PRODUCT MONOGRAPH

[Pr]APO-FLUTICASONE HFA

Fluticasone Propionate Inhalation Aerosol

250 mcg/metered dose

Apotex Standard

Corticosteroid for Oral Inhalation

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Fluticasone Propionate Inhalation Aerosol
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral Inhalation	Inhalation Aerosol/250 mcg/metered dose	1,1,1,2-tetrafluroethane (HFA-134a).

For a complete listing see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

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

- the prophylactic management of steroid-responsive bronchial asthma in adults and adolescents 16 years of age and older.

APO-FLUTICASONE HFA (fluticasone propionate) should not be used in patients whose asthma can be well controlled with a low or medium dose inhaled corticosteroid (ICS) as it is only available in 250 mcg/metered dose and should be administered with a minimum of two inhalations twice daily.

APO-FLUTICASONE HFA (fluticasone propionate) is not indicated for the relief of acute bronchospasm.

Geriatrics (≥65 years of age):
There is no need to adjust the dose in patients over 65 years of age.

Pediatrics (under 16 years of age):
The safety and efficacy of APO-FLUTICASONE HFA have not been established in children less than 16 years of age.

CONTRAINDICATIONS

- Patients with a history of hypersensitivity to any of its ingredients (see DOSAGE FORMS, 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 DOSAGE FORMS,

COMPOSITION AND PACKAGING).

- In the primary treatment of status asthmaticus or other acute episodes of asthma.

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 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 OVERDOSAGE). Possible systemic effects include Cushing's Syndrome, Cushingoid features, adrenal suppression, growth retardation in 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 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 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 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 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 fluticasone propionate.

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 adults on corticosteroids. In such 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.

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 ADVERSE REACTIONS).

Special Populations

Use In Women

Fertility
There are no data on human fertility (see TOXICOLOGY, Reproduction and Teratology).

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 flucticasone 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 (see DETAILED PHARMACOLOGY).

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.

Nursing Women
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.

Use in Children under 16 years of age
APO-FLUTICASONE HFA is not recommended for use in children under 16 years of age.

Spacer Devices
Spacer devices may be used in patients 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 DETAILED PHARMACOLOGY, Pharmacokinetics, Use with Spacers)

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.

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.

ADVERSE REACTIONS

Adverse Drug 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 and adolescents. 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.

A reduction of growth velocity in children and adolescents 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 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.

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.

Clinical Trial Adverse Drug 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 drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Use in Adolescents and Adults

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 formulated with CFC propellants at a dosage of 500 mcg twice daily for one year.

Table 1 Adverse Experience Incidence (percentage of patients) 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 adolescents).

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

Overall, the incidence and nature of the adverse events reported for fluticasone propionate inhalation aerosol and fluticasone propionate inhalation aerosol CFC formulation were similar.

Post-Market Adverse Drug 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 or a combination of these factors.

Endocrine Disorders

Rare: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation (in 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 and irritability (predominantly in adolescents).

Respiratory, Thoracic and Mediastinal Disorders
Very rare: Paradoxical bronchospasm (see WARNINGS AND PRECATUIONS).

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.

Drug-Drug Interactions

Table 2 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 "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 "Drug Interactions, Overview")
Acetylsalicylic acid	T		Use with caution in conjunction with corticosteroids in hypoprothrombinemia.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Patients should be made aware that for optimum benefit, APO-FLUTICASONE HFA must be used regularly, even when asymptomatic.
- Patients should be regularly reassessed by a healthcare professional so that the dose of APO-FLUTICASONE HFA they are receiving remains optimal and is only changed on medical advice.
- After asthma stability has been achieved, it is desirable to titrate to the lowest effective dosage to help reduce the possibility of side effects.
- Onset of effect occurs within 4 to 7 days. The maximum benefit may not be achieved for up to 2 weeks or longer after starting treatment. Individual patients may experience a variable time to onset and degree of symptom relief.

Recommended Dose and Dosage Adjustment

Adults and adolescents 16 years of age and older

APO-FLUTICASONE HFA inhalation aerosol is only available in 250 mcg/metered dose. It is intended that each prescribed dose of APO-FLUTICASONE HFA be given by a minimum of two inhalations twice daily.

