# PRODUCT MONOGRAPH

# NU-FLUTICASONE

**Fluticasone Propionate Aqueous Nasal Spray**

**50 mcg/metered dose**

**Apotex Standard**

**Corticosteroid for Nasal Use**

**NU-PHARM INC.**
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**October 15, 2009**

Control#: 133393

## Table of Contents

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Fluticasone Propionate Aqueous Nasal Spray
Nu-Pharm Standard

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form/Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Intranasal | Suspension/ 50 mcg per metered dose | None<br>*For a complete listing see Dosage Forms, Composition and Packaging Section.* |

### INDICATIONS AND CLINICAL USE

NU-FLUTICASONE (fluticasone propionate aqueous nasal spray) is indicated for the treatment of seasonal allergic rhinitis including hay fever, and perennial rhinitis poorly responsive to conventional treatment. In patients with allergic rhinitis, fluticasone propionate aqueous nasal spray is also indicated for the management of associated sinus pain and pressure.

Regular usage is essential for full therapeutic benefit since maximum relief may not be obtained until after 2 to 3 days of treatment.

### CONTRAINDICATIONS

NU-FLUTICASONE (fluticasone propionate aqueous nasal spray) is contraindicated in patients with a history of hypersensitivity to any of its ingredients, and in patients with untreated fungal, bacterial, or tuberculosis infections of the respiratory tract.

### WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

In patients previously on systemic steroids, either over prolonged periods or in high doses, the replacement with a topical 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.

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.

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.

**General**

Patients should be informed that the full effect of NU-FLUTICASONE (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.

**Steroid Replacement by NU-FLUTICASONE Nasal Spray**

The replacement of a systemic steroid with fluticasone propionate must be gradual and carefully supervised by the physician. The guidelines under "DOSAGE AND ADMINISTRATION" should be followed in all such cases.

**Proper Use of the Drug**

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).

**Long Term Effects**

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

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.

**Ear Nose and Throat**

**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.

**Endocrine and Metabolism**

**Systemic Effects**

Use of excessive doses of corticosteroids may lead to signs or symptoms of hypercorticism, suppression of HPA function, and/or reduction of growth velocity in children or teenagers. 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.

Although systemic effects have been minimal with recommended doses of fluticasone propionate aqueous nasal spray, potential risk increases with larger doses. Therefore, larger than recommended doses of fluticasone propionate aqueous nasal spray should be avoided.

**Hypothyroidism**

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

**Hepatic/Biliary/Pancreatic**

**Cirrhosis**

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

**Immune**

**Effect on Infection**

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.

**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 foetus, 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**

Fluticasone propionate is not presently recommended for children younger than 4 years of age due to limited clinical data in this age group.

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

## ADVERSE REACTIONS

**Clinical Trials Adverse Drug Reactions**

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. These studies conducted in 948 adults and in 499 children evaluated 14-28 days of treatment with recommended doses of fluticasone propionate compared with placebo.

| **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 od (n=322) %** | **Placebo (n=314) %** | **Fluticasone * 100 mcg od (n=167) %** | **Futicasone* 200 mcg od (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 12-75 years with perennial allergic 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**

Infrequent 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.

**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

Under normal circumstances, very low plasma concentrations of fluticasone propionate are achieved after intranasal dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions involving fluticasone propionate are unlikely.

A drug interaction study of intranasal fluticasone propionate in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects.

This study has shown that other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. However, there have been a few case reports during 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 co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole) as there is potential for increased systemic exposure to fluticasone propionate.

**Use of Corticosteroids and Acetylsalicylic Acid**
Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypothrombinemia.

## DOSAGE AND ADMINISTRATION

**See WARNINGS AND PRECAUTIONS**.

The therapeutic effects of corticosteroids, unlike those of decongestants, are not immediate. Since the effect of NU-FLUTICASONE (fluticasone propionate aqueous nasal spray) depends on its regular use, patients must be instructed to take the nasal inhalation at regular intervals and not, as with other nasal sprays, as they feel necessary.

**Adults and Children 12 years of age and older:**
The usual dosage is two sprays (50 micrograms/each metered dose) in each nostril once a day, (total daily dosage, 200 micrograms). Some patients with severe rhinitis may benefit from two sprays in each nostril every 12 hours. The recommended maximum daily dose is 400 micrograms (four sprays in each nostril).

**Children 4-11 years of age:**
The usual dosage is one or two sprays (50 micrograms/each metered dose) in each nostril in the morning (100 or 200 micrograms per day). The recommended maximum daily dose is 200 micrograms (two sprays in each nostril).

The safety and efficacy of fluticasone propionate aqueous nasal spray in children below 4 years of age have not been established and therefore, NU-FLUTICASONE Nasal Spray is not recommended in this patient population.

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

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. NU-FLUTICASONE should not be continued beyond three weeks in the absence of significant symptomatic improvement.

