axis inhibitory potencies. In these tests, fluticasone propionate has a relative therapeutic index of 56 and 91 to fluocinolone acetonide in rat and mice respectively. Fluticasone propionate has a therapeutic index that is >200 times that of beclomethasone dipropionate.

Comparison of systemic activity after topical and subcutaneous dosing of fluticasone propionate shows that, in both rats and particularly in mice, fluticasone propionate is more potent when given subcutaneously. Fluticasone propionate was equipotent with betamethasone alcohol in rats and mice. Fluticasone propionate was 13-38 and 4 times less potent than fluocinolone acetonide in rats and mice respectively.

After oral dosing in rats, fluticasone propionate caused some thymus involution, adrenal atrophy and HPA axis suppression but was 6-38 and 60-200 times less potent than betamethasone alcohol in rats and mice respectively.

Toxicology

Two dogs received 1 mg fluticasone propionate by inhalation daily for 3 days. Marked suppression of plasma cortisol concentrations and adrenal function occurred which only began to recover 7 days after the final dose. The total dose given was approximately 110 mcg/kg/day,

which is approximately 3 times higher than the maximum recommended inhaled daily dose (2000 mcg).

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (140 to 800 times the maximum human exposure based on comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related CFCs.

Toxicology studies conducted with fluticasone propionate have shown only those class effects typical of potent corticosteroids, and these have occurred only at doses greatly in excess of that 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.

The non-CFC propellant, HFA134a, has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of two years.

Acute Toxicity

The results of the acute toxicity studies with fluticasone propionate, administered by inhalation, orally, subcutaneously and intravenously, demonstrated a large margin of safety over the anticipated maximum daily exposure in humans of 2000 mcg/day. The approximate LD_{50} values are shown in the following table:

Table 12 Acute Toxicity Studies with Fluticasone Propionate in Animals

Species	Route	Approximate LD_{50} (mg/kg)
Mouse	Oral	>1000
Rat	Oral	>1000
Mouse	Subcutaneous	>1000
Rat	Subcutaneous	>1000
Rat	Intravenous	>2
Rat	Inhalation	>1.66
Dog	Inhalation	>0.82

High oral doses of 1 g/kg were well tolerated in both the mouse and rat. The only (reversible) changes observed were a slowing in growth rate and microscopically-evident cortical depletion of the thymus of animals killed 3 days after dosing.

Subcutaneous doses of fluticasone propionate at 1 g/kg were administered to mice and rats. Animals progressively lost condition and body weight and the effects seen were thymic depletion and various lesions associated with a compromised immune system. In addition, gastric steroid ulcers were seen. These observed changes are the expected response to glucocorticoid therapy. The lack of reversible thymic effects in subcutaneously dosed animals is almost certainly due to the deposition and leaching of insoluble steroid from the injection site.

When given intravenously to rats at a dose of 2 mg/kg, the only changes seen were slightly subdued behaviour immediately after treatment and reversible thymic involution.

Acute administration of the complete contents of a 200 metered-dose inhaler of fluticasone

propionate to dogs (approx. 0.82 mg/kg) produced no effects of toxicological significance.

Chronic Toxicity Studies

Subacute toxicity studies were conducted in adult and juvenile rats for periods up to 35 days and in Beagle dogs for periods up to 44 days.

Fluticasone propionate was administered as follows:

Table 13 Chronic Toxicity Studies with Fluticasone Propionate in Animals

Species	Route	Doses*	Dosing Period
Rat	Oral (gavage)	1000 mcg/kg/day	15 days
Dog	Oral (gavage)	3000 mcg/kg/day	7 days
Rat	Subcutaneous	250/90 mcg/kg/day 10 mcg/kg/day	36 days 35 days
Dog	Subcutaneous	160 mcg/kg/day	36 days
Rat	Inhalation	60 mcg/L/day 18.2 mcg/L/day 475 mcg/kg/day	7 days 14 days 30 days
Dog	Inhalation	20 mg/animal/day 9 mg/animal/day	10 days 44 days

* maximum dose of fluticasone propionate administered

Clinical observations were similar for all routes of administration in both species. These consisted of reduced weight gain and general loss of condition. Inhalation studies in the dog resulted in clinical signs associated with the administration of a potent glucocorticoid and consistent with the symptoms of Canine Cushing's Syndrome.