The recommended dose is two inhalations of APO-FLUTICASONE HFA twice daily, approximately 12 hours apart. The starting dose is based on patient's previous asthma therapy and asthma severity.

- For patients previously treated with high dose ICS, APO-FLUTICASONE HFA is recommended two inhalations twice daily (1000 mcg daily dose).
- Very severe patients requiring higher doses of corticosteroids such as patients currently requiring oral steroids may use doses up to 1000 mcg twice daily (2000 mcg daily dose).

The maximum recommended dosage is 1000 mcg twice daily (2000 mcg daily dose).

APO-FLUTICASONE HFA (fluticasone propionate) should not be used to relieve acute bronchospasm.

APO-FLUTICASONE HFA (fluticasone propionate) should not be used in patients whose asthma can be well controlled with low or medium dose inhaled corticosteroid (ICS).

Children under 16 years of age
APO-FLUTICASONE HFA is not recommended for use in children under 16 years of age.

Dosage Administration
APO-FLUTICASONE HFA should be administered with a minimum of two inhalations twice daily, approximately 12 hours apart.

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 DETAILED 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. 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 days in adults. 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 fluticasone propionate 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.

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

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

Patients must be instructed, as described in the PART III: CONSUMER 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 mouthpiece 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.

OVERDOSAGE

Acute inhalation of fluticasone propionate 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.

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.

ACTION AND CLINICAL PHARMACOLOGY

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.

In comparison with beclomethasone dipropionate, fluticasone propionate has demonstrated greater topical potency.

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 (see DETAILED PHARMACOLOGY).

Pharmacokinetics

Following intravenous administration, the pharmacokinetics of fluticasone propionate are proportional to dose. Fluticasone propionate is extensively distributed within the body. The volume of distribution at steady state is approximately 300 litres and had a very high clearance which is estimated to be 1.1 litre/minute indicating extensive hepatic extraction. 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.

Following oral administration of fluticasone propionate, 87-100% of the dose is excreted in the feces. Following doses of either 1 or 16 mg, up to 20% and 75% respectively, is excreted in the feces as the

parent compound. There is a non-active major metabolite. Absolute oral bioavailability is negligible (<1%) due to a combination of incomplete absorption from the gastrointestinal tract and extensive first-pass metabolism.

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 powder for inhalation and fluticasone propionate inhalation aerosol was 7.8% and 10.9% respectively. Systemic absorption of fluticasone propionate occurs mainly through the lungs, and is initially rapid then prolonged.

The percentage of fluticasone propionate bound to human plasma proteins averages 99%. Fluticasone propionate is extensively metabolised by the CYP3A4 enzyme to an inactive carboxylic acid derivative.

STORAGE AND STABILITY

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.

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Inhalation Aerosol

APO-FLUTICASONE HFA (fluticasone propionate) inhalation aerosol is a pressurized metered- dose inhaler (MDI) consisting of an aluminum canister fitted with a metering valve. 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 the 250 mcg/actuation strength. The 250 mcg strength of APO-FLUTICASONE HFA inhalation aerosol is available in the 120 dose container.

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

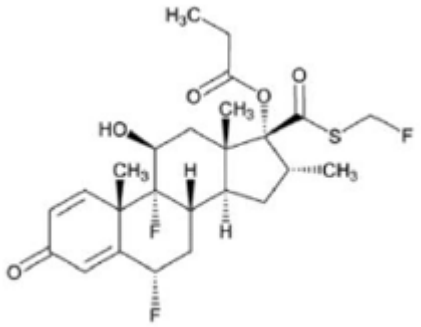
Proper name: fluticasone propionate

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.

CLINICAL TRIALS

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*	Reference[†]	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 69.32 (43.69)	61.15 67.22 (49.53)	104.03	96.95-111.63
T_{max}[§] (h)	1.70 (48.24)	1.56 (48.70)		
$T_{1/2}$[§] (h)	7.59 (35.13)	6.92 (25.87)		

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

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

[#] Based on Geometric Least Squares Means.

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

Fluticasone Propionate in Adults and Adolescents

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

Three studies in adults have compared the effect of fluticasone propionate at half the daily dose of beclomethasone dipropionate over the whole range of asthma severity (see Table 3 below).

