PRODUCT MONOGRAPH

24HR NASAL ALLERGY RELIEF

Fluticasone Propionate Aqueous Nasal Spray

Manufacturer Standard

50 mcg / metered spray

Corticosteroid for Nasal Use

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	All Nonmedicinal Ingredients
Intranasal	Nasal spray / 50 mcg	benzalkonium chloride, dextrose monohydrate, microcrystalline cellulose and carboxymethylcellulose sodium, phenylethyl alcohol, polysorbate 80, and purified water.

INDICATIONS AND CLINICAL USE

24HR NASAL ALLERGY RELIEF (fluticasone propionate aqueous nasal spray) is indicated for:

- the treatment of the symptoms associated with seasonal allergic rhinitis including hay fever, and perennial rhinitis.
- the management of sinus pain and pressure symptoms associated with allergic rhinitis.

Geriatrics (> 65 years of age):
A limited number of patients 65 years of age and older have been treated with fluticasone propionate aqueous nasal spray in clinical trials. The adverse events reported in this population were similar to those reported in younger patients.

Pediatrics and Adolescents (< 18 years of age):
24HR NASAL ALLERGY RELIEF is not recommended for children and adolescents younger than 18 years of age.

CONTRAINDICATIONS

24HR NASAL ALLERGY RELIEF (fluticasone propionate aqueous nasal spray) is contraindicated in:

- patients who are hypersensitive to fluticasone propionate, or to any ingredient in the formulation or component of the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- patients with untreated fungal, bacterial or tuberculosis infections of the respiratory tract.

WARNINGS AND PRECAUTIONS

General

Patients should be informed that the full effect of 24HR NASAL ALLERGY RELIEF (fluticasone propionate aqueous nasal spray) therapy is not achieved until 2 to 3 days of treatment have been completed. Treatment of seasonal rhinitis should, if possible, start before the exposure to allergens.

Although fluticasone propionate aqueous nasal spray will control seasonal allergic rhinitis in most cases, an abnormally heavy challenge of summer allergens may in certain instances necessitate appropriate additional therapy.

Under most circumstances, treatment with corticosteroids should not be stopped abruptly but tapered off gradually. Patients should be advised to inform subsequent physicians of prior use of corticosteroids.

(See PART III PATIENT MEDICATION INFORMATION).

Carcinogenesis and Mutagenesis

See TOXICOLOGY.

Ear/Nose/Throat

Epistaxis

In clinical trials of 2 weeks to 1 year in duration, epistaxis was observed more frequently in subjects treated with fluticasone propionate aqueous nasal spray than those who received placebo (see ADVERSE REACTIONS).

Nasal Ulceration

Postmarketing cases of nasal ulceration have been reported in patients treated with fluticasone propionate aqueous nasal spray (see ADVERSE REACTIONS).

Candida Infection

In clinical trials with fluticasone propionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of 24HR NASAL ALLERGY RELIEF. Patients using 24HR NASAL ALLERGY RELIEF over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

Nasal Septal Perforation

Postmarketing cases of nasal septal perforation have been reported in patients treated with fluticasone propionate aqueous nasal spray (see ADVERSE REACTIONS).

Impaired Wound Healing

Monitor patients periodically for signs of adverse effects on the nasal mucosa. Avoid use in patients with recent nasal ulcers, nasal surgery, or nasal trauma, because of the inhibitory effect of corticosteroids on wound healing (see Immune, Effect of Corticosteroids on Wound Healing).

Endocrine and Metabolism

Hypercorticism and Adrenal Suppression

Although systemic effects have been minimal with recommended doses of fluticasone propionate aqueous nasal spray, potential risk increases with larger doses. Therefore, larger then recommended doses of 24HR NASAL ALLERGY RELIEF should be avoided.

When intranasal steroids are used at higher than recommended dosages in susceptible individuals at recommended dosages, systemic corticosteroid effects such as hypercorticism (Cushing's syndrome, Cushingoid features) and suppression of HPA function may occur. These effects are much less likely to occur with intranasal corticosteroids than with oral corticosteroids.

In patients previously on systemic steroids, either over prolonged periods or in high doses, the replacement with a topical (i.e., intranasal) corticosteroid can be accompanied by symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression and, in severe cases, adrenal insufficiency may occur, necessitating the temporary resumption of systemic steroid therapy.

Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress.

Effects on Growth

Reduced growth velocity has been observed in children treated with intranasal corticosteroids. Therefore, children and adolescents should be maintained on the lowest dose which achieves adequate symptom control. Physicians should closely follow the growth of children and adolescents taking corticosteroids, by any route, and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if growth appears slowed.

Hypothyroidism

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

Hematologic

Use of Corticosteroids and Acetylsalicylic Acid

Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypothrombinemia (see DRUG INTERACTIONS).

Hepatic/Biliary/Pancreatic

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.

Cirrhosis

There is an enhanced effect of corticosteroids in patients with cirrhosis.

Immune

Hypersensitivity Reactions including Anaphylaxis

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, contact dermatitis, and rash) have been reported after administration of fluticasone propionate aqueous nasal spray. Discontinue 24HR NASAL ALLERGY RELIEF if such reactions occur (see CONTRAINDICATIONS). Rarely, immediate hypersensitivity reactions may occur after the administration of 24HR NASAL ALLERGY RELIEF.

Immunosuppression

The long term effects of fluticasone propionate in humans are still unknown, in particular, its local effects; the possibility of atrophic rhinitis and/or pharyngeal candidiasis should be kept in mind. As with all medications containing a corticosteroid, 24HR NASAL ALLERGY RELIEF should be administered with caution, and only if necessary, in patients with active or quiescent tuberculosis infections of the respiratory tract; chronic or untreated infections such as systemic fungal, bacterial, viral, or parasitic; or ocular herpes simplex.

Corticosteroids may mask some signs of infection and new infections may appear. A decreased resistance to localized infections has been observed during corticosteroid therapy; this may require treatment with appropriate therapy or stopping the administration of fluticasone propionate.

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 nonimmune 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 affects 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 pooled intramuscular immunoglobulin (IG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Effect of Corticosteroids on Wound Healing

In patients who have had recent nasal surgery or trauma, a nasal corticosteroid should be used with caution until healing has occurred, because of the inhibitory effect of corticosteroids on wound healing.

Ophthalmologic

Nasal and inhaled corticosteroids may result in the development of glaucoma, cataracts and/or central serous chorioretinopathy (CSCR). CSCR is a posterior segment disease characterized by localized, limited serous detachments of the neurosensory retina often associated with focal detachments of an altered retinal pigment epithelium (RPE). Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure (IOP), glaucoma, and/or cataracts (see ADVERSE REACTIONS).

Psychological and behavioural

Although rare, there is a potential of psychological and behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression which have been reported.

Respiratory

Careful attention must be given to patients with asthma or other clinical conditions in whom a rapid decrease in systemic steroids may cause a severe exacerbation of their symptoms.

Special Populations

Pregnant Women:

The safety of fluticasone propionate in pregnancy has not been established. If used, the expected benefits should be weighed against the potential hazard to the fetus, particularly during the first trimester of pregnancy.