In the presence of excessive nasal mucous secretion or oedema 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 NU-FLUTICASONE. 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 NU-FLUTICASONE. Initially, NU-FLUTICASONE 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.

## 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.

## ACTION AND CLINICAL PHARMACOLOGY

Fluticasone propionate is a potent anti-inflammatory steroid. When administered intranasally in therapeutic doses, it has a direct anti-inflammatory action on the nasal mucosa, the mechanism of which is not yet completely defined.

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.

In clinical trials, no hypothalamic-pituitary-adrenal (HPA) axis effects have been observed. Following intranasal dosing of fluticasone propionate, (200 mcg/day) no significant change in 24-hour serum cortisol AUC was found compared to placebo (ratio 1.01, 90% CI 0.9- 1.14).

## STORAGE AND STABILITY

Store at room temperature 15-30 °C (59-86°F). Shake gently before use.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

NU-FLUTICASONE Nasal Spray is a white to off-white, milky suspension for topical administration to the nasal mucosa by means of a metering atomizing spray pump. Each metered dose of NU-FLUTICASONE Nasal Spray contains 50 mcg of fluticasone propionate.

Inactive Ingredients: benzalkonium chloride (as a preservative), dextrose monohydrate, microcrystalline cellulose and carboxymethylcellulose sodium, phenylethyl alcohol, polysorbate 80 and purified water.

NU-FLUTICASONE Nasal Spray is available in amber glass bottles of 16 g net weight (120 metered sprays).

## PART II: SCIENTIFIC INFORMATION

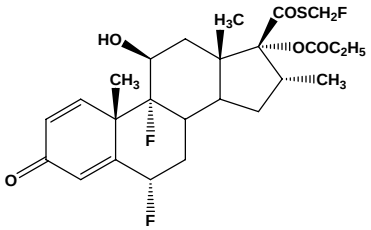
## PHARMACEUTICAL INFORMATION

### 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

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

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] | |
|---|---|---|---|---|---|---|
| | | Nu-Pharm | 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.

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 NU-FLUTICASONE Nasal Spray, 50 mcg/metered dose (Nu-Pharm 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** | **Fluticasone Propionate Nasal Spray (Nu-Pharm Inc.)** | **Flonase®† Nasal Spray (GlaxoSmithKline)** | **% 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) | | |

§ Expressed as the arithmatic mean (CV%) only

# based on least squares estimates
† Flonase® (GlaxoSmithKline, USA), was purchased in the USA.

## DETAILED PHARMACOLOGY

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

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

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

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

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

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

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

Comparison of systemic activity after topical and subcutaneous dosing of fluticasone propionate shows that, in both rats and particularly in mice, fluticasone propionate is more potent when given subcutaneously.

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

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

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

Two dogs received 1 mg fluticasone propionate by inhalation daily for 3 days. Marked suppression of plasma cortisol concentrations and adrenal function occurred which only began to recover 7 days after the final dose. The total dose given was approximately 110 mcg/kg/day, which is 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, oestrogenic, and anti-gonadotrophic activity. Fluticasone propionate had some progestational activity in oestrogen-primed weanling rabbits, and also showed some anti-androgenic and anti-oestrogenic activity. Weak anti-anabolic activity, another characteristic of potent glucocorticoids was observed in the castrated rat. Fluticasone propionate lacked mineralocorticoid activity but caused significant diuresis and urinary excretion of sodium and potassium.

**Clinical Pharmacology**

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 20mg per day (10mg 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.

In controlled clinical studies, fluticasone propionate was found to be consistently effective in the relief of nasal obstruction, rhinorrhoea, sneezing, and nasal itching.

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.

Evaluations of potential pharmacologic effects on other organ systems in volunteers following repeated twice-daily dosing with fluticasone propionate, given as 10 mg orally or 200 mcg intranasally, indicated no effects on heart rate, blood pressure, or 12-lead electrocardiograms. Repeated intranasal doses had no effect on pulmonary function as assessed by $FEV_1$.
Patients administered intranasal doses of up to 800mcg twice daily for 4 weeks also demonstrated no evidence of effects on vital signs, 12-lead electrocardiograms, pulmonary function tests, or routine laboratory tests.

**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.

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

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

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

Thus, the low oral bioavailability of fluticasone propionate expected due to extensive first-pass metabolism is compounded by incomplete absorption from the gastrointestinal tract particularly in the dog.