Table 3 Summary of Comparative Trials of Fluticasone Propionate versus Twice the Daily Dose of Other Inhaled Corticosteroids

Population Studied	Daily Doses		Asthma Severity	Treatment Duration (weeks)	Number of Patients	Comments Efficacy* Cortisols†	
	Fluticasone Propionate (mcg)	Beclomethasone Dipropionate (mcg)					
Adults	200	400	Mild/Moderate	4	261	FP=BDP	FP>BDP
Adults	500	1000	Moderate	6	585	FP=BDP	FP=BDP
Adults	1000	2000	Severe	6	154	FP=BDP	FP>BDP

* primary efficacy parameter = morning PEF (= indicates similar efficacy, > indicates significantly greater efficacy)
† mean morning plasma cortisol levels (= indicates similar cortisol levels, > indicates significantly higher cortisol levels)
FP = fluticasone propionate
BDP = beclomethasone dipropionate

Throughout this dose range (i.e. 200 to 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.

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 the above 3 studies, comparing fluticasone propionate with beclomethasone dipropionate, the mean plasma cortisol levels, both basal and stimulated, 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.

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 70-75% 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 adults 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.

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.

DETAILED PHARMACOLOGY

Fluticasone propionate was shown to be approximately twice as potent in topical activity as beclomethasone dipropionate according to the McKenzie vasoconstrictor assay.

In human volunteers, fluticasone propionate was 9.5 times more potent than fluocinolone acetonide and intermediate in potency between betamethasone-17-valerate (less potent) and clobetasol-17-propionate (more potent).

Although relative vasoconstrictor activity does not necessarily imply similar relative therapeutic efficacy, evidence for local anti-inflammatory action without systemic effects has been demonstrated by studies in laboratory animals and confirmed in human clinical pharmacology studies.

An observational retrospective epidemiological cohort study utilising electronic health records from the United Kingdom was conducted to evaluate the risk of major congenital malformations following first trimester exposure to inhaled fluticasone propionate alone and salmeterol-fluticasone propionate combination relative to non- fluticasone propionate containing inhaled corticosteroids. No placebo comparator was included in this study given the disease being studied. As an epidemiologic study, biases may not be controlled to the same extent as in a clinical trial.

Within the asthma cohort of 5362 first trimester inhaled corticosteroid-exposed pregnancies in which major congenital malformations were diagnosed by one year of age, 131 major congenital malformations were identified; in the 1612 (30%) pregnancies which were exposed to fluticasone propionate or salmeterol- fluticasone propionate, 42 diagnosed major congenital malformations were identified. In 3750 (70%) pregnancies which were exposed to non-FP inhaled corticosteroid (ICS), 89 diagnosed major congenital malformations were identified. The adjusted odds ratio for major congenital malformations diagnosed by 1 year was 1.1 (95%CI: 0.5 to 2.3) for fluticasone propionate exposed vs non- fluticasone propionate inhaled corticosteroid exposed women with moderate asthma and 1.2 (95%CI: 0.7 to 2.0) for women with considerable to severe asthma. No difference in the risk of major congenital malformations was identified following first trimester exposure to fluticasone propionate alone versus salmeterol- fluticasone propionate combination. Absolute risks of major congenital malformations across the asthma severity strata ranged from 2.0 to 2.9 per 100 fluticasone propionate-exposed pregnancies.

Animal

Animal studies of the relative anti-inflammatory and hypothalamic-pituitary-adrenal (HPA) axis inhibitory potencies of topically applied drug demonstrated that fluticasone propionate has an advantageous therapeutic index (>200 times that of beclomethasone dipropionate).

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.

Topical anti-inflammatory activity was measured in rats and mice using the inflammatory response to croton oil applied topically to the ear. Results showed that fluticasone propionate was essentially equipotent with fluocinolone acetonide in both rats and mice.

Systemic responses to repeated topical applications of fluticasone propionate were assessed by measurement of thymus involution and reduction in stress-induced plasma corticosterone (HPA axis suppression) in rats and mice, and adrenal atrophy in the rat. In these tests fluticasone propionate was 50 to 100 fold less potent than fluocinolone acetonide in the rat (56-fold greater therapeutic index) and 100 times less potent than fluocinolone acetonide in mice (relative therapeutic index 91). Therefore, in both species, the separation between topical anti-inflammatory and systemic activity after topical application, was highly favourable to fluticasone propionate.