Like other glucocorticosteroids, fluticasone propionate is teratogenic to rodent species (see TOXICOLOGY). Adverse effects typical of potent corticosteroids are only seen at high systemic exposure levels; direct intranasal application ensures minimal systemic exposure. The relevance of these findings to humans has not yet been established. Infants born of mothers who have received substantial doses of glucocorticosteroids during pregnancy should be carefully observed for hypoadrenalism.

Nursing Women:

Glucocorticosteroids are excreted in human milk. It is not known whether fluticasone propionate is excreted in human milk. When measurable plasma levels were obtained in lactating laboratory rats following subcutaneous administration there was evidence of fluticasone propionate in the breast milk. However, following intranasal administration to primates, no drug was detected in the plasma, and it is therefore unlikely that the drug would be detectable in milk. The use of fluticasone propionate in nursing mothers, requires that the possible benefits of the drug be weighed against the potential hazards to the infant.

Pediatrics and Adolescents (< 18 years of age):

24HR NASAL ALLERGY RELIEF is not recommended for children and adolescents younger than 18 years of age.

Geriatrics (> 65 years of age):

A limited number of patients 65 years of age and older have been treated with fluticasone propionate aqueous nasal spray in clinical trials. The adverse events reported in this population were similar to those reported in younger patients.

Monitoring and Laboratory Tests

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Systemic and local corticosteroid use may result in the following:

- Epistaxis, nasal ulcerations, *candida albicans* infection, nasal septal perforation and impaired wound healing [see WARNINGS AND PRECAUTIONS]
- Cataracts and glaucoma [see WARNINGS AND PRECAUTIONS]
- Immunosuppression [see WARNINGS AND PRECAUTIONS]
- Hypothalamic-pituitary-adrenal (HPA) axis effects, including:
    - Hypercorticism and adrenal suppression [see WARNINGS AND PRECAUTIONS]
    - Growth retardation [see WARNINGS AND PRECAUTIONS]

- Psychological and behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression [see WARNINGS AND PRECAUTIONS]

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug 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.

Adverse reactions in controlled clinical studies with fluticasone propionate aqueous nasal spray have been primarily associated with irritation of the nasal mucous membranes, and are consistent with those expected from application of a topical medication to an already inflamed membrane. The adverse reactions reported by patients treated with fluticasone propionate aqueous nasal spray were similar to those reported by patients receiving placebo.

The most frequently reported adverse reactions (≥ 1% in any treatment group) considered by the investigator to be potentially related to fluticasone propionate aqueous nasal spray or placebo in trials of seasonal allergic rhinitis are listed below (Table 1). These studies conducted in 948 adults and in 499 children evaluated 14 to 28 days of treatment with recommended doses of fluticasone propionate compared with placebo.

Table 1 Adverse Reactions Reported Most Frequently in Clinical Trials of Seasonal Allergic Rhinitis

	Adults (age ≥ 12 years)			Children (age 4 - 11 years)		
	Fluticasone* 100 mcg BID (n=312) %	Fluticasone* 200 mcg QD (n=322) %	Placebo (n=314) %	Fluticasone* 100 mcg QD (n=167) %	Fluticasone* 200 mcg QD (n=164) %	Placebo (n=168) %
Nasal burning	2.2	3.4	2.5	1.8	2.4	1.2
Pharyngitis	1.3	1.6	<1	<1	0	0
Runny nose	<1	1.6	<1	<1	<1	<1
Blood in nasal mucus	0	1.6	<1	0	<1	0
Epistaxis	1.6	2.8	2.2	3.0	3.7	3.6
Sneezing	<1	1.2	2.2	0	<1	0
Crusting in nostrils	0	0	0	1.2	0	0
Nasal congestion	0	0	0	0	1.2	0
Nasal ulcer	<1	0	0	1.2	1.2	1.2
Headache	1.3	2.5	1.9	1.2	1.2	1.2

*Fluticasone propionate aqueous nasal spray.

In two 6 month trials involving 831 patients aged 12 to 75 years with perennial rhinitis, the adverse reactions reported by patients treated with fluticasone propionate aqueous nasal spray

were similar in type and incidence to those reported in seasonal trials, with the exception of epistaxis (≤ 13.3%) and blood in nasal mucous (≤ 8.3%). In addition to the events reported most frequently in the seasonal trials, patients receiving fluticasone propionate aqueous nasal spray in the 6 month trials reported nasal soreness (≤ 2.5%), nasal excoriation (≤ 2.0%), sinusitis (≤ 1.6%), and nasal dryness (≤ 1.3%).

Less Common Clinical Trial Adverse Drug Reactions (incidence of 0.1 - 1% and greater than placebo)
Uncommon adverse reactions (incidence of 0.1 to 1% and greater than placebo) reported by patients receiving fluticasone propionate aqueous nasal spray at the recommended daily dose of 200 mcg (or 100 mcg per day for children 4 to 11 years of age) in the aforementioned clinical trials included: pharyngeal irritation, nasal stinging, nausea and vomiting, unpleasant smell and taste, and sinus headache (0.3%); lacrimation, eye irritation, xerostomia, cough, urticaria, and rash (0.2%); and nasal septum perforation (0.1%).

Post-Market Adverse Drug Reactions
The following events have been identified during post-approval use of fluticasone propionate in clinical practice.

General:
Headache and hypersensitivity reactions including angioedema, skin rash, edema of the face or tongue, pruritis, urticaria, bronchospasm, wheezing, dyspnea and anaphylaxis/anaphylactoid reactions have been reported. Particularly with previous or concurrent use of systemic steroids (e.g., IV or oral), there have also been very rare cases of osteonecrosis reported and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression.

Ear, Nose and Throat:
Alteration or loss in sense of taste and/or smell and, rarely, nasal septal perforation, nasal ulcer, sore throat, throat irritation and dryness, cough, hoarseness and voice changes.

Eye:
Dryness and irritation of the eyes, conjunctivitis, blurred vision, and very rarely, glaucoma, increased intraocular pressure and cataracts.

DRUG INTERACTIONS

Overview
Fluticasone propionate is cleared by extensive first-pass metabolism mediated by cytochrome P450 3A4 in the gut and liver.

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 world wide post-market use of adrenal cortisol suppression associated with concomitant use of azole anti-fungals and inhaled fluticasone propionate. Therefore, care is advised when coadministering potent cytochrome P450 3A4 inhibitors (e.g., ketoconazole) as there is potential for increased systemic exposure to fluticasone propionate.

Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in patients with hypothrombinemia.

Drug-Drug Interactions

Table 2 Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Ritonavir	CT CS	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 CS	Potential increased systemic exposure to fluticasone propionate.	Care is advised when coadministering potent cytochrome P450 3A4 inhibitors. (See DRUG INTERACTIONS; Overview)
Acetylsalicylic acid	T		Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypothrombinemia. (See DRUG INTERACTIONS; Overview and WARNINGS AND PRECAUTIONS; Hematologic)

CS – Class Statement
CT – Clinical Trial
T - Theoretical

DOSAGE AND ADMINISTRATION

Dosing Considerations

24HR NASAL ALLERGY RELIEF is available without a prescription for adults and adolescents 18 years of age and older. 24HR NASAL ALLERGY RELIEF is not recommended for children under 4 years of age.