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

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 318L). 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 $LD_{5O}$ values are shown in the following table:

| Species | Route | Approximate $Ld_{5o}$ (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:

| 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<br>10 mcg/kg/day | 36 days<br>35 days |
| Dog | Subcutaneous | 160 mcg/kg/day | 36 days |
| Rat | Inhalation | 60 mcg/L/day<br>18.2 mcg/L/day<br>475 mcg/kg/day | 7 days<br>14 days<br>30 days |
| Dog | Inhalation | 20 mg/animal/day<br>9 mg/animal/day | 10 days<br>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 haematological and clinical chemistry parameters. Effects were seen on the red cell parameters and a characteristic leukopenia resulting from a lymphopenia accompanied by a neutrophilia. Endogenous cortisol and corticosterone were depressed in dogs and rats respectively.

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

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

Chronic inhalation toxicity studies using fluticasone propionate were conducted for up to 18 months in rats, using snout-only exposure. In two 6 month studies rats received doses of up to 80 mcg/kg/day; the maximum daily dose administered during the 18 month study was 57 mcg/kg. Changes seen in haematological, biochemical and urinalysis parameters were those typical of glucocorticoid overdosage. Histological findings included lymphoid depletion and thymic and adrenal atrophy. There was at least partial regression of all clinical changes either during the

treatment period or within the recovery period. At all dose levels the observed changes were considered to have arisen directly or indirectly from the immunomodulatory or physiological actions of a corticosteroid. None of these changes was of pathological significance.

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

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

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

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

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

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

**Mutagenicity**

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

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

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

These parenteral doses are 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 foetal defects. A very small fraction (<0.005%) of the dose crossed the placenta following oral administration to rats (100 mcg/kg/day) and rabbits (300 mcg/kg/day).

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

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

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

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**PART III: CONSUMER INFORMATION**

**NU-FLUTICASONE Nasal Spray**
(Fluticasone Propionate Aqueous Nasal Spray)
Nu-Pharm Standard

This leaflet is part III of a three-part "Product Monograph" published when NU-FLUTICASONE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NU-FLUTICASONE. Contact your doctor or pharmacist if you have any questions about the drug.

## ABOUT THIS MEDICATION

**What the medication is used for:**
NU-FLUTICASONE Nasal Spray is used to treat seasonal allergic rhinitis (including hay fever) and perennial rhinitis. Symptoms of these conditions include pain and pressure around the nose and eyes (sinuses), itching, a blocked up feeling in the nose and excessive sneezing.

**What it does:**
NU-FLUTICASONE reduces the irritation and inflammation in the lining of the nose and nasal passages and so it relieves the pain and pressure around the nose and eyes, the blocked up feeling in the nose, the runny nose itching and sneezing.

**When it should not be used:**
Do not use NU-FLUTICASONE if any of the following applies to you:

- If you have a known allergy to fluticasone propionate or any of the ingredients used to make NU-FLUTICASONE Nasal Spray (see "What the important non-medicinal ingredients are").
- If you have untreated fungal bacterial or tuberculosis infections of the respiratory tract.

**What the medicinal ingredient is:**
Fluticasone Propionate

**What the important nonmedicinal ingredients are:**
Benzalkonium chloride (as a preservative), dextrose mono-hydrate, microcrystalline cellulose and carboxymethylcellulose sodium, phenylethyl alcohol, polysorbate 80 and purified water.

**What dosage form it comes in:**
NU-FLUTICASONE Nasal Spray is a white to off-white, milky suspension for topical administration to the nasal mucosa by means of a metering atomizing spray pump.

Each metered dose of NU-FLUTICASONE Nasal Spray contains 50 mcg of fluticasone propionate.

NU-FLUTICASONE Nasal Spray is available in amber glass bottles of 16 g net weight (120 metered sprays).

## WARNINGS AND PRECAUTIONS

Follow the 'Instructions for Use' found in the **Proper Use Of This Medications Section**, found below. If you have any problems tell your doctor or pharmacist.

**Important Points to Remember**

- Have you ever had to stop taking other medicines for this illness because you were allergic to it or it caused problems? If the answer is YES, tell your doctor as soon as possible if you have not already done so.
- Tell your doctor if you notice any discharge from your nose is yellow or green if you have not already done so.
- If your symptoms have not improved after three weeks of treatment with NU-FLUTICASONE Nasal Spray then tell your doctor.
- Please talk to your doctor for continuous treatment with NU-FLUTICASONE, especially for children under 12 years of age.
- NU-FLUTICASONE is not recommended for children below 4 years of age.
- Please tell your doctor if you are pregnant or plan on becoming pregnant or if you are breast feeding a baby. Your doctor may decide not to prescribe this medicine in these circumstances.

## INTERACTIONS WITH THIS MEDICATION

Make sure your doctor knows what other medication you are taking (such as those for allergies, nervousness, depression, migraine etc.), including those you can buy without a prescription as well as herbal and alternative medicines.

Due to the interaction between Ritonavir (a medicine used to treat HIV infection or AIDS) with either intranasal or inhaled fluticasone propionate, it is important that your doctor knows that you are taking Ritonavir.