Changes typical of glucocorticoid overdosage were seen in both haematological and clinical chemistry parameters. Effects were seen on the red cell parameters and a characteristic leukopenia resulting from a lymphopenia accompanied by a neutrophilia. Endogenous cortisol and corticosterone were depressed in dogs and rats, respectively.

Microscopic pathology was again consistent with the administration of a potent glucocorticoid showing thymic and adrenal atrophy, lymphoid depletion in rats and dogs and glycogenic vacuolation of the liver in dogs. There was no change or evidence of irritancy attributable to fluticasone propionate in the respiratory tract in any of the inhalation studies.

There were no specific effects on the maturation of juvenile rats after subcutaneous dosing.

Chronic inhalation toxicity studies using fluticasone propionate were conducted for up to 18 months in rats, using snout-only exposure. In two 6 month studies, rats received doses of up to 80 mcg/kg/day; the maximum daily dose administered during the 18 month study was 57 mcg/kg. Changes seen in haematological, biochemical and urinalysis parameters were those typical of glucocorticoid overdosage. Histological findings included lymphoid depletion and thymic and adrenal atrophy. There was at least partial regression of all clinical changes either during the treatment period or within the recovery period. At all dose levels the observed changes were considered to have arisen directly or indirectly from the immunomodulatory or physiological actions of a corticosteroid. None of these changes was of pathological significance.

Inhalation studies with fluticasone propionate of up to 12 months duration were also conducted in dogs. In one 6 month study, doses of fluticasone propionate administered were 60, 150 or 450 mcg/animal/day, while in the second study, groups received 68, 170 or 510 mcg/animal/day. In a third study, dogs received 7.5, 18 or 50.7 mcg/animal/day for 12 months.

The most commonly observed dose-related clinical signs were characteristic corticosteroid effects consisting of poor coat and/or skin condition, increased hair loss, loose faeces, distended abdomen and obesity.

Haematological and biochemical parameters were typical of glucocorticoid overdosage and consisted of a moderate to marked leukopenia and lymphopenia and increased erythrocytes, serum enzymes, protein and cholesterol.

Dose-related histopathological changes consisted of thymic involution, adrenal atrophy, lymphoid depletion in lymph nodes and spleen, and glycogenic infiltration of the liver. No histopathological changes were seen in the respiratory tract after inhalation of fluticasone propionate.

Most of the fluticasone propionate-induced changes showed a rapid regression after cessation of treatment by inhalation. Some symptoms persisted throughout the recovery period after subcutaneous administration probably due to prolonged release of fluticasone propionate from subcutaneous depots.

Two dogs (510 mcg/day group, 26 weeks) died of opportunistic infections as a result of reduced immunocompetence arising from excess corticosteroid administration.

Mutagenicity

Fluticasone propionate did not induce gene mutation in prokaryotic microbial cells, and there was no evidence of toxicity or gene mutational activity in eukaryotic Chinese hamster cells in vitro. The compound did not induce point mutation in the Fluctuation assay, and did not demonstrate gene convertogenic activity in yeast cells. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro, and fluticasone propionate was not demonstrably clastogenic in the mouse micronucleus test when administered at high doses by oral or subcutaneous routes. Furthermore, the compound did not delay erythroblast division in bone marrow.

Reproduction and Teratology

Subcutaneous studies in the mouse and rat at 150 and 100 mcg/kg/day, respectively, revealed maternal and foetal toxicity characteristic of potent glucocorticoid compounds, including reduction in maternal weight gain, embryonic growth retardation, increased incidences of retarded cranial ossification, and of omphalocoele and cleft palate in rats and mice, respectively.

In the rabbit, subcutaneous doses of 30 mcg/kg/day and above were incompatible with sustained pregnancy. This is not unexpected since rabbits are known to be particularly sensitive to glucocorticoid treatment.

These parenteral doses are up to 5 times the recommended maximum human inhaled dose (2000 mcg/day).