The therapeutic effects of corticosteroids, unlike those of decongestants, are not immediate. An improvement of symptoms usually becomes apparent within a few days after the start of therapy, some patients may start to feel relief as soon as the first day. However, symptomatic relief may not occur in some patients for as long as two weeks. An absence of an immediate effect should be explained to the patient. Similarly, when corticosteroids are discontinued, symptoms may not return for several days. 24HR NASAL ALLERGY RELIEF should not be continued beyond three weeks in the absence of significant symptomatic improvement.

In the presence of excessive nasal mucous secretion or edema of the nasal mucosa, the drug may fail to reach the site of action. In such cases it is advisable to use a nasal vasoconstrictor for two to three days prior to starting treatment with 24HR NASAL ALLERGY RELIEF. Patients should carefully follow the correct method of use, which is to blow the nose, then insert the nozzle carefully into the nostril, compress the opposite nostril and actuate the spray while inspiring through the nose, with the mouth closed (see PART III PATIENT MEDICATION INFORMATION). Patients should consult a pharmacist or doctor if they have difficulties or are unsure how to use 24HR NASAL ALLERGY RELIEF.

Careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids when transferred to 24HR NASAL ALLERGY RELIEF. Initially, 24HR NASAL ALLERGY RELIEF and the systemic corticosteroid must be given concomitantly, while the dose of the latter is gradually decreased. The usual rate of withdrawal of the systemic steroid is the equivalent of 1.0 mg of prednisone every four days if the patient is under close supervision. If continuous supervision is not feasible, the withdrawal of the systemic steroid should be slower, approximately 1.0 mg of prednisone (or equivalent) every ten days. If withdrawal symptoms appear, the previous dose of the systemic steroid should be resumed for a week before further decrease is attempted.

Recommended Dose and Dosage Adjustment

Adults (18 years of age and older):

The usual dosage is two sprays (50 mcg each) in each nostril once a day (total daily dosage, 200 mcg). If the patient's symptoms are under control after one week of use, the dose should be lowered to one spray in each nostril once a day.

After three months of daily use, the patient should consult the doctor if he/she can keep using.

If the symptoms do not improve after 7 days of starting use, stop to use and consult a doctor as you may have something more than allergies, such as infections.

Pediatrics and Adolescents (< 18 years of age):

24HR NASAL ALLERGY RELIEF is not recommended in this patient population.

Geriatrics (> 65 years of age):

No dosage adjustment is required in patients over 65 years of age.

Hepatic Impairment:

Formal pharmacokinetic trials using fluticasone propionate aqueous nasal spray have not been conducted in subjects with hepatic impairment. Since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Renal Impairment:

Formal pharmacokinetic trials using fluticasone propionate aqueous nasal spray have not been conducted in subjects with renal impairment.

Missed Dose

If a single dose is missed, instruct the patient to take the next dose when it is due. Do not instruct the patient to take an extra dose.

Administration
24HR NASAL ALLERGY RELIEF should be administered only by the intranasal route. It is necessary to prepare the nasal spray by pressing down on the nozzle several times before first use or after a few days of non-use or if the nozzle has just been cleaned. 24HR NASAL ALLERGY RELIEF may be administered at any time of day. Illustrated instructions for proper use appear in PART III: PATIENT MEDICATION INFORMATION.

OVERDOSAGE

Like any other nasally administered corticosteroid, acute overdosing is unlikely in view of the total amount of active ingredient present. However, when used chronically in excessive doses or in conjunction with other corticosteroid formulations, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of fluticasone propionate should be discontinued slowly, consistent with accepted procedures for discontinuation of chronic steroid therapy (see DOSAGE AND ADMINISTRATION).

The restoration of HPA axis function may be slow. During periods of pronounced physical stress (i.e., severe infections, trauma, surgery) a supplement with systemic steroids may be advisable.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone propionate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor that is 18 times that of dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. The clinical significance of these findings is unknown.

Topical nasal steroids act by reducing late-phase allergic reactions and mucous secretion, inhibiting vascular permeability, preventing eicosanoid formation, inhibiting allergen-induced mediator release, and reducing eosinophil and basophil infiltration in nasal epithelium. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. Fluticasone propionate controls multiple key inflammatory substances (histamine, chemokines, leukotrienes, cytokines, tryptases and prostaglandins) whereas most common non-prescription allergy pills act on histamine alone. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in rhinitis. In 7 trials in adults, fluticasone propionate aqueous nasal spray has decreased nasal mucosal eosinophils in 66% of patients (35% for placebo) and basophils in 39% of patients (28% for placebo). The direct relationship of these findings to long-term symptom relief is not known.

The onset of action is not immediate, and two to three days treatment may be required before

maximum relief is obtained. This is because the anti-inflammatory activities of glucocorticoids are related to specific steroid effects, which involve several biochemical events, including protein synthesis.

Following intranasal dosing of fluticasone propionate, (200 mcg/day) steady state maximum plasma concentrations were not quantifiable in most subjects (<0.01 ng/mL). The highest C_{max} observed was 0.017 ng/mL. Direct absorption in the nose is negligible due to the low aqueous solubility with the majority of the dose being eventually swallowed. When administered orally the systemic exposure is <1% due to poor absorption and pre-systemic metabolism. The total systemic absorption arising from both nasal and oral absorption of the swallowed dose is therefore negligible.

Pharmacodynamics

HPA Axis Effect

The potential systemic effects of fluticasone propionate aqueous nasal spray on the HPA axis were evaluated. Fluticasone propionate aqueous nasal spray given as 200 mcg once daily or 400 mcg twice daily was compared with placebo or oral prednisone 7.5 or 15 mg given in the morning.

Fluticasone propionate aqueous nasal spray at either dosage for 4 weeks did not affect the adrenal response to 6-hour cosyntropin stimulation, while both dosages of oral prednisone significantly reduced the response to cosyntropin.

Cardiac Electrophysiology

A study specifically designed to evaluate the effect of fluticasone propionate aqueous nasal spray on the QT interval has not been conducted.

Pharmacokinetics

Absorption:

Clinical studies in normal human subjects have shown that following intranasal administration of fluticasone propionate at the recommended daily dose of 200 mcg, plasma concentrations were not quantifiable in most subjects (<0.01 ng/mL). The highest C_{max} observed was 0.017 ng/mL. Direct absorption in the nose is negligible due to the low aqueous solubility with the majority of the dose being eventually swallowed. When administered orally, the systemic exposure is <1% due to poor absorption and pre-systemic metabolism. The total systemic absorption arising from both nasal and oral absorption of the swallowed dose is therefore negligible.

Distribution:

Fluticasone propionate has a large volume of distribution at steady state (approximately 318 L). Plasma protein binding is moderately high (91%).

Metabolism:

Fluticasone propionate is cleared rapidly from the systemic circulation, principally by hepatic metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Swallowed fluticasone propionate is also subject to extensive first pass metabolism. Care should be taken when co-administering potent CYP3A4 inhibitors such as ketoconazole and ritonavir as there is potential for increased systemic exposure to fluticasone propionate.

Elimination:
Single intravenous doses of 1 mg in healthy volunteers revealed that the elimination rate is linear over the 250 to 1000 mcg dose range and are characterized by a high plasma clearance (CL=1.1 L/min). Peak plasma concentrations are reduced by approximately 98% within 3 to 4 hours and only low plasma concentrations were associated with the 7.8 hours terminal half-life. The renal clearance of fluticasone propionate is negligible (<0.2%) and less than 5% of the dose is excreted as the carboxylic acid metabolite. The major route of elimination is the excretion of fluticasone propionate and its metabolites in the bile.

