PRODUCT MONOGRAPH

PrFLONASE®

fluticasone propionate aqueous nasal spray USP

50 mcg/metered spray

Corticosteroid for nasal use

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fluticasone propionate aqueous nasal spray USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

INDICATIONS AND CLINICAL USE

FLONASE® (fluticasone propionate aqueous nasal spray) is indicated for the treatment of seasonal and perennial allergic rhinitis and for the management of sinus pain and pressure associated with allergic rhinitis in patients 4 – 17 years of age.

Pediatrics (< 4 years of age):

Fluticasone propionate is not recommended for children younger than 4 years of age.

CONTRAINDICATIONS

FLONASE® (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 FLONASE® (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 FLONASE® 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.

To ensure proper dosage and administration of the drug, the patient should be instructed by a physician or other health professional in the use of fluticasone propionate (see PART III CONSUMER INFORMATION).

Carcinogenesis and Mutagenesis

See TOXICOLOGY.

Ear/Nose/Throat

Epistaxis
In clinical trials of 2 to 26 weeks' duration, epistaxis was observed more frequently in subjects treated with FLONASE® Nasal Spray than those who received placebo (see ADVERSE REACTIONS).

Nasal Ulceration
Postmarketing cases of nasal ulceration have been reported in patients treated with FLONASE® (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 FLONASE®. Patients using FLONASE® 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 FLONASE® (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 FLONASE® aqueous nasal spray, potential risk increases with larger doses. Therefore, larger than recommended doses of FLONASE® aqueous nasal spray 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 FLONASE®. Discontinue FLONASE® if such reactions occur (see CONTRAINDICATIONS). Rarely, immediate hypersensitivity reactions may occur after the administration of FLONASE®.

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, FLONASE® 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 and/or cataracts. 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).

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 (4 to 11 years of age):
FLONASE® is indicated for short-term treatment in children 4 to 11 years of age. However, until greater clinical experience has been gained, the continuous, long-term treatment of children under age 12 is not recommended.

Pediatrics (less than 4 years of age):
The safety and effectiveness of FLONASE® in children below 4 years of age have not been evaluated.

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:
    - o Hypercorticism and adrenal suppression [see WARNINGS AND PRECAUTIONS]
    - o Growth retardation [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 FLONASE® (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 FLONASE® 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 FLONASE® or placebo in trials of seasonal allergic rhinitis are listed below (Table 1). These studies conducted in 948 adults and in 499 children evaluated 14-28 days of treatment with recommended doses of FLONASE® compared with placebo.

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

	Adults and Adolescents (age ≥ 12 years)			Children (age 4 -11 years)		
	FLONASE® 100 mcg BID (n=312) %	FLONASE® 200 mcg QD (n=322) %	Placebo (n=314) %	FLONASE® 100 mcg QD (n=167) %	FLONASE® 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

Includes studies FLN203, FLN204, FLN305, FLN306, FLN320, FLN321.

In two 6 month trials involving 831 patients aged 12-75 years with perennial rhinitis, the adverse reactions reported by patients treated with FLONASE® 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 FLONASE® 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 0.1-1% 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 4-11 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.

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 proprionate 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

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. 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. FLONASE® 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 FLONASE®. Patients should be instructed on 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 CONSUMER INFORMATION).

Careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids when transferred to FLONASE®. Initially, FLONASE® 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

Adolescents (12 – 17 years of age):
The usual dosage is two sprays (50 mcg each) in each nostril once a day (total daily dosage, 200 mcg). Some patients with severe rhinitis may benefit from two sprays in each nostril every 12 hours. The recommended maximum daily dose is 400 mcg (four sprays in each nostril).

Pediatrics (4-11 years of age):
The usual dosage is one or two (50 mcg /actuation) sprays in each nostril in the morning (100 or 200 mcg per day). The recommended maximum daily dose is 200 mcg (two sprays in each nostril). Once adequate control of symptoms is achieved, dose reduction to one spray in each nostril once a day is recommended.