## PROPER USE OF THIS MEDICATION

It is important that you inhale each dose through the nose as instructed by your doctor or nurse. The label will usually tell you how many doses to take and how often. If it does not, or if you are not sure, ask your doctor or pharmacist.

- DO NOT inhale more doses or use your nasal spray more often than your doctor advises.
- It takes a few days for this medication to work. **It is very important that you use it regularly. Do not stop** treatment even if you feel better unless told to do so by your doctor.

**Usual dose:**
**Adults and Children 12 years of age and older:**
The usual dosage is 2 sprays (2 x 50 micrograms) in each nostril once a day in the morning. Your doctor may advise you to increase this to 2 sprays (2 x 50 micrograms) in each nostril twice a day.

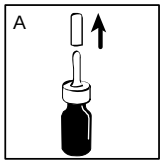
**Children 4-11 years of age:**
The usual dosage is one spray (50 micrograms) in each nostril once a day in the morning. Your doctor may advise you to increase this to 2 sprays (2 x 50 micrograms) in each nostril, once a day.

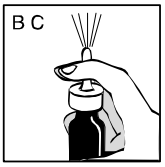
**Overdose:** Tell your doctor if you have used more than you were told to use.

**Missed Dose:** If you miss a dose, do not worry; take a dose when you remember and take the next dose when it is due.

**Instructions for use of NU-FLUTICASONE Nasal Spray**

**BEFORE USING**




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

B. Hold the spray as shown with your forefinger and middle finger on either side of the nozzle and your thumb underneath the bottle.

C. If using NU-FLUTICASONE Nasal Spray for the first time or if you have not used it for a week or more test the spray as follows: with the nozzle pointing away from you, press down several times as shown until a fine mist comes out of the nozzle.

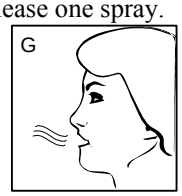
**USING THE SPRAY**



D. Blow your nose gently.

E. Close one nostril as shown in the diagram and put the nozzle in the other nostril. Tilt your head forward slightly and keep the spray upright.

F. Start to breathe in through your nose and WHILE BREATHING IN press down with your fingers ONCE to release one spray.

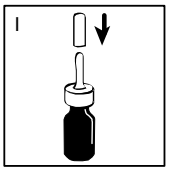




G. Breathe out through your mouth. If a second spray in that nostril is required repeat steps F and G.

H. Repeat E, F, and G for the other nostril.

**AFTER USE**




I. Wipe the nozzle with a tissue or handkerchief and replace the cover.

**CLEANING**

J. Gently pull off the nozzle. Wash it in warm water.

K. Shake off excess water and allow to dry in a warm place but avoid excessive heat.

L. Gently push the nozzle back on top of the brown bottle. Replace the dust cover.

M. If the nozzle becomes blocked it can be removed as above and left to soak in warm water. Rinse under a cold tap, allow to dry and refit. Do not try to unblock the nozzle by inserting a pin or other sharp objects.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Occasionally you may sneeze a little after using this spray but this soon stops. You may experience an unpleasant taste or smell.

If you feel unwell or have any other problems tell your doctor and follow the advice given.

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

| Symptom/effect | | Talk with your doctor or pharmacist: Only if severe | Talk with your doctor or pharmacist: In all cases | Stop taking drug and call your doctor or pharmacist |
|---|---|---|---|---|
| Common | Nose or throat pain | | ✓ | |
| | Nose bleed | ✓ | | |
| | Eye pain, blurred vision | | ✓ | |
| Rare | Sudden wheeziness and chest pain or tightness | | | ✓ |
| | Swelling of the eyelids, face or lips | | | ✓ |
| | Lumpy skin rash or 'hives' anywhere on the body | | | ✓ |

***This is not a complete list of side effects. For any unexpected effects while taking NU-FLUTICASONE Nasal Spray, contact your doctor or pharmacist.***

## HOW TO STORE IT

NU-FLUTICASONE Nasal Spray should be stored at room temperature 15-30˚C (59 – 86˚F). Shake gently before use. Keep out of reach of children. If your doctor decides to stop your treatment, do not keep any left over medicine unless your doctor tells you to.

REPORTING SUSPECTED SIDE EFFECTS

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

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free to 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 0701C**
    **Ottawa, ON K1A 0K9**

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

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

## MORE INFORMATION

**REMEMBER** that this medication is for **YOU.** Only a doctor can prescribe it for you. Never give it to others. It may harm them even if their symptoms are the same as yours.

**If you have any further questions or are not sure about anything, then you should ask your doctor or pharmacist.**

You may want to read this leaflet again. **PLEASE DO NOT THROW IT AWAY** until you have finished your medication.

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Nu-Pharm Inc. at:

1-800-267-1438

This leaflet was prepared by Nu-Pharm Inc. Richmond Hill, Ontario L4B 1E4.

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