DISCLAIMER

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Fluticasone Propionate Nasal Spray, USP, 50 mcg

Rx ONLY

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Fluticasone Propionate Nasal Spray, USP safely and effectively. See full prescribing information for Fluticasone Propionate Nasal Spray, USP.

Fluticasone Propionate Nasal Spray, USP, 50 mcg
FOR INTRANASAL USE
Initial U.S. Approval: 1994

RECENT MAJOR CHANGES

Indications and Usage (1) 01/2015

INDICATIONS AND USAGE

Fluticasone propionate nasal spray, USP is a corticosteroid indicated for the management of the nasal symptoms of perennial nonallergic rhinitis in adult and pediatric patients aged 4 years and older. (1)

DOSAGE AND ADMINISTRATION

For intranasal use only. Recommended starting dosages:
- Adults: 2 sprays per nostril once daily (200 mcg per day). (2.1)
- Adolescents and children aged 4 years and older: 1 spray per nostril once daily (100 mcg per day). (2.2)

DOSAGE FORMS AND STRENGTHS

Nasal spray: 50 mcg of fluticasone propionate in each 100-mg spray. (3)

CONTRAINDICATIONS

Hypersensitivity to any ingredient. (4)

WARNINGS AND PRECAUTIONS
- Epistaxis, nasal ulceration, *Candida albicans* infection, nasal septal perforation, and 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. (5.1)
- Close monitoring for glaucoma and cataracts is warranted. (5.2)
- Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, contact dermatitis, and rash) have been reported after administration of fluticasone propionate nasal spray, USP. Discontinue fluticasone propionate nasal spray, USP if such reactions occur. (5.3)
- Potential worsening of infections (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infection; ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.4)
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue fluticasone propionate nasal spray, USP slowly. (5.5)
- Monitor growth of pediatric patients. (5.7)

ADVERSE REACTIONS

The most common adverse reactions (>3%) are headache, pharyngitis, epistaxis, nasal burning/nasal irritation, nausea/vomiting, asthma symptoms, and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hi-Tech Pharmacal Co., Inc. at 1-800-262-9010 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole): Use not recommended. May increase risk of systemic corticosteroid effects. (7.1)

USE IN SPECIFIC POPULATIONS

Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fluticasone propionate nasal spray, USP is indicated for the management of the nasal symptoms of perennial nonallergic rhinitis in adult and pediatric patients aged 4 years and older.

2 DOSAGE AND ADMINISTRATION

Administer fluticasone propionate nasal spray, USP by the intranasal route only. Prime fluticasone propionate nasal spray, USP before using for the first time or after a period of non-use (1 week or more) by shaking the contents well and releasing 6 sprays into the air away from the face. Shake fluticasone propionate nasal spray, USP gently before each use.

Patients should use fluticasone propionate nasal spray, USP at regular intervals since its effectiveness depends on its regular use. Maximum effect may take several days and individual patients will experience a variable time to onset and different degree of symptom relief.

2.1 Adults

The recommended starting dosage in adults is 2 sprays (50 mcg of fluticasone propionate each) in each nostril once daily (total daily dose, 200 mcg). The same total daily dose, 1 spray in each nostril administered twice daily (e.g., 8 a.m. and 8 p.m.) is also effective. After the first few days, patients may be able to reduce their dose to 1 spray in each nostril once daily for maintenance therapy.

Maximum total daily doses should not exceed 2 sprays in each nostril (total dose, 200 mcg/day). There is no evidence that exceeding the recommended dose is more effective.

2.2 Adolescents and Children (Aged 4 Years and Older)

The recommended starting dosage in adolescents and children, aged 4 years and older is 1 spray in each nostril once daily (total daily dose, 100 mcg). Patients not adequately responding to 1 spray in each nostril may use 2 sprays in each nostril once daily (total daily dose, 200 mcg). Once adequate control is achieved, the dosage should be decreased to 1 spray in each nostril once daily.

The maximum total daily dosage should not exceed 2 sprays in each nostril (200 mcg/day). There is no evidence that exceeding the recommended dose is more effective.

3 DOSAGE FORMS AND STRENGTHS

Fluticasone propionate nasal spray, USP is a nasal spray suspension. Each 100-mg spray delivers 50 mcg of fluticasone propionate.