Following oral administration of fluticasone propionate up to 300 mcg/kg to the rabbit, there were no maternal effects nor increased incidence of external, visceral, or skeletal foetal defects. A very small fraction (<0.005%) of the dose crossed the placenta following oral administration to rats (100 mcg/kg/day) and rabbits (300 mcg/kg/day).

Carcinogenicity

No treatment-related effects were observed on the type or incidence of neoplasia in a 18 month oral (gavage) study in mice administered fluticasone propionate at dose levels of up to 1 mg/kg/day. In a lifetime (2 years) snout-only inhalation study in rats, at dose levels of up to 57mcg/kg/day, there was an increase in the incidence of tumours in the mammary gland, liver and pancreas. These were not considered as evidence of tumorigenic effect of fluticasone propionate based on the absence of statistical support of an increase in incidence and the historical tumour incidence data.

Local Tolerance

Intranasal administration of fluticasone propionate aqueous nasal spray to cynomolgus monkeys for 28 days at 400 mcg/day did not cause local irritancy to the nasal cavity or respiratory tract, or systemic toxicity.

Micronised fluticasone propionate was considered to be non-irritating in the rabbit eye when assessed using a modified Draize test and, in the guinea pig split adjuvant test for evaluating contact sensitivity, results were completely negative.

Acute eye irritancy tests conducted with 1000 mcg of fluticasone propionate inhalation aerosol in the rabbit showed no effect on the conjunctiva, cornea, or iris.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrFLOVENT HFA (fluticasone propionate inhalation aerosol;, 50 mcg/metered dose, 125 mcg/metered dose, and 250 mcg/metered dose), PrFLOVENT DISKUS (fluticasone propionate powder for inhalation), 100, 250, submission control 243742, Product Monograph, GlaxoSmithKline Inc. (March 1, 2021)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAPO-FLUTICASONE HFA
Fluticasone Propionate Inhalation Aerosol

Read this carefully before you start taking **APO-FLUTICASONE HFA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-FLUTICASONE HFA**.

What is APO-FLUTICASONE HFA used for?

APO-FLUTICASONE HFA helps manage breathing problems in children (12 months and older) and adolescents and adults (aged 16 years and older) who need regular treatment for their asthma.

Asthma is a chronic inflammatory disease of the lungs characterized by episodes of difficulty in breathing. People with asthma have extra sensitive or "twitchy" airways. During an asthma attack the airways react by narrowing, making it more difficult for the air to flow in and out of the lungs.

Control of asthma requires avoiding irritants that cause asthma attacks and taking the appropriate medications. For example, patients should avoid exposure to house dust mites, mold, pets, tobacco smoke and pollens.

How does APO-FLUTICASONE HFA work?

Fluticasone propionate is one of a group of medicines called corticosteroids used to treat breathing problems because they have an anti-inflammatory action. They reduce the swelling and irritation in the walls of the small air passages in the lungs and so ease breathing problems. Corticosteroids also help to prevent attacks of asthma.

What are the ingredients in APO-FLUTICASONE HFA?

Medicinal ingredients: fluticasone propionate.
Non-medicinal ingredients: APO-FLUTICASONE HFA is suspended in a CFC-free propellant, (1, 1, 1, 2 – tetrafluoroethane HFA-134a).

APO-FLUTICASONE HFA comes in the following dosage forms:

APO-FLUTICASONE HFA is a pressurized metered dose inhaler containing 50 mcg, 125 mcg and 250 mcg of fluticasone propionate per inhalation.

Do not use APO-FLUTICASONE HFA:

- If you are allergic or have had an allergic reaction to fluticasone propionate or any of the ingredients in this medication.
- To treat a sudden attack of breathlessness. You will probably need a different kind of medicine in a different colour pack which your doctor may already have given you. If you have more than one medicine, be careful not to confuse them.
- If you have an untreated fungal, bacterial or tuberculous infection, unless advised

by your doctor.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-FLUTICASONE HFA. Talk about any health conditions or problems you may have, including if you:

- Have ever had to stop taking other medicines for this illness because you were allergic to them or they caused problems.
- Have ever had a yeast infection (thrush) in your mouth.
- Have a history of tuberculosis (TB) infections.
- Are taking other "steroids" by mouth or inhalation.
- Are suffering from any chest infection (e.g. cold, bronchitis).
- Are suffering from or being treated for diabetes. You may need more frequent blood sugar monitoring or a dosage adjustment of your diabetes medication.
- Have thyroid problems.
- Are pregnant, planning to become pregnant or breastfeeding.
- Are taking a medicine called ritonavir, used to treat HIV infection.
- Have liver problems or cirrhosis.
- Have a rare blood disorder called hypoprothrombinemia and are taking acetylsalicylic acid.