Until greater clinical experience has been gained, the continuous, long-term treatment of children under age 12 is not recommended.

Pediatrics (< 4 years of age):
The safety and efficacy of FLONASE® in children below 4 years of age have not been established and therefore, FLONASE® is not recommended in this patient population.

Hepatic impairment: Formal pharmacokinetic trials using FLONASE® 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 FLONASE® 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

FLONASE® 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. FLONASE® may be administered at any time of day. Illustrated instructions for proper use appear in PART III: CONSUMER 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.

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. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in rhinitis. In 7 trials in adults, FLONASE® 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 FLONASE® on the HPA axis were evaluated. FLONASE® 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. FLONASE® 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 FLONASE® 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 250-1000 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.

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

STORAGE AND STABILITY

Store between 4° and 30° C. Shake gently before use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

FLONASE® 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.

FLONASE® contains micronised fluticasone propionate 0.05% w/w and the following non-medicinal ingredients: benzalkonium chloride, dextrose, microcrystalline cellulose and carboxymethylcellulose sodium, phenylethyl alcohol, Polysorbate 80, and purified water.

FLONASE® is available in an amber glass bottle containing sufficient formulation for 120 metered sprays (16 g net weight).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

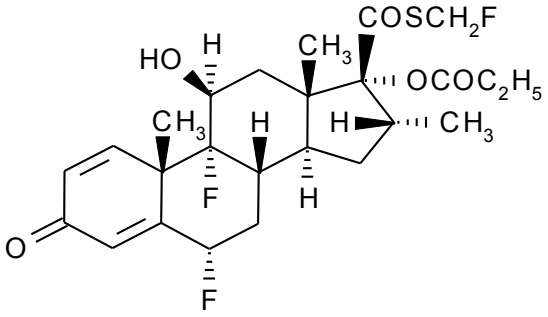
Drug Substance

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

Molecular formula and Molecular mass: $C_{25}H_{31}F_3O_5S$ 500.6

Structural formula:



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

The safety and efficacy of FLONASE® (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 FLONASE® 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 771adults and adolescents 12 years and older, and in multicentre, double-blind, randomized, parallel group, placebo-controlled clinical trials (FLN_320, FLN_321) of 499 pediatric patients (4 to 11 years of age).

Trial Design and Patient Demographics

Table 3 Summary of the design and patient demographics in pivotal clinical trials of FLONASE® 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 18-62 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 seasonal allergic rhinitis.	4 week treatment with: FPANS 100 mcg BID (n=100) FPANS 200 mcg QD (n=101) Placebo (n=100)	301 patients Aged 18-66 years 190 Male 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 12-17 years 226 Male 17 Female

Study #	Trial design	Duration and Route of administration	Study subjects enrolled Age Range Gender
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 – 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 18-69 years 37 Male 53 Female
FLN 320	A multicenter, double-blind randomized, placebo-controlled, parallel group study of the safety and efficacy of aqueous fluticasone propionate given once daily versus placebo for two weeks in paediatric patients with seasonal allergic rhinitis.	2 weeks treatment with: FPANS 100 mcg QD (n=84) FPANS 200 mcg QD (n=81) Placebo QD (n=85)	250 patients Aged 4-11 years 163 Male 87 Female
FLN 321	A multicenter, double-blind randomized, placebo-controlled, parallel group study of the safety and efficacy of aqueous fluticasone propionate given once daily versus placebo for four weeks in paediatric patients with seasonal allergic rhinitis.	4 weeks treatment with: FPANS 100 mcg QD (n=83) FPANS 200 mcg QD (n=83) Placebo once daily (n=83)	249 patients Aged 4-11 years 161 Male 88 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 FLONASE® 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 FLONASE® 100 mcg administered twice daily and FLONASE® 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 FLONASE® 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 FLONASE® 100 mcg administered twice daily and FLONASE® 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 FLONASE® 200 mcg twice daily compared to 200 mcg once daily. There was no significant difference between the treatment regimens for the other symptoms assessed.