4 CONTRAINDICATIONS

Fluticasone propionate nasal spray, USP is contraindicated in patients with hypersensitivity to any of its ingredients [*see **Warnings and Precautions** (5.3), **Description** (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Local Nasal Effects

Epistaxis

In clinical trials of 2 to 26 weeks' duration, epistaxis was observed more frequently in subjects treated with fluticasone propionate nasal spray, USP than those who received placebo [*see **Adverse Reactions** (6.1)*].

Nasal Ulceration

Postmarketing cases of nasal ulceration have been reported in patients treated with fluticasone propionate nasal spray, USP [*see **Adverse Reactions** (6.2)*].

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 fluticasone propionate nasal spray, USP. Patients using fluticasone propionate nasal spray, USP over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

Nasal Septal Perforation

Postmarketing cases of nasal septal perforation have been reported in patients treated with fluticasone propionate nasal spray, USP [*see **Adverse Reactions** (6.2)*].

Impaired Wound Healing
Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should avoid using fluticasone propionate nasal spray, USP until healing has occurred.

5.2 Glaucoma and Cataracts
Use of intranasal 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, glaucoma, and/or cataracts.

5.3 Hypersensitivity Reactions including Anaphylaxis
Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, contact dermatitis, and rash) have been reported after administration of fluticasone propionate nasal spray, USP. Discontinue fluticasone propionate nasal spray, USP if such reactions occur [*see **Contraindications** (4)*]. Rarely, immediate hypersensitivity reactions may occur after the administration of fluticasone propionate nasal spray, USP.

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

Intranasal corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.5 Hypercorticism and Adrenal Suppression
When intranasal corticosteroids are used at higher than recommended dosages or in susceptible individuals at recommended dosages, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of fluticasone propionate nasal spray, USP should be discontinued slowly consistent with accepted procedures for discontinuing oral corticosteroid therapy.

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. In addition, some patients may experience symptoms of corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression). 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. In patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, rapid decreases in systemic corticosteroid dosages may cause a severe exacerbation of their symptoms.

5.6 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors
The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin, conivaptan, lopinavir, nefazodone, voriconazole) with fluticasone propionate nasal spray, USP is not recommended because increased systemic corticosteroid adverse effects may occur [*see **Drug Interactions** (7.1), **Clinical Pharmacology** (12.3)*].

5.7 Effect on Growth
Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients [*see **Use in Specific Populations** (8.4)*]. Monitor the growth routinely of pediatric patients receiving fluticasone propionate nasal spray, USP. To minimize the systemic effects of intranasal corticosteroids, including fluticasone propionate nasal spray, USP, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms [*see **Dosage and Administration** (2), **Use in Specific Populations** (8.4)*].

6 ADVERSE REACTIONS
Systemic and local corticosteroid use may result in the following:
- Epistaxis, nasal ulceration, *Candida albicans* infection, nasal septal perforation, and impaired wound healing [*see **Warnings and Precautions** (5.1)*]
- Cataracts and glaucoma [*see **Warnings and Precautions** (5.2)*]
- Immunosuppression [*see **Warnings and Precautions** (5.4)*]
- Hypercorticism and adrenal suppression [*see **Warnings and Precautions** (5.5)*]
- Effect on growth [*see **Warnings and Precautions** (5.7)*]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled U.S. clinical trials, more than 3,300 subjects with allergic and nonallergic rhinitis received treatment with intranasal fluticasone propionate. In general, adverse reactions in clinical trials have been primarily associated with irritation of the nasal mucous membranes, and the adverse reactions were reported with approximately the same frequency by subjects treated with placebo. Less than 2% of subjects in clinical trials discontinued because of adverse reactions; this rate was similar for vehicle placebo and active comparators.

The safety data described below are based on 7 placebo-controlled clinical trials in subjects with allergic rhinitis. The 7 trials included 536 subjects (57 girls and 108 boys aged 4 to 11 years, 137 female and 234 male adolescents and adults) treated with fluticasone propionate 200 mcg once daily over 2 to 4 weeks and 2 placebo-controlled clinical trials which included 246 subjects (119 female and 127 male adolescents and adults) treated with fluticasone propionate 200 mcg once daily over 6 months (Table 1). Also included in Table 1 are adverse reactions from 2 trials in which 167 children (45 girls and 122 boys aged 4 to 11 years) were treated with fluticasone propionate 100 mcg once daily for 2 to 4 weeks.