Other warnings you should know about:

APO-FLUTICASONE HFA is not for the treatment of acute asthma attacks. A fast acting 'reliever' medicine, such as salbutamol (e.g., VENTOLIN), should be used for any sudden attacks of breathlessness or wheezing (e.g., asthma attacks).

It is very important that you use your medicine regularly as directed by your doctor to control your asthma. APO-FLUTICASONE HFA helps to prevent breathlessness and wheezing from happening due to asthma.

You may need to also take steroid tablets or syrup during a severe asthma attack, during other illnesses or during times of stress. Your doctor may give you some steroid tablets or syrup to carry with you as well as a steroid warning card, which will give you advice on when and how to use them.

You should avoid coming into contact with anyone who has measles or the chicken pox while taking inhaled corticosteroids. If you or your child are exposed, tell your doctor right away.

All cortisone-type medicines, especially when used for a long time, may possibly interfere with the usual growth pattern in growing adolescents. You may want to discuss this with your doctor.

When using drugs like APO-FLUTICASONE HFA for long term treatment, you may be at risk of:

- Breaking a bone (bone fractures);
- Osteoporosis (increased risk of bone fractures).

Take extra care to avoid any injury, especially falls.

Drugs like APO-FLUTICASONE HFA can cause eye disorders:

- Cataracts: Clouding of the lens in the eye, blurry vision, eye pain;
- Glaucoma: An increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss;

- Central serous chorioretinopathy (CSCR): blurry vision or other changes in vision.

Contact your healthcare professional if you experience blurry vision or other vision problems.

You should have regular eye exams.

If you notice the following warning signs, you should contact a healthcare professional as soon as possible or go to the nearest hospital.

- **A sudden worsening of your shortness of breath and wheezing shortly after using your fast-acting relief medication or after using APO-FLUTICASONE HFA.**
- **You do not feel relief within 10 minutes after using your fast-acting relief medication or the relief does not last for at least 3 hours.**
- **Measurement from your peak flow meter indicates a value less than 60 percent of predicted or personal best.**
- **You are breathless at rest.**
- **Your pulse is more than 120 beats per minute.**

If you experience the following symptoms, inform your doctor immediately as they may indicate that your asthma is getting worse and your treatment may need to be reassessed.

- A change in your symptoms such as more coughing, attacks of wheezing, chest tightness, or an unusual increase in the severity of the breathlessness.
- You wake up at night with chest tightness, wheezing or shortness of breath.
- You use increasing amounts of your fast-acting relief medication.
- Measurement from your peak flow meter indicates a value between 60 to 80% of predicted or personal best.

After you start taking APO-FLUTICASONE HFA, your doctor may change the dosages of your other asthma medicines. Rarely, this may make a patient feel worse rather than better. This especially applies to oral corticosteroids, including prednisone. If your doctor decreases your oral steroid dose, and you become unwell, tell your doctor immediately.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-FLUTICASONE HFA:

- Ritonavir, a medicine used to treat HIV infection or AIDS
- Medicines used to treat fungal infections, such as ketoconazole

How to take APO-FLUTICASONE HFA:

It is very important that you use 2 puffs of APO-FLUTICASONE HFA every day, twice a day (even if you have no symptoms), unless otherwise instructed by your doctor. This will help you to keep free of symptoms throughout the day and night.

It may take several days for this medicine to work and it is **very important that you use APO-FLUTICASONE HFA regularly every day**. If your shortness of breath or wheeze does not get better in 7 days, tell your doctor.

Do not stop taking APO-FLUTICASONE HFA suddenly – even if you feel better. Your

doctor can provide you with information about how to slowly stop the medication if necessary. If your doctor decides to stop treatment, do not keep any left-over medicine unless your doctor tells you to. Do not take more doses or use your inhaler more often than your doctor advises. If you have to go into the hospital for an operation, take your inhaler with you and tell the doctor what medicine(s) you are taking.