Pediatric Results

Pediatric seasonal allergic rhinitis studies FLN 320 and FLN 321 demonstrated statistical and/or numeric improvements in mean total clinician rated nasal symptom scores (TNSS; nasal obstruction, rhinorrhea, sneezing, nasal itching) in patients receiving FLONASE® 100 mcg once daily and FLONASE 200 mcg once daily compared to patients receiving placebo (Table 5).

There was no statistically significant difference in TNSS or overall response between patients treated with FLONASE® 100 mcg once daily compared to patients treated with FLONASE® 200 mcg once daily.

Table 5 Results of pivotal clinical trials in children with Seasonal Allergic Rhinitis - Total nasal symptom scores (TNSS)

Mean Clinician-Rated Total Nasal Symptom Scores (TNSS) (maximum score 400)						
Day	**FLN 320**			**FLN-321**		
	Placebo mean (SE)	**FPANS 100 mcg QD mean (SE)**	**FPANS 200 mcg QD mean (SE)**	**Placebo mean (SE)**	**FPANS 100 mcg QD mean (SE)**	**FPANS 200 mcg QD mean (SE)**
Day 1	234 (8.4)	235 (7.9)	237 (7.1)	253 (8.6)	237 (8.0)	242 (9.0)
Day 8	183 (10.6)	131 (9.2)*	130 (9.7)*	188 (8.0)	146 (9.7)	142 (9.4) ‡
Day 15	148 (9.5)	117 (9.1) †	127 (9.7)	161 (8.4)	133 (9.0)	121 (8.2)
Day 29	--	--	--	143 (10.0)	110 (9.3)	109 (9.2)

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

Perennial Rhinitis

The efficacy and safety of FLONASE® 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) and in multicentre, double-blind, randomized, parallel group, placebo-controlled clinical trials (FLNT60, FLNT61) of 510 pediatric patients (4 to 11 years of age).

Trial Design and Patient Demographics

Table 6 Summary of the design and patient demographics in pivotal clinical trials of FLONASE® 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 12-74 years 184 Male 181 Female
FLN 311	A mutlicentre, 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 12-71 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 12-83 years Not Available
FLNT_60	A double-blind comparison of fluticasone propionate aqueous nasal spray 100mcg QD, fluticasone propionate aqueous nasal spray 200mcg QD, and placebo QD in the treatment of perennial rhinitis in children aged 4-11 years.	4 weeks treatment with: FPANS 100 mcg QD (n=132) FPANS 200 mcg QD (n=131) Placebo QD (n=136)	415 patients randomized 3-14 years 257 male 158 female
FLNT_61	A double-blind comparison of fluticasone propionate aqueous nasal spray 100mcg QD, fluticasone propionate aqueous nasal spray 100mcg BID, and beclomethasone dipropionate aqueous nasal spray 200mcg BID in the treatment of perennial rhinitis in pediatric patients aged 6-11 years.	12 weeks treatment with: FPANS 100 mcg QD (n=30) FPANS 100 mcg BID (n=35) BDPANS 200 mcg BID (n=30)	95 patients randomized 6-12 years 64 male 31 female

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 FLONASE® 100 mcg twice daily and FLONASE® 200 mcg once daily resulted in a significant improvement in clinician rated total nasal symptom score (TNSS; nasal obstruction, rhinorrhea, sneezing, nasal itching) (Table 7).

Overall, there was no statistically significant difference between FLONASE® 100 mcg administered twice daily and FLONASE® 200 mcg administered once daily.

Table 7 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 FLONASE® 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.

Pediatric Results

Pediatric perennial rhinitis study FLNT_60 found that FLONASE® at 100mcg OD and 200 mcg OD demonstrated statistical and/or numerical improvements over placebo in terms of symptom control (Table 8).

In general there weren't differences in symptom control between the FLONASE® dosing regimens in study FLNT_60 (Table 8), or the FLONASE® dosing regimens in study FLNT_61.