Special Populations and Conditions:
Clinical pharmacology in special populations has not been evaluated.

STORAGE AND STABILITY

Store at room temperature 15°C to 30°C. Shake gently before use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

24HR NASAL ALLERGY RELIEF is an aqueous suspension of microfine fluticasone propionate (0.05% w/w) for topical administration to the nasal mucosa by means of a metering, atomising spray pump. Each 100 mg of spray delivered by the nasal adaptor (1 actuation), contains 50 mcg of fluticasone propionate.

24HR NASAL ALLERGY RELIEF contains micronised fluticasone propionate 0.05% w/w and the following non-medicinal ingredients: benzalkonium chloride, dextrose monohydrate, microcrystalline cellulose and carboxymethylcellulose sodium, phenylethyl alcohol, polysorbate 80, and purified water.

24HR NASAL ALLERGY RELIEF is available in an amber glass bottle containing sufficient formulation for 60 or 120 metered sprays (8 g or 16 g net weight).

PART II: SCIENTIFIC INFORMATION

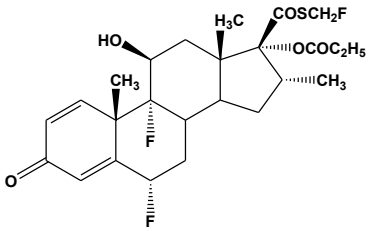
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: fluticasone propionate (BAN, INN, USAN).

Chemical Name: S-fluoromethyl 6α,9α-difluoro-11β -hydroxy-16α -methyl-3-oxo-17α -propionyloxyandrosta-1,4-diene-17β-carbothioate

Structural Formula:



Molecular Formula: $C_{25}H_{31}F_3O_5S$

Molecular Weight: 500.6 g/mol

Physicochemical properties: Fluticasone propionate is a white to off-white powder. It is freely soluble in dimethyl sulfoxide and dimethylformamide, sparingly soluble in acetone, dichloromethane, ethyl acetate and chloroform, slightly soluble in methanol and 95% ethanol, and practically insoluble in water. Fluticasone propionate decomposes without melting. Onset of decomposition occurs at about 225°C.

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative, randomized, single-dose two-way crossover bioavailability study using 100 healthy male and/or female volunteers was conducted to compare the relative bioavailability of 24HR NASAL ALLERGY RELIEF, 50 mcg/metered dose (Apotex Inc.) and Flonase® (GlaxoSmithKline, USA) Nasal Spray, 50 mcg/spray administered as 4 X 50 mcg sprays (2 per nostril) under fasting conditions. The mean pharmacokinetic parameters obtained from the study are listed in the following table:

Fluticasone Propionate Nasal Spray 200 mcg (2 x 50 mcg (2 sprays in each nostril)) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means#**	**90% Confidence Interval#**
AUCt (pg•h/mL)	39.073 45.004 (54)	39.424 48.062 (63)	99.2	91.2 – 107.9
Cmax (pg/mL)	6.588 7.245 (46)	6.510 7.264 (52)	101.4	94.0 – 109.4
AUCinf (pg•h/mL)	56.314 64.14 (55)	54.645 65.80 (66)	108.2	97.0 – 120.7
Tmax§ (h)	1.55 (61)	1.59 (88)		
Thalf§ (h)	9.99 (54)	8.83 (56)		

* Fluticasone Propionate Nasal Spray (Apotex Inc.)
§ Expressed as the arithmatic mean (CV%) only
# based on least squares estimates
† Flonase® Nasal Spray (GlaxoSmithKline, USA), was purchased in the USA.

A clinical efficacy study was conducted between April and September 2005 to demonstrate bioequivalence. The study consisted of a double blind, multi-center, placebo controlled, parallel group, randomised clinical study. Of the 565 subjects (male and female) who completed the placebo run-in period (Period 1) and were randomised to one of the three treatments (Period 2), 524 subjects were valid for the clinical equivalency analysis and 551 subjects were valid for the clinical efficacy analysis. Drug concentration/time profiles and pharmacokinetic parameters were not determined in this study.

The primary efficacy and equivalence measures were based on the average morning and evening Reflective TNSS of rhinorrhea, nasal congestion, nasal itchiness and sneezing. The endpoint was the change in Reflective TNSS from baseline to the average of the last 7 days.

The secondary efficacy and equivalence measures were based on the average morning and evening Instantaneous TNSS of rhinorrhea, nasal congestion, nasal itchiness and sneezing. The endpoint was the change in Instantaneous TNSS from baseline to the average of the last 7 days of treatment. The following table summarizes the results of the clinical study:

Measures	Statistics[1]	Fluticasone Propionate (50 mcg/spray; 2 sprays per nostril daily)			Equivalence Assessment[2]	
		Apotex	Flonase®†	Placebo	Ratio (Test/Ref) of Means (%)	90% Confidence Interval
	N	220	214	109		
rTNSS	Mean ± SD	-3.3* ± 2.9	-3.4* ± 2.7	-1.9 ± 2.5	98	87 - 108
iTNSS	Mean ± SD	-3.2* ± 2.8	-2.9* ± 2.6	-1.6 ± 2.5	108	96 - 120

[1] Based on the Intent-To-Treat population

[2] Based on the Per-Protocol population

* Significantly different from placebo ($p<0.001$)

† Flonase® is marketed by GlaxoSmithKline, Canada, and was purchased in Canada.

The safety and efficacy of fluticasone propionate aqueous nasal spray has been examined in Seasonal Allergic Rhinitis, Perennial Rhinitis, and Sinus Pain/Pressure of Allergic Rhinitis.

Seasonal Allergic Rhinitis

The efficacy and safety of fluticasone propionate aqueous nasal spray in patients with seasonal allergic rhinitis have been evaluated in multicentre, double-blind, randomized, parallel group, placebo-controlled clinical trials (FLN 203, FLN 204, FLN 305) of 771 adults and adolescents 12 years and older.

Trial Design and Patient Demographics

Table 3 Summary of the design and patient demographics in pivotal clinical trials of fluticasone propionate aqueous nasal spray in patients with Seasonal Allergic Rhinitis

Study #	Trial design	Duration and Route of administration	Study subjects enrolled Age Range Gender
FLN 203	A multicentre, double-blind randomized, placebo-controlled, parallel group study of the efficacy and safety of once- versus twice-daily intranasal administration of aqueous fluticasone for two weeks in adult patients with seasonal allergic rhinitis.	2 Weeks treatment with: FPANS 200 mcg QD (n=77) FPANS 100 mcg BID (n=75) Placebo (n=75)	227 patients Aged 18 to 62 years 130 Male 97 Female
FLN 204	A multicentre, double-blind randomized, placebo-controlled, parallel group study of the efficacy and safety of once- versus twice-daily intranasal administration of aqueous fluticasone propionate for four weeks in adult patients with	4 week treatment with: FPANS 100 mcg BID (n=100) FPANS 200 mcg QD (n=101) Placebo (n=100)	301 patients Aged 18 to 66 years 190 Male