Table 1. Adverse Reactions with Fluticasone Propionate Nasal Spray, USP with >3% Incidence and More Common than Placebo in Subjects ≥4 Years with Allergic Rhinitis

Adverse Reaction	Fluticasone Propionate 100 mcg Once Daily (n = 167) %	Fluticasone Propionate 200 mcg Once Daily (n = 782) %	Placebo (n = 758) %
Headache	6.6	16.1	14.6
Pharyngitis	6.0	7.8	7.2
Epistaxis	6.0	6.9	5.4
Nasal burning/nasal irritation	2.4	3.2	2.6
Nausea/vomiting	4.8	2.6	2.0
Asthma symptoms	7.2	3.3	2.9
Cough	3.6	3.8	2.8

Other adverse reactions with fluticasone propionate nasal spray, USP observed with an incidence less than or equal to 3% but greater than or equal to 1% and more common than with placebo included: blood in nasal mucus, runny nose, abdominal pain, diarrhea, fever, flu-like symptoms, aches and pains, dizziness, and bronchitis.

6.2 Postmarketing Experience
In addition to adverse events reported from clinical trials, the following adverse events have been identified during postapproval use of intranasal fluticasone propionate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate or a combination of these factors.

General Disorders and Administration Site Conditions
Hypersensitivity reactions, including angioedema, skin rash, edema of the face and tongue, pruritus, urticaria, bronchospasm, wheezing, dyspnea, and anaphylaxis/anaphylactoid reactions, which in rare instances were severe.

Ear and Labyrinth Disorders
Alteration or loss of 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 Disorders
Dryness and irritation, conjunctivitis, blurred vision, glaucoma, increased intraocular pressure, and cataracts.

Cases of growth suppression have been reported for intranasal corticosteroids, including fluticasone propionate [*see **Warnings and Precautions** (5.7)*].

7 DRUG INTERACTIONS
7.1 Inhibitors of Cytochrome P450 3A4
Fluticasone propionate is a substrate of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin, conivaptan, lopinavir, nefazodone, voriconazole) with fluticasone propionate nasal spray, USP is not recommended because increased systemic corticosteroid adverse effects may occur.

Ritonavir
A drug interaction trial with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations [*see **Clinical Pharmacology** (12.3)*]. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate products, including fluticasone propionate nasal spray, USP, with ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.

Ketoconazole
Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol area under the curve (AUC), but had no effect on urinary excretion of cortisol.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Teratogenic Effects
Pregnancy Category C. There are no adequate and well-controlled trials with fluticasone propionate nasal spray, USP in pregnant women. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal reproduction studies are not always predictive of human response, fluticasone propionate nasal spray, USP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking fluticasone propionate nasal spray, USP.

Mice and rats at fluticasone propionate doses approximately 1 and 4 times, respectively, the maximum recommended human daily intranasal dose (MRHDID) for adults (on a mg/m^2 basis at maternal subcutaneous doses of 45 and 100 mcg/kg/day, respectively) showed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

No teratogenicity was seen in rats at doses up to 3 times the MRHDID (on a mg/m^2 basis at maternal inhalation doses up to 68.7 mcg/kg/day).

In rabbits, fetal weight reduction and cleft palate were observed at a fluticasone propionate dose approximately 0.3 times the MRHDID for adults (on a mg/m^2 basis at a maternal subcutaneous dose of 4 mcg/kg/day). However, no teratogenic effects were reported at fluticasone propionate doses up to approximately 20 times the MRHDID for adults (on a mg/m^2 basis at a maternal oral dose up to 300 mcg/kg/day). No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration [*see **Clinical Pharmacology** (12.3)*].

Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

8.3 Nursing Mothers

It is not known whether fluticasone propionate is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of tritiated fluticasone propionate at a dose approximately 0.4 times the MRHDID for adults on a mg/m^2 basis resulted in measurable radioactivity in milk.

Since there are no data from controlled trials on the use of intranasal fluticasone propionate nasal spray, USP by nursing mothers, caution should be exercised when fluticasone propionate nasal spray, USP is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of fluticasone propionate nasal spray, USP in children aged 4 years and older have been established [*see **Adverse Reactions** (6.1), **Clinical Pharmacology** (12.3)*]. Six hundred fifty (650) subjects aged 4 to 11 years and 440 subjects aged 12 to 17 years were studied in US clinical trials with fluticasone propionate nasal spray. The safety and effectiveness of fluticasone propionate nasal spray, USP in children younger than 4 years have not been established.

Effects on Growth

Controlled clinical trials have shown that intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. This effect was observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including fluticasone propionate nasal spray, USP, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of intranasal corticosteroids, including fluticasone propionate nasal spray, USP, each patient's dosage should be titrated to the lowest dosage that effectively controls his/her symptoms.