The medicine in APO-FLUTICASONE HFA must not be swallowed and should only be inhaled.

If you are also using a rapid onset, short duration, inhaled bronchodilator such as salbutamol (e.g., VENTOLIN), use your inhaled bronchodilator before using APO-FLUTICASONE HFA. Wait a few minutes after using your inhaled bronchodilator before taking APO-FLUTICASONE HFA.

Talk to your doctor before using APO-FLUTICASONE HFA with a spacer device (holding chamber) because your dose may need to be changed.

Usual dose:

Adults and Adolescents 16 years or older

The usual dose is 100 to 500 micrograms twice daily. Patients with very severe asthma, requiring higher doses of corticosteroids such as those patients currently requiring oral steroids may use doses up to 1000 micrograms twice daily.

Children 4 to 16 years
The usual dose for APO-FLUTICASONE HFA is 100 micrograms twice daily.

Children 12 months to 4 years
The usual dose is 100 micrograms twice daily, administered via a pediatric spacer device with a face mask.

Spacer devices (holding chambers) may be used in patients who have difficulty coordinating the actuation of a metered dose inhaler with inhalation. Talk to your doctor before using APO-FLUTICASONE HFA with a spacer device because your dose may need to be changed. If using a spacer device, follow the instructions of the device's manufacturer.

APO-FLUTICASONE HFA should not be used in children less than 12 months of age.

How to Prime APO-FLUTICASONE HFA:
Before you use your APO-FLUTICASONE HFA for the first time, or if your inhaler has not been used for a week or more, it must be primed. Remove the mouthpiece cover, shake the inhaler well for 5 seconds and with the inhaler pointing away from your face, release one puff into the air. Shake again for 5 seconds and release a second puff into the air. Priming helps ensure that APO-FLUTICASONE HFA is working properly and delivering the correct dose of medicine to you.

How to use your APO-FLUTICASONE HFA properly:
It is important that you take each dose as instructed by your doctor, nurse, or pharmacist. Your doctor will decide which strength of APO-FLUTICASONE HFA you should use.

Use APO-FLUTICASONE HFA only with the actuator supplied with the product. Discard canister after 120 sprays for the 120 dose canister.

1. Open

To remove the snap-on mouthpiece cover, hold between the thumb and forefinger, squeeze gently and pull apart as shown. Check inside and outside of the inhaler including the mouthpiece for the presence of loose objects. Your inhaler is now ready to use.

2. Shake

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

3. Exhale

Hold the inhaler upright between fingers and thumb with your thumb on the base, below the mouthpiece. Breathe out as far as comfortable.

Once you have fully exhaled, place the mouthpiece between your teeth without biting, and close your lips around it.

4. Inhale

Just after starting to breathe in through your mouth, press firmly down on the top of the inhaler while still breathing in steadily and deeply.

Remove the inhaler from your mouth and hold your breath for 10 seconds or as long as is comfortable. **Breathe out slowly**.

Each prescribed dose is usually given by a minimum of 2 puffs. Before taking your next puff, hold the inhaler upright and wait 30 seconds before repeating steps 2 through 4.

To keep out dust and lint, replace the mouthpiece cover by firmly pushing and snapping the cover into position. Do not use excessive force. Always store your inhaler with the mouthpiece pointing down.

5. Rinse

Rinse out your mouth and gargle with water. Do not swallow the water.

Important

Do not rush step 4. It is important that you start to breathe in as slowly as possible just before operating 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 step 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/Elderly:
Some patients may need help and an adult may need to operate the inhaler for them. Encourage the patient to breathe out and operate the inhaler immediately as the patient starts to breathe in. Practice the technique together. Children or people with weak hands should hold the inhaler with both hands. Put the two forefingers on top of the inhaler and both thumbs on the base below the mouthpiece.

If using a spacer device, follow the manufacturer's instructions.

Cleaning:
To prevent your inhaler from blocking up, it is important to clean it at least once a week, following the instructions below. If your inhaler does block up, the same cleaning instructions should be followed. If you notice a build-up of medicine around the mouthpiece, do not attempt to unblock it with a sharp object, such as a pin.