Study #	Trial design	Duration and Route of administration	Study subjects enrolled Age Range Gender
	seasonal allergic rhinitis.		111 Female
FLN 305	A multicentre, double-blind randomized, placebo-controlled, parallel group study of the efficacy and safety of aqueous fluticasone propionate given once- versus twice-daily versus placebo for two weeks in adolescent patients with seasonal allergic rhinitis.	2 weeks treatment with: FPANS 100 mcg BID (n=73) FPANS 200 mcg QD (n=89) Placebo (n=81)	243 patients Aged 12 to 17 years 226 Male 17 Female
FLIT18	A multicentre, double-blind randomized, placebo-controlled, parallel group study of fluticasone propionate aqueous nasal spray 200 mcg once daily versus 100 mcg twice daily in ragweed allergic rhinitis.	4 week treatment with: FPANS 200 mcg QD (n=138) FPANS 100 mcg BID (n=139) Placebo (n=139)	416 patients Aged 17 to 72 years 189 Male 227 Female
FLNT 48	A single centre, double-blind, randomized, crossover study of intranasal fluticasone propionate 200 mcg once daily versus 200 mcg twice daily in severe ragweed allergic rhinitis, assessing days 5-14 in each treatment period.	4 weeks of treatment with: -FPANS 200 mcg in the morning & placebo in the evening for the first 2 weeks followed by FPANS 200 mcg BID for 2 weeks. (n=45) -FPANS 200 mcg BID for 2 weeks followed by FPANS 200 mcg in the morning & placebo in the evening for 2 weeks. (n=45)	90 patients Aged 18 to 69 years 37 Male 53 Female

FPANS = fluticasone propionate aqueous nasal spray, QD= once daily, BID = twice daily

Adult and Adolescent Results

Adult and adolescent seasonal allergic rhinitis studies FLN 203, FLN 204, FLN 305 demonstrated that treatment with fluticasone propionate aqueous nasal spray 200 mcg once daily resulted in a statistically significantly improvement in mean total nasal symptom scores (TNSS; nasal obstruction, rhinorrhea, sneezing, nasal itching) compared to patients treated with placebo (Table 4).

Overall, there was no statistically significant difference between fluticasone propionate aqueous nasal spray 100 mcg administered twice daily and fluticasone propionate aqueous nasal spray 200 mcg administered once daily.

Table 4 Results of pivotal clinical trials in adult and adolescent patients with Seasonal Allergic Rhinitis - Total nasal symptom scores (TNSS)

Mean Clinician-Rated Total Nasal Symptom Scores (TNSS) (maximum score 400)									
Day	FLN 203			FLN 204			FLN 305		
	Placebo	FPANS 100 mcg BID	FPANS 200 mcg QD	Placebo	FPANS 100 mcg BID	FPANS 200 mcg QD	Placebo	FPANS 100 mcg BID	FPANS 200 mcg QD
Day 1	250	253	253	262	243	251	245	253	242
Day 8	190	125†	136†	205	115†	129†	178	127*	122*
Day 15	182	114†	135†	185	102†	114†	152	94*	117§
Day 29	--	--	--	153	85†	93†	--	--	--

FPANS = fluticasone propionate aqueous nasal spray, BID= twice daily; QD=once daily
*P-value ≤0.001 compared with placebo
†P-value ≤0.01 compared with placebo
§P-value ≤0.05
P-values based on differences from baseline (Day 1) using the van Elteren statistic (not adjusted for multiple comparisons).

Adult and adolescent ragweed allergic rhinitis study FLIT18 demonstrated that patients treated with fluticasone propionate aqueous nasal spray 200 mcg once daily demonstrated a statistically significant improvement in the number of symptom-free days for nasal symptoms (nasal blockage, sneezing, nasal itching; p<0.001) and eye watering/irritation (p=0.006) compared to patients who received placebo. There was no statistically significant difference between fluticasone propionate aqueous nasal spray 100 mcg administered twice daily and fluticasone propionate aqueous nasal spray 200 mcg once daily.

Adult ragweed allergic rhinitis clinical trial (FLNT48) demonstrated that the percentage of symptom-free days was significantly higher for symptoms of nasal itching (p=0.004) and eye symptoms (p=0.004) in patients treated with fluticasone propionate aqueous nasal spray 200 mcg twice daily compared to 200 mcg once daily. There was no significant difference between the treatment regimens for the other symptoms assessed.

Perennial Rhinitis

The efficacy and safety of fluticasone propionate aqueous nasal spray in patients with perennial rhinitis have been evaluated in multicentre, double-blind, randomized, parallel group, placebo-controlled clinical trials (FLN 310, FLN 311, FLNT 43) of 1453 adults and adolescents (age 12 and older).

Trial Design and Patient Demographics

Table 5 Summary of the design and patient demographics in pivotal clinical trials of fluticasone propionate aqueous nasal spray in patients with Perennial Rhinitis

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects Enrolled (n=number) Age Range Gender
FLN 310	A multicentre, double-blind, randomized, placebo-controlled, parallel clinical trial to evaluate the safety and efficacy of the once daily versus twice daily intranasal administration of aqueous fluticasone propionate in patients with perennial allergic rhinitis.	24 weeks treatment with: FPANS 100 mcg, BID (n=121) FPANS 200 mcg QD (n=128) Placebo QD (n=116)	365 patients Aged 12 to 74 years 184 Male 181 Female
FLN 311	A multicentre, double-blind, randomized, placebo-controlled, parallel group clinical trial to evaluate the safety and efficacy of once daily versus twice-daily intranasal administration of aqueous fluticasone propionate versus aqueous beclomethasone dipropionate in patients with perennial allergic rhinitis.	24 weeks treatment with: FPANS 100 mcg BID (n=119) FPANS 200 mcg QD (n=118) BDPANS 168 mcg BID (n=116) Placebo BID (n=113)	466 patients Aged 12 to 71 years 227 Male 239 Female
FLNT43	A multicentre, double-blind, randomized, placebo-controlled, parallel study of fluticasone propionate aqueous nasal spray 200 mcg given once daily, fluticasone propionate aqueous nasal spray 200 mcg given twice daily with beclomethasone dipropionate aqueous nasal spray given 200 mcg twice daily and with placebo aqueous nasal spray in the treatment of patients with perennial rhinitis.	12 weeks treatment with: FPANS 200 mcg QD & placebo QD (n=129) FPANS 200 mcg BID (n=130) BDPANS 200 mcg BID (n=130) Placebo BID (n=127)	622 patients Aged 12 to 83 years Not Available

BID= twice daily; QD=once daily; FPANS = fluticasone propionate aqueous nasal spray, BDPANS = beclomethasone dipropionate aqueous nasal spray. Only FPANS and placebo results are presented.

Adult and Adolescent Results

Adult and Adolescent perennial allergic rhinitis studies FLN 310 and FLN 311 demonstrate that treatment with fluticasone propionate aqueous nasal spray 100 mcg twice daily and fluticasone propionate aqueous nasal spray 200 mcg once daily resulted in a significant improvement in clinician rated total nasal symptom score (TNSS; nasal obstruction, rhinorrhea, sneezing, nasal itching) (Table 6).

Overall, there was no statistically significant difference between fluticasone propionate aqueous nasal spray 100 mcg administered twice daily and fluticasone propionate aqueous nasal spray 200 mcg administered once daily.