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.

In rats, fluticasone propionate given subcutaneously was compared with betamethasone alcohol and fluocinolone acetonide using thymus involution, adrenal atrophy, and inhibition of carrageenan granuloma formulation as assessments of systemic activity. Fluticasone propionate was equipotent with betamethasone alcohol and between 13 and 38 times less potent than fluocinolone acetonide.

In mice, using thymus involution and HPA axis suppression, fluticasone propionate given subcutaneously, was approximately equipotent with betamethasone alcohol and approximately 4 times less potent than fluocinolone acetonide.

After oral dosing in rats, fluticasone propionate caused some thymus involution, adrenal atrophy and HPA axis suppression but was 6 to 38 times less potent than betamethasone alcohol. In the mouse, oral fluticasone propionate is 60 to 200 times less potent than betamethasone alcohol.

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).

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.

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, which have been used extensively in metered-dose inhalers.

Pharmacokinetics

Pharmacokinetic data from rats, dogs and humans indicate that clearance is high relative to hepatic blood flow. Consequently, first-pass metabolism is extensive and oral bioavailability is negligible (<1% in man).

Studies examining the distribution of radiolabelled fluticasone propionate in the rat have shown that orally administered drug is absorbed and then excreted in the bile on first-pass through the liver. Thus only minute traces of radioactivity pass into the systemic circulation.

Inhalational administration to rats involves a significant ingestion of dose, with subsequent excretion via the faeces. Direct pulmonary dosing in dogs involved higher systemic exposure to fluticasone propionate.

The vast majority of a radiolabelled dose following intravenous (rat and dog), oral and subcutaneous (mouse, rat and dog) administration is excreted via the faeces, and evidence from bile-duct cannulated animals indicates that the major route of excretion is via the bile. Renal excretion is of minor importance, as urinary excretion accounts for less than 5% of a parenteral dose. No unchanged drug is excreted in the bile of rats or dogs, but a significant amount (up to 40%) of unchanged compound was found in the faeces of dogs dosed orally with fluticasone propionate.

Thus, the low oral bioavailability of fluticasone propionate expected due to extensive first-pass metabolism is compounded by incomplete absorption from the gastrointestinal tract, particularly in the dog. The major route of metabolism in rats, dogs and humans is the hydrolysis of the fluorinated carbothioate group to yield the inactive carboxylic acid.

When administered orally to pregnant rats (100 mcg/kg) or rabbits (300 mcg/kg), a very small fraction of the dose (<0.005%) passes across the placenta.

Following inhaled doses of 2000 mcg per day (1000 mcg twice daily) for 14 days in healthy volunteers, peak plasma concentrations of about 0.3 ng/mL were observed at 30- 60 minutes post-dosing.

Following inhaled dosing in healthy volunteers, the absolute bioavailability has been estimated to be 7.8% for fluticasone propionate powder for inhalation and 10.9% for fluticasone propionate inhalation aerosol. Since the bioavailability of the swallowed portion of an inhaled dose which reaches the

gastrointestinal tract is virtually zero, the systemic absorption would be a reflection of the amount of drug reaching the lungs.

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.

Studies with radiolabelled and unlabelled fluticasone propionate administered orally to human volunteers indicate that the majority of the dose (87 to 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.

Single oral doses of 16 mg in healthy volunteers produced plasma levels of less than 0.5 ng/mL.

Single intravenous doses of 2 mg in healthy volunteers revealed that the clearance of fluticasone propionate approximates liver blood flow (900 mL/min), with renal clearance (0.11 mL/min) accounting for less than 1%. These results indicate that hepatic extraction is almost complete and that oral bioavailability is close to zero.

Following intravenous administration, the pharmacokinetics of fluticasone propionate are proportional to the dose. Fluticasone propionate is extensively distributed within the body. The volume of distribution at steady state is approximately 300 litres and has a very high clearance which is estimated to be 1.1 litre/minute indicating extensive hepatic extraction. 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.