Table 8 Study FLNT_60 – Mean Percentage of Symptom-Free Days (Days 1-28)

Mean Percentage Symptom Free Days			
	FPANS 100mcg OD	FPANS 200mcg OD	Placebo
Nasal blockage - on waking	26	25	20
Nasal blockage - rest of day	36	35	30
Rhinorrhea	47*	46*	35
Sneezing	63*	61*	52
Nasal itching	57	58	55
Overall assessment	25	24*	16

FPANS = fluticasone propionate aqueous nasal spray, BID= twice daily; QD=once daily
*p<0.05 versus placebo

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 9 Summary of the design and patient demographics in pivotal clinical trials of FLONASE® 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 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 50 mcg / spray QD Dose: 2 sprays in each nostril every morning. (n=101) Placebo QD (n=105)	206 patients Aged 12 to 71 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 10).

Table 10 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 17-35 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 μg 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 250-1000 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 LD50 values are shown in the following table:

Table 11 Acute Toxicity, Dosing Route and LD50

SPECIES	ROUTE	APPROXIMATE LD50 (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 12 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	36 days
		10 mcg/kg/day	35 days
Dog	Subcutaneous	160 mcg/kg/day	36 days
Rat	Inhalation	60 mcg/L/day	7 days
		18.2 mcg/L/day	14 days
		475 mcg/kg/day	30 days
Dog	Inhalation	20 mg/animal/day	10 days
		9 mg/animal/day	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 10-100 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: CONSUMER INFORMATION

PrFLONASE®

fluticasone propionate aqueous nasal spray

This leaflet is part III of a three-part "Product Monograph" published when FLONASE® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FLONASE®. Contact your doctor or pharmacist if you have any questions about the drug. This medicine is for you. Only a doctor can prescribe it to you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

ABOUT THIS MEDICATION

What the medication is used for:

FLONASE® is used to treat:

- **seasonal allergic rhinitis** (including hay fever)
- **perennial (year-round) rhinitis**
- **Sinus pain and pressure** associated with allergic rhinitis

What it does:

When you spray FLONASE® into your nose it helps reduce the following symptoms associated with rhinitis:

- stuffy nose,
- runny nose,
- itchy nose,
- sneezing,
- eye redness,
- itchy and watery eyes

When it should not be used:

- if you are allergic to fluticasone propionate or any of the other ingredients in FLONASE®.
- if you have an untreated:
  - fungal (yeast)
  - bacterial infection
  - tuberculosis infection of your respiratory tract

What the medicinal ingredient is:

fluticasone propionate

What the nonmedicinal ingredients are:

benzalkonium chloride, carboxymethylcellulose sodium, dextrose, microcrystalline cellulose, phenylethyl alcohol, Polysorbate 80, and purified water.

What dosage forms it comes in:

Nasal spray: 50 mcg per spray (120 metered doses per device)

WARNINGS AND PRECAUTIONS

Before you use FLONASE® talk to your doctor or pharmacist if you:

- Are pregnant or planning to become pregnant.
- Are breastfeeding.
- Are allergic to any other corticosteroid.
- Have severe liver disease.
- Have been exposed to chickenpox or measles.
- Have thyroid problems.
- Have yellow or green discharge from your nose.
- Are recovering from recent surgery, trauma or ulcers in your nose.
- Have a history of nose bleeds.
- 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).
- Have a history of allergic reactions.
- Are less than 4 years old.

You should avoid coming into contact with people who have measles or chickenpox while taking FLONASE®. If you are exposed, tell your doctor right away.

Drugs like FLONASE® 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.

You should have regular eye exams.

In children under 12 years of age, it is not recommended to use FLONASE® for continuous, long-term treatment.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Drugs that may interact with FLONASE® include:

- Ritonavir used to treat HIV/ AIDS.
- Ketoconazole used to treat fungal infections.
- Acetylsalicylic acid used for pain and fever relief.