Table 6 Results of pivotal clinical trials in patients with Perennial Rhinitis - Total nasal symptom scores (TNSS)

Mean Clinician-Rated Total Nasal Symptom Scores (TNSS) (maximum score 400)						
Day	FLN 310			FLN 311		
	Placebo	FPANS 100 mcg BID	FPANS 200 mcg QD	Placebo	FPANS 100 mcg BID	FPANS 200 mcg QD
Pretreatment	211.6	215.8	209.4	190.0	192.6	193.1
Week 24	143.0	95.6*	103.5*	128.3	94.4*	105.4*

BID= twice daily; QD=once daily, FPANS = fluticasone propionate aqueous nasal spray
*P-value ≤0.001 compared with placebo
P-values based on differences from pretreatment using pairwise comparisons based on least significant difference (LSD) using the MSError from ANOVA or ANCOVA. P-values not adjusted for multiple comparisons.

FLNT43 demonstrated that patients treated with fluticasone propionate aqueous nasal spray 200 mcg once daily and 200 mcg twice daily had significant improvements in the percentage of symptom-free days for symptoms of rhinorrhoea ($p \leq 0.002$ for both strengths), sneezing ($p \leq 0.001$ for both strengths), and the overall assessment of symptoms ($p < 0.05$ for both strengths), compared to patients receiving placebo. There were differences between treatment regimens on nasal blockage on waking or during the day.

Sinus Pain and Pressure in Allergic Rhinitis

The efficacy and safety of fluticasone propionate in adults and adolescents with sinus pain and pressure associated with nasal congestion due to allergic rhinitis have been evaluated in two multicentre, double-blind, randomized, parallel group, placebo controlled clinical trials (FNM40184 and FNM40185).

Trial Design and Patient Demographics

Table 7 Summary of the design and patient demographics in pivotal clinical trials of fluticasone propionate aqueous nasal spray in patients with Sinus Pain and Pressure

Study #	Trial design	Duration and Route of administration	Study subjects
FNM40184	A multi-centre, randomised, double-blind, parallel-group, study examining the effect of fluticasone propionate aqueous nasal spray 200mcg QD in subjects with sinus pain and pressure associated with nasal congestion due to allergic rhinitis	2 weeks of treatment with: FPANS 50mcg /spray QD Dosage: 2 sprays in each nostril every morning. (n=98) Placebo QD (n=97)	195 patients Aged 12 to 74 years 67 Male 128 Female
FNM40185	A multicentre, randomised, double-blind, parallel-group, study	2 weeks of treatment with: FPANS 50 mcg / spray QD	206 patients Aged 12 to 71

Study #	Trial design	Duration and Route of administration	Study subjects
	examining the effect of fluticasone propionate aqueous nasal spray 200mcg QD in subjects with sinus pain and pressure associated with nasal congestion due to allergic rhinitis.	Dose: 2 sprays in each nostril every morning. (n=101) Placebo QD (n=105)	years 87 Male 119 Female

FPANS = fluticasone propionate aqueous nasal spray; QD=once daily

Results

Treatment with fluticasone propionate 200 mcg once daily resulted in significant improvement in patient-rated sinus pain and pressure associated with nasal congestion in patients with allergic rhinitis at week 2 (Table 8).

Table 8 Studies FNM40184, FNM40185- Mean Patient-Rated Sinus Pain and Pressure Score, Visual Analogue 0-100 Score

	FNM40184			FNM40185		
Mean Patient-Rated Sinus Pain and Pressure Visual Analogue Score (SE)	**Placebo**	**FPANS 200QD**	**p-Value**	**Placebo**	**FPANS 200QD**	**p-Value**
Change during Week 2	-21.9 (2.83)	-32.0 (2.77)	0.011	-26.5 (2.70)	-35.4 (2.60)	0.023

FPANS = fluticasone propionate aqueous nasal spray; QD=once daily

DETAILED PHARMACOLOGY

Mechanism of Action

Topical nasal steroids act by reducing late-phase allergic reactions and mucous secretion, inhibiting vascular permeability, preventing eicosanoid formation, inhibiting allergen-induced mediator release, and reducing eosinophil and basophil infiltration in nasal epithelium. The local anti-inflammatory activity of fluticasone propionate has been documented by a reduction in the numbers of nasal mucosal eosinophils and basophils after 2 weeks of treatment.

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 - 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.

Pharmacodynamics
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 17 to 35 times higher than the recommended daily dose (200 to 400 mcg) and four times higher than the maximum intranasal dose given to humans in clinical trials (1600 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, estrogenic, and anti-gonadotrophic activity. Fluticasone propionate had some progestational activity in estrogen-primed weanling rabbits, and also showed some anti-androgenic and anti-estrogenic 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.

Human studies indicate that the anti-inflammatory activity of intranasal fluticasone propionate is topical rather than systemic. As with other intranasal glucocorticoids, fluticasone propionate is deposited primarily in the nasal passages; a portion is cleared from the nasal mucosa by mucociliary action and then swallowed.

In normal human subjects, single oral doses of fluticasone propionate up to 16 mg produced no effect on the HPA axis as evaluated by morning plasma cortisol concentrations.

In an oral, escalating dose, placebo controlled study, evening plasma cortisol was reduced after 13 days of 20 mg per day (10 mg twice daily), but HPA axis effects were not confirmed by associated changes in morning plasma cortisol or 24-hour urinary free cortisol measurements. Oral doses of 40 or 80 mg per day for 10 days suppressed morning plasma cortisol levels.

Intranasal administration of fluticasone propionate 2 mg per day (1 mg twice daily, and representing 10 times the usual recommended therapeutic dosage) to healthy volunteers for 7½ days had no effect on HPA axis function as assessed by morning and evening plasma cortisol and excretion of 24 hour urinary free cortisol.

Following intranasal administration of fluticasone propionate at the recommended daily dose of 200 mcg to healthy volunteers for 4 days, no significant change in 24 hour serum cortisol was found compared to placebo (ratio 1.01, 90% CI 0.9 - 1.14).

In two clinical trials, assessments of morning plasma cortisol, response to synthetic ACTH stimulation, and 24 hour urinary free cortisol also demonstrated no treatment effects on the HPA axis in 394 patients receiving daily intranasal doses of 50 to 1,600 mcg fluticasone propionate for 2 - 4 weeks.

Pharmacokinetics
Pharmacokinetic data from rat, dog and man, indicate that clearance is high relative to hepatic blood flow. Consequently, first-pass metabolism is extensive and oral bioavailability is negligible.

Clinical studies in normal human subjects have shown that following intranasal administration of fluticasone propionate at the recommended daily dose of 200 mcg, plasma concentrations were not quantifiable in most subjects (<0.01 ng/mL). The highest C_{max} observed was 0.017 ng/mL. Direct absorption in the nose is negligible due to the low aqueous solubility with the majority of

the dose being eventually swallowed. When administered orally, the systemic exposure is <1% due to poor absorption and pre-systemic metabolism. The total systemic absorption arising from both nasal and oral absorption of the swallowed dose is therefore negligible.

Fluticasone propionate has a large volume of distribution at steady state (approximately 318 L). Plasma protein binding is moderately high (91%). Fluticasone propionate is cleared rapidly from the systemic circulation, principally by hepatic metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Swallowed fluticasone propionate is also subject to extensive first pass metabolism.