To clean your inhaler:
1. Remove the mouthpiece cover.
2. Do not remove the canister from the plastic casing.
3. Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth, tissue or cotton swab. Do not put the metal canister into water.
4. Replace the mouthpiece cover.
5. After cleaning, release one puff into the air to make sure that the inhaler works.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-FLUTICASONE HFA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

If you have used **larger doses than recommended by your doctor** for a long period of time, you should talk to your doctor or pharmacist for advice. A gradual reduction of your dose may be needed. Do not stop taking the medication suddenly.

Missed Dose:

It is very important that you use APO-FLUTICASONE HFA regularly; however, if you miss a single dose, do not worry - just take the next dose when it is due.

What are possible side effects from using APO-FLUTICASONE HFA?

These are not all the possible side effects you may feel when taking APO-FLUTICASONE HFA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- headache
- feeling anxious
- disturbed sleep
- behavioural changes (including hyperactivity and irritability)

- hoarseness and voice changes, inability to speak
- mild yeast infection of the mouth or throat (thrush, Candidiasis) or, rarely, in the esophagus. Common signs are white, slightly raised, sore patches on your tongue and inner cheeks. Remember to rinse and gargle your mouth with water and spit after using APO-FLUTICASONE HFA. Cleaning dentures may also help.
- increased bruising
- upper respiratory tract infection, viral infections
- stuffy/runny nose
- cough
- fever
- sore throat or irritation

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Thrush: Yeast infection of the mouth or throat; thick white patches in the mouth, tongue or on the throat, sore throat.		√	
UNCOMMON			
Allergic Reactions: Lumpy skin rash or hives anywhere on the body.			√
RARE			
Churg-Strauss Syndrome: A flu-like illness, rash, pins and needles or numbness of arms or legs, severe sinusitis and worsening lung or breathing problems.		√	
Esophageal candidiasis: Yeast infection of the esophagus (food tube); difficulty swallowing.		√	
VERY RARE			
Slowed growth in children and adolescents.		√	
Cushing's Syndrome: Round "moon face", rapid weight gain especially around the body. Excess sweating and thinning of the skin with easy bruising and dryness. Muscle and bone weakness.		√	
Bone Fractures or Osteoporosis: In situations where healthy people would not normally break a bone you may have sudden pain in any location and especially in the wrist, spine or hip. This may be a fracture.		√	
Glaucoma: Increased pressure in your eyes, eye pain.		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Cataract: Clouding of the lens in the eye, blurry vision, and/or eye pain.		√	
Decreased Adrenal Function: Tiredness, weakness, nausea and vomiting, low blood pressure.		√	
Allergic Reactions: Sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat, difficulty swallowing or breathing.			√
Bronchospasm: Sudden worsening of shortness of breath and wheezing shortly after using APO-FLUTICASONE HFA.			√
Hyperglycemia (Increased amount of sugar in blood): Excessive thirst, frequent urination, dry skin, blurred vision and fatigue.		√	
Osteonecrosis: Persistent pain and/or limited range of motion of a joint or a limb.		√	
UNKNOWN			
Decreased ability to fight infections. Symptoms of infection may include fever, pain, chills, feeling tired, sore throat.	√		
Worsening of lung symptoms such as wheezing, shortness of breath, cough and chest tightness.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep your medicine in a safe place where children cannot reach it. Your medicine may harm them.

After use, replace the mouthpiece cover firmly and snap it into position. Do not use excessive force.

Store APO-FLUTICASONE HFA at room temperature (15°C to 30°C) with the mouthpiece pointing down. Protect from frost and direct sunlight.

As with most inhaled medications in pressurized canisters, the effect of this medication may decrease when the canister is cold. If the inhaler becomes very cold, remove the metal canister and warm it **in your hand** for a few minutes. **Never** use other forms of heat.

Warning – The metal canister is pressurized. Do not puncture it, even when you think it is empty.

If you want more information about APO-FLUTICASONE HFA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html). Find the Patient Medication Information on the manufacturer's website (http://www.apotex.ca/products) or by calling 1-800-667-4708.

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