PROPER USE OF THIS MEDICATION

FLONASE®:

- is for use in the nose only. Do NOT spray it in your eyes or mouth
- takes 2-3 days to work. Take it each day without missing a dose to get the best results.

Take FLONASE® exactly as recommended by your doctor. If you have any difficulties or you are unsure about how or when to take FLONASE®, check with your doctor or pharmacist. **Do not** take more of your medicine or take it more often than your doctor tells you.

For **seasonal allergic rhinitis,** FLONASE® works best if it is started before you are exposed to allergens. You should work with your doctor to determine the best time to start taking FLONASE®.

If your symptoms have not improved after 3 weeks of taking FLONASE® tell your doctor. **Do not** stop treatment even if you feel better unless told to do so by your doctor.

Usual dose:

For adolescents aged 12 – 17 years:
Recommended daily dose: 2 sprays into each nostril, once a day (200 mcg a day)
Maximum daily dose: 2 sprays into each nostril, twice a day (400 mcg a day)

For children aged 4-11 years:
Recommended daily dose: 1 spray into each nostril once a day (100 mcg a day)
Maximum daily dose: 2 sprays into each nostril, once a day (200 mcg a day)

Depending on how FLONASE® is working for you, your doctor may increase your dose to the maximum daily dose.

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.

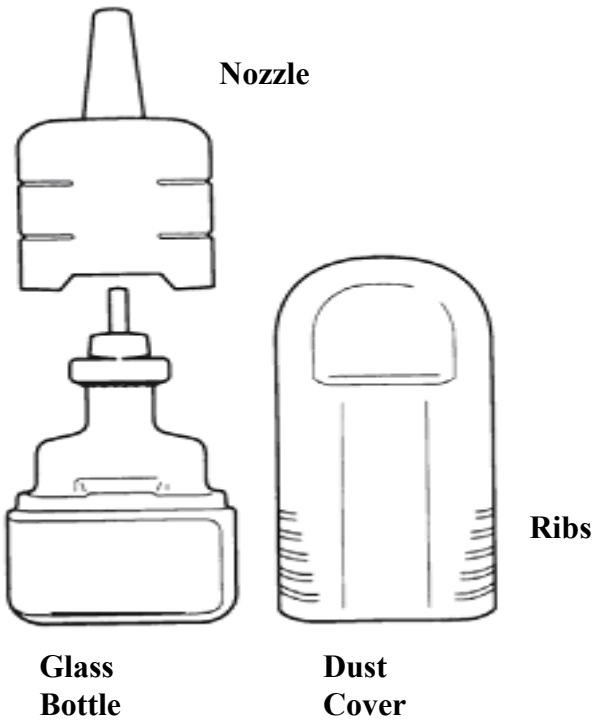
If you have taken larger doses than instructed for a long period of time, you should ask your doctor or pharmacist for advice.

Missed Dose:

If you miss a dose, take your next dose at the usual time. **Do NOT** double the dose or take extra doses to make up for the missed one.

Instructions for use:

Parts of your FLONASE® nasal spray:



The **Dust Cover:**

- Protects the nozzle and keeps it clean.
- Remember to take this off before using the spray.
- Do not throw the cover away. Always keep the cover on when you are not using the device.

The **Nozzle** will fit comfortably inside your nose. The medicine comes out from the nozzle.

Before Using Your FLONASE® nasal spray:

Your FLONASE® nasal spray must be primed if you:

- are using it for the first time.
- have not used it for a few days.
- have just cleaned it.