Single intravenous doses of 1 mg in healthy volunteers revealed that the elimination rate is linear over the 250 to 1000 mcg dose range and are characterized by a high plasma clearance (CL=1.1 L/min). Peak plasma concentrations are reduced by approximately 98% within 3 - 4 hours and only low plasma concentrations were associated with the 7.8 hours terminal half-life. The renal clearance of fluticasone propionate is negligible (<0.2%) and less than 5% of the dose is excreted as the carboxylic acid metabolite. The major route of elimination is the excretion of fluticasone propionate and its metabolites in the bile.

TOXICOLOGY

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 400 mcg/day. The approximate LD_{50} values are shown in the following table:

Table 9 Acute Toxicity, Dosing Route and LD_{50}

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.

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 10 Fluticasone Propionate Dosing in Subacute Toxicity Studies

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

Key: * 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 Cushings' Syndrome.

Changes typical of glucocorticoid overdosage were seen in both hematological 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 hematological, 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 feces, distended abdomen and obesity.

Hematological 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 fetal toxicity characteristic of potent glucocorticoid compounds, including reduction in maternal weight gain, embryonic growth retardation, increased incidences of retarded cranial ossification, and of omphalocele 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 approximately 10 to 100 times the recommended human intranasal dose (200 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 fetal 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 an 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.

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PART III: PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

24HR NASAL ALLERGY RELIEF

(Fluticasone Propionate Aqueous Nasal Spray)
Manufacturer Standard

Read this carefully before you start taking 24HR NASAL ALLERGY RELIEF and each time you buy a new pack. 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 24HR NASAL ALLERGY RELIEF.

UNDERSTANDING 24HR NASAL ALLERGY RELIEF

What is 24HR NASAL ALLERGY RELIEF used for?

- 24HR NASAL ALLERGY RELIEF is an effective, medicine that relieves seasonal (i.e., hay fever) and year-round allergy symptoms caused by pollen, mold, dust and pets.
- 24HR NASAL ALLERGY RELIEF relieves these allergy symptoms: sneezing; itchy nose and throat; runny nose and itchy, watery eyes. It also relieves nasal congestion and sinus pain and pressure.

What problems can 24HR NASAL ALLERGY RELIEF help with?
Allergies can cause uncomfortable symptoms like congestion and itchy eyes. These symptoms can be triggered by allergens like pollen, mold, dust or pet dander.

24HR NASAL ALLERGY RELIEF helps relieve a broad range of symptoms from many allergens. For example, 24HR NASAL ALLERGY RELIEF helps with:

Symptoms		Triggers		
Nasal symptoms	**Eye symptoms**	**Outdoor allergens**	**Animal allergens**	**Indoor allergens**
• Congestion • Runny nose • Sneezing • Itchy nose	• Itchy eyes • Watery eyes	• Weed pollen • Grass pollen • Tree pollen • Mold spores	• Cats • Dogs	• Dust • Dust mites • Mold

How does 24HR NASAL ALLERGY RELIEF work?
24HR NASAL ALLERGY RELIEF works directly within your nose and nasal passages to help reduce your allergic reaction at the source to relieve the symptoms that make you uncomfortable.

24HR NASAL ALLERGY RELIEF controls several key inflammatory substances (histamine, chemokines, leukotrienes, cytokines, tryptases and prostaglandins) your body releases when you have an allergic reaction, whereas most non-prescription allergy medications will only act on one of these substances (i.e., histamine).

Because of the way it works, it may take several days for 24HR NASAL ALLERGY RELIEF to reach maximum effect. That's why it's best to use 24HR NASAL ALLERGY RELIEF regularly, once a day as directed.

What are the ingredients in 24HR NASAL ALLERGY RELIEF?
Medicinal ingredients: fluticasone propionate (a corticosteroid)

Non-medicinal ingredients: benzalkonium chloride, dextrose monohydrate, microcrystalline cellulose and carboxymethylcellulose sodium, phenylethyl alcohol, polysorbate 80, and purified water.

24HR NASAL ALLERGY RELIEF comes in the following dosage forms:
24HR NASAL ALLERGY RELIEF comes in a nasal spray device that will deliver either 60 or 120 sprays. Each spray delivers a mist containing 50 mcg of fluticasone propionate.

Do not use 24HR NASAL ALLERGY RELIEF:
- In children and adolescents under 18 years of age unless on the advice of a doctor.
- If you are allergic to it or any of its ingredients.
- If you have an untreated fungal (yeast), bacterial or tuberculosis infection of your respiratory tract.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take 24HR NASAL ALLERGY RELIEF. Talk about any health conditions or problems you may have, including if you:
- Are pregnant (or planning to become pregnant).
- Are breastfeeding a baby.
- Take a medicine for HIV infection (such as ritonavir)
- Suffer from severe liver disease.
- Have been exposed to chickenpox or measles.
- Have a problem with your thyroid.
- Have yellow or green discharge from your nose.
- Have a fever or a nasal or sinus infection.
- Are recovering from recent surgery, trauma or ulcers in your nose.
- Are taking or have previously taken other steroids either as an injection or by mouth.
- Have a blood clotting problem AND are taking Acetylsalicylic Acid (ASA).

Other warnings you should know about:
- You should avoid coming into contact with measles, chickenpox or tuberculosis while taking 24HR NASAL ALLERGY RELIEF. If you are exposed, tell your doctor.
- Drugs like 24HR NASAL ALLERGY RELIEF may 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.
  - Detached retina: blurry vision, dark area in your vision or other changes in vision.
  - Contact your doctor if you experience blurry vision or other vision problems. You should have regular eye exams.
- Slower growth in adolescents (12 – 17 years of age) may occur. You and your doctor should monitor your child's growth.

24HR NASAL ALLERGY RELIEF is not recommended for continuous, long-term treatment in children.

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 24HR NASAL ALLERGY RELIEF:
- Ritonavir (a medicine used to treat HIV infection or AIDS).
- Ketoconazole (a medicine used to treat fungal infections).
- Acetylsalicylic acid (a medicine for pain and fever relief).

USING 24HR NASAL ALLERGY RELIEF

How to take 24HR NASAL ALLERGY RELIEF:
Do not share this bottle with anyone else as this may spread germs.

For best results, it's important to get a full dose.
Here's how, in five easy steps.

1. Shake

Gently shake spray bottle.

Remove translucent cap.

2. Prime
Do this when:

- Starting new bottle
- Haven't used it in a week
- Just cleaned nozzle

Otherwise go to step 3

Aim away from face. Grasp spray bottle as shown. Pump until fine mist appears.

Won't I waste product by priming?

It's not a waste to prime the pump, because it helps you get a full dose. Getting a full dose is important for getting the relief you deserve. Don't worry about running out due to priming. There is enough medicine in the spray bottle to allow for priming sprays plus the number of sprays labeled on the bottle. Always point the spray bottle away from your face when priming.

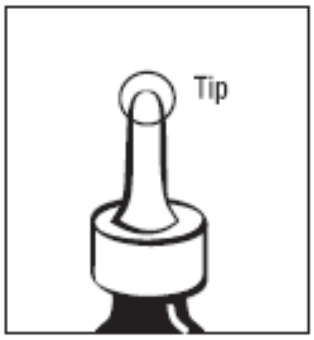
3. Blow Nose

Blow nose gently to clear nostrils.