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 who have difficulty coordinating inhalation with the actuation of the APO-FLUTICASONE HFA metered dose inhaler (MDI).

TOXICOLOGY

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 7 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 8 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 57 mcg/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.

REFERENCES

1. Product Monograph, [Pr] FLOVENT HFA, fluticasone propionate inhalation aerosol 50, 125, and 250 mcg/metered dose, and fluticasone propionate powder for inhalation 100, 250, and 500 mcg/blister, GlaxoSmithKline Inc., Date of Revision: October 30, 2018.Submission Control No: 218581.

PART III: CONSUMER INFORMATION

Pr APO-FLUTICASONE HFA
Fluticasone Propionate Inhalation Aerosol
Apotex Standard

This leaflet is part III of a three-part "Product Monograph" for APO-FLUTICASONE HFA and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-FLUTICASONE HFA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
APO-FLUTICASONE HFA is a medicine which your doctor will have chosen to suit you and your condition. APO-FLUTICASONE HFA helps breathing problems in adolescents and adults (aged 16 years and older) who need regular treatment.

APO-FLUTICASONE HFA should not be used in patients whose asthma can be well controlled with a low or medium dose inhaled corticosteroid (ICS).

APO-FLUTICASONE HFA should not be used for regular treatment of asthma in patients under 16 years of age.

This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

What it does:
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.

When it should not be used:
- Do not use if you are allergic or have had an allergic reaction to fluticasone propionate or any of the ingredients in this medication.
- Do not use this medicine 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.
- Do not use if you have an untreated fungal, bacterial or tuberculous infection, unless advised by your doctor.

What the medicinal ingredient is:
fluticasone propionate.

What the nonmedicinal ingredients are:
APO-FLUTICASONE HFA is suspended in a CFC-free propellant, 1, 1, 1, 2 – tetrafluroethane (HFA-134a).

What dosage forms it comes in:
APO-FLUTICASONE HFA is a pressurized metered dose inhaler containing 250 mcg of fluticasone propionate per inhalation.

WARNINGS AND PRECAUTIONS

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.

Before you use APO-FLUTICASONE HFA, talk to your doctor or pharmacist 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.

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 physician 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.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with APO-FLUTICASONE HFA include: Ritonavir (a medicine used to treat HIV infection or AIDS) and azole antifungals (e.g. ketoconazole). Make sure that your doctor knows what other medicines you are taking (such as those for allergies, nervousness, depression, migraine), including those you can buy without a prescription as well as herbal and alternative medicines.

PROPER USE OF THIS MEDICATION

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.

Usual dose:

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.

Adults and Adolescents 16 years or older

The recommended dose is two inhalations twice daily, approximately 12 hours apart. The starting dose is based on patient's previous asthma therapy and severity. For patients previously treated with high dose ICS, APO-FLUTICASONE HFA is recommended two inhalations twice daily (1000 mcg daily dose). 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 (2000 mcg daily dose).

APO-FLUTICASONE HFA should not be used in patients whose asthma can be well controlled with a low or medium dose inhaled corticosteroid.

Children under 16 years of age

APO-FLUTICASONE HFA is not recommended for use in children under 16 years of age.

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.

Overdose:

In case of drug overdose, contact a health care practitioner, 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.

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.

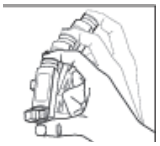
Remove the mouthpiece cover, shake the inhaler well for 5 seconds and with the inhaler pointing away from your face, release one puff into the air. Shake again for 5 seconds and release a second puff into the air. Priming helps ensure that APO-FLUTICASONE HFA is working properly and delivering the correct 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.

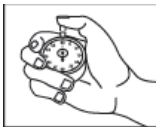
2. Shake
Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.



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.

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 just after the patient starts to breathe in. Practice the technique together. 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

If any of these affects you severely, tell your doctor, nurse or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN 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 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.		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN 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 rare	**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.		√	
	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.			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN 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 rare	**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.		√	

This is not a complete list of side effects. For any unexpected effects while taking APO-FLUTICASONE HFA, contact your doctor or pharmacist.

HOW TO STORE IT

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.

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.

MORE INFORMATION

You may need to read this package insert again. **Please do not throw it away** until you have finished your medicine.

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 Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Consumer Information on the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

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