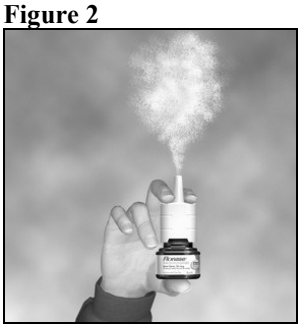
How to prime your FLONASE® nasal spray:

1. Shake the bottle gently, then remove the dust cover by gently squeezing the ribs between your finger and thumb and lifting off. (Figure 1)

Figure 1

2. Hold the bottle (as shown) with your forefinger and middle finger on either side of the nozzle and your thumb underneath the bottle. (Figure 2)

Figure 2



3. With the nozzle pointing away from you, press down and release several times until a fine mist comes out of the nozzle. (Figure 2)

4. The nasal spray is now ready to use.

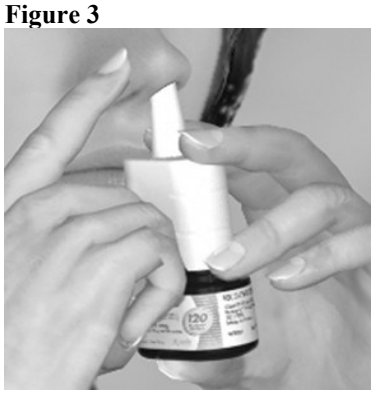
How to use FLONASE®:

Shake gently before each use.

Step 1: Blow your nose gently to clear your nostrils.

Step 2: Close one nostril. Tilt your head forward slightly. Keeping the bottle upright, carefully insert the nozzle into the other nostril. (Figure 3)

Figure 3



Step 3: Start to breathe in through your nose and WHILE BREATHING IN press firmly and quickly down with your fingers 1time to release the spray.

Step 4: Breathe out through your mouth.

Step 5: If a second spray in that nostril is required repeat steps 2, 3 and 4.

Step 6: Repeat 2, 3, and 4 for the other nostril. (Figure 4)

Figure 4

Step 7: Wipe the nozzle with a clean tissue or handkerchief and replace the dust cover. (Figure 5)

Figure 5

Cleaning your FLONASE® nasal spray

Your nasal spray should be cleaned at least once a week.

1. Remove the dust cover and then gently pull off the nozzle by pulling upwards.
2. Wash the nozzle under warm tap water.

   Shake off excess water and allow it to dry at room temperature.
3. Gently push the nozzle back on top of the bottle. Replace the dust cover.
4. If the nozzle becomes blocked it can be removed and left to soak in warm water. Rinse it under a cold tap, allow it to dry and place it back on the bottle. **Do not try to unblock the nozzle by inserting a pin or other sharp objects.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- A dry, irritated or burning sensation in your nose(you may also get streaks of blood when you blow your nose)
- Nosebleeds
- Sneezing, runny nose, congestion
- Soreness, or sores in your nose or mouth
- Headache
- Dry or irritated eyes, blurred vision
- Change in sense of taste and/or smell
- Sore throat, throat irritation, dryness, hoarseness or cough

Side effects that may occur with the use of corticosteroid nasal sprays are:

- Slower healing of wounds. Do not use FLONASE® 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.
- Slower growth in children has occurred with use of corticosteroid nasal spray. Slower growth in adolescents (12-17 years of age) may occur with use of corticosteroid nasal sprays. Your physician should monitor your growth regularly if you are in these age groups.

FLONASE® can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical assistance
		Only if severe	In all cases	
Very Rare	**Allergic Reactions:** chest pain or tighness, 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.			✓
Unknown	**Cushing's Syndrome:** Rapid weight gain especially around the body and face. Round "moon" face, excess sweating; thinning of the skin with easy bruising and dryness; muscle and bone weakness.		✓	
	Decreased Adrenal Function: tiredness, weakness, nausea and vomiting.		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek emergency medical assistance**
		Only if severe	**In all cases**	
	Osteonecrosis (tiny breaks in a bone leading to eventual collapse): Progressive or persistent pain or limited range of motion in a joint or limb.		✓	
	Cataracts: Clouding of the lens in the eye, blurry vision, and/or eye pain.		✓	
	Glaucoma: increased pressure in your eyes, eye pain.			✓

This is not a complete list of side effects. For any unexpected effects while taking FLONASE®*, contact your doctor or pharmacist.*

HOW TO STORE IT

Store between 4° and 30°C. Do not use FLONASE® after the expiry date shown on the pack.

Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.gsk.ca or by contacting the sponsor,
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