4. Aim

Warning
Do not spray in your eyes or mouth. Only for use in your nose.

Close one nostril and put tip of spray nozzle in other nostril.



Put just the tip into your nose. Aim slightly away from centre of nose.

5. Breathe and spray

While sniffing gently, press down on spray nozzle once or twice (according to dosing instructions). You'll feel a light mist in your nose. Breathe out through your mouth. Repeat in other nostril. Wipe spray nozzle with clean tissue and replace cap.

What if I feel stinging in my nose, or I sneeze?
Some people may feel a slight stinging, or may sneeze after spraying 24HR NASAL ALLERGY RELIEF in their nostrils. This feeling should go away in a few seconds.

Usual dose:
24HR NASAL ALLERGY RELIEF works best when you use it daily.

Adults 18 years of age and older:
- Week 1 – use 2 sprays in each nostril once daily, preferably in the morning.
- Week 2 through 3 months – use 1 spray in each nostril once daily, if your symptoms are under control.
- After 3 months of daily use – ask your doctor if you can keep using.

If you have any difficulties or you are unsure about how or when to take 24HR NASAL ALLERGY RELIEF, check with your doctor or pharmacist.

Overdose:

If you think you have taken too much 24HR NASAL ALLERGY RELIEF, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

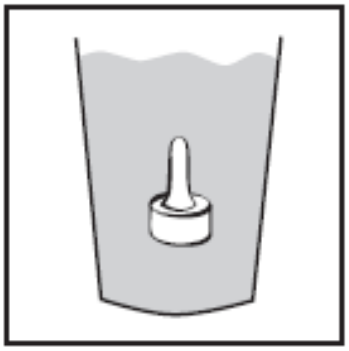
Missed Dose:
If you miss a dose, do not worry; just use your regular dose the next day. Don't add an extra dose.

KEEP IT CLEAN
A clean spray nozzle helps ensure a full dose. Clean it weekly, or if it's clogged. Don't try to unblock nozzle with pin or sharp object— that can damage it.

1. Remove spray nozzle by grasping at base and pulling up.

2. Rinse under running water, and dry at room temperature.

3. Aim away from your face and gently replace spray nozzle until you hear a soft click.



If spray nozzle is clogged, soak in warm water. Then repeat steps 2 and 3.

How long should a bottle of 24HR NASAL ALLERGY RELIEF last?
This table shows roughly how long your bottle will last. It assumes you follow the instructions for priming the pump, and that you follow the recommended dosing. After you've used the number of sprays shown on the label, each spray may not deliver a full dose—even if there is liquid left in the bottle.

If the label says...	The bottle should last...
60 sprays	2 weeks
120 sprays	4 weeks

If my symptoms go away, should I stop using 24HR NASAL ALLERGY RELIEF?
You may be tempted to stop using 24HR NASAL ALLERGY RELIEF when you start to feel better. It's important you keep using 24HR NASAL ALLERGY RELIEF daily as long as you're exposed to allergens that bother you, like pollen, mold, dust or pet dander. This way you'll keep feeling relief.

If your symptoms do not improve within 7 days of starting use or you get new symptoms such as severe facial pain or think nasal discharge you may have something more than allergies, such as an infection. You should stop treatment and speak with your doctor.

If you suffer allergy symptoms only during certain times, like when pollen levels are high, you may stop using 24HR NASAL ALLERGY RELIEF when that time ends.

Can I keep using 24HR NASAL ALLERGY RELIEF year round?
Some people suffer from allergies all year. If you are age 18 or older and have used 24HR NASAL ALLERGY RELIEF steadily for three months check with your doctor to make sure it's OK to keep using 24HR NASAL ALLERGY RELIEF daily. In fact, it's a good idea for anyone with persistent allergies to talk with a doctor every so often about symptoms and medicines.

WHAT TO EXPECT

How soon will I get relief?
You may start to feel relief the first day you use 24HR NASAL ALLERGY RELIEF. Keep using it every day, though. It takes several days before 24HR NASAL ALLERGY RELIEF builds up to full effectiveness. For seasonal allergies, 24HR NASAL ALLERGY RELIEF works best if it is started before the exposure to allergens occurs. Speak with your pharmacist to determine the best time to begin 24HR NASAL ALLERGY RELIEF to help treat symptoms.

How long will the relief last?
24HR NASAL ALLERGY RELIEF is meant to control your symptoms every day, all day and all night. To help you get this lasting relief, it's important to use 24HR NASAL ALLERGY RELIEF regularly, once a day as directed.

What are possible side effects from using 24HR NASAL ALLERGY RELIEF?
Serious side effects are rare with 24HR NASAL ALLERGY RELIEF because 24HR NASAL ALLERGY RELIEF works in your nose and nasal passages. Very little of it travels through your body. However, like all medicines, 24HR NASAL ALLERGY RELIEF can cause side effects in some people.

The following are possible side effects you may feel when taking 24HR NASAL ALLERGY RELIEF. If you experience any side effects not listed here, contact your healthcare professional.

- A dry, irritated or burning sensation in your nose
- Nosebleeds (you may also get streaks of blood when you blow your nose)
- Sneezing, runny nose, congestion
- Soreness, or sores in your nose or mouth
- Headache
- Dry or irritated eyes, blurred vision
- Unpleasant or change in sense of taste and/or smell
- Sore throat, throat irritation, dryness, hoarseness or cough
- You get a constant whistling sound from your nose. This may be a sign of damage inside your nose.
- Slower healing of wounds. Do not use 24HR NASAL ALLERGY RELIEF until your nose has healed if you have a sore in your nose, if you have surgery on your nose, or if your nose has been injured.

- Worsening of the symptoms of infections such as existing tuberculosis, fungal, bacterial or parasitic infections or herpes of the eye.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM:

Talk to your healthcare professional if you experience:
- **Cushing's Syndrome:** Rapid weight gain especially around the body and face; excess sweating; thinning of the skin with easy bruising and dryness; muscle and bone weakness.
- **Decreased Adrenal Function:** tiredness, weakness, nausea and vomiting.
- **Osteonecrosis** (tiny breaks in a bone leading to eventual collapse): Progressive or persistent pain or limited range of motion in a joint or limb.
- **Psychological or Behavioural:** Anxiety, depression or aggression, restlessness or trouble sleeping may occur, especially in children.
- **Cataracts:** glare, reduced vision.

Stop taking 24HR NASAL ALLERGY RELIEF and get immediate medical help if you experience:
- **Allergic Reactions:** chest pain or tightness, wheezing, coughing or having difficulty breathing, suddenly feeling weak or lightheaded (which may lead to collapse or loss of consciousness), swelling around the face, mouth or tongue, eyes or lips with difficulty swallowing, skin rashes (hives) or redness
- **Glaucoma:** increased pressure in your eyes, eye pain.

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 out of reach and sight of children. Your medicine may harm them.

Store between 15°C and 30°C. Do not use 24HR NASAL ALLERGY RELIEF after the expiry date shown on the pack.

If you want more information about 24HR NASAL ALLERGY RELIEF:
- 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://health-products.canada.ca/dpd-bdpp/index-eng.jsp. Find the Patient Medication Information on the manufacturer's website http://www.apotex.ca/products or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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