A 1-year placebo-controlled trial was conducted in 150 pediatric subjects (aged 3 to 9 years) to assess the effect of fluticasone propionate nasal spray, USP (single daily dose of 200 mcg) on growth velocity. From the primary population receiving fluticasone propionate nasal spray, USP (n = 56) and placebo (n = 52), the point estimate for growth velocity with fluticasone propionate nasal spray, USP was 0.14 cm/year lower than placebo (95% CI: -0.54, 0.27 cm/year). Thus, no statistically significant effect on growth was noted compared with placebo. No evidence of clinically relevant changes in HPA axis function or bone mineral density was observed as assessed by 12-hour urinary cortisol excretion and dual-energy x-ray absorptiometry, respectively.

The potential for fluticasone propionate nasal spray, USP to cause growth suppression in susceptible patients or when given at higher than recommended dosages cannot be ruled out.

8.5 Geriatric Use

A limited number of subjects aged 65 years and older (n = 129) or 75 years and older (n = 11) have been treated with fluticasone propionate nasal spray, USP in clinical trials. While the number of subjects is too small to permit separate analysis of efficacy and safety, the adverse reactions reported in this population were similar to those reported by younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Formal pharmacokinetic trials using fluticasone propionate nasal spray, USP 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.

8.7 Renal Impairment

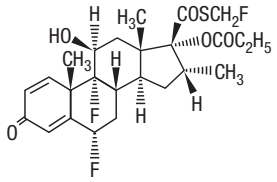
Formal pharmacokinetic trials using fluticasone propionate nasal spray, USP have not been conducted in subjects with renal impairment.

10 OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism [*see **Warnings and Precautions** (5.5)*]. Intranasal administration of 2 mg (10 times the recommended dose) of fluticasone propionate twice daily for 7 days was administered to healthy human volunteers. Adverse events reported with fluticasone propionate were similar to placebo, and no clinically significant abnormalities in laboratory safety tests were observed. Single oral doses up to 16 mg have been studied in human volunteers with no acute toxic effects reported. Repeat oral doses up to 80 mg daily for 10 days in volunteers and repeat oral doses up to 10 mg daily for 14 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. Acute overdosage with this dosage form is unlikely since 1 bottle of fluticasone propionate nasal spray, USP contains approximately 8 mg of fluticasone propionate.

11 DESCRIPTION

The active component of Fluticasone Propionate Nasal Spray, USP is fluticasone propionate, a corticosteroid having the chemical name *S* - (fluoromethyl) 6α,9-difluoro-11ß,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17ß-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

Fluticasone Propionate Nasal Spray, USP, 50 mcg is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. Fluticasone Propionate Nasal Spray, USP also contains benzalkonium chloride (0.02% w/w), carboxymethylcellulose sodium, dextrose, microcrystalline cellulose, phenylethyl alcohol (0.25% w/w), polysorbate 80, and purified water and has a pH between 5.8 and 6.8.

After initial priming, each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter.

12 CLINICAL PHARMACOLOGY

12.1 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. Data from the McKenzie vasoconstrictor assay in man are consistent with these results. The clinical significance of these findings is unknown.

The precise mechanism through which fluticasone propionate affects rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. In 7 trials in adults, fluticasone propionate nasal spray, USP 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.

12.2 Pharmacodynamics

HPA Axis Effect

The potential systemic effects of fluticasone propionate nasal spray, USP on the HPA axis were evaluated. Fluticasone propionate nasal spray, USP given as 200 mcg once daily or 400 mcg twice daily was compared with placebo or oral prednisone 7.5 or 15 mg given in the morning. Fluticasone propionate nasal spray, USP at either dosage for 4 weeks did not affect the adrenal response to 6-hour cosyntropin stimulation, while both dosages of oral prednisone significantly reduced the response to cosyntropin.

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

The activity of fluticasone propionate nasal spray, USP is due to the parent drug, fluticasone propionate. Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration.

Absorption

Indirect calculations indicate that fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2%. Trials using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. After intranasal treatment of patients with rhinitis for 3 weeks, fluticasone propionate plasma concentrations were above the level of detection (50 pg/mL) only when recommended doses were exceeded and then only in occasional samples at low plasma levels.

Distribution

Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averaged 99%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Elimination

Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. The total blood clearance of fluticasone propionate is high (average: 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total.

Metabolism: The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the CYP3A4 pathway. This metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Excretion: Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations

Fluticasone propionate nasal spray was not studied in any special populations, and no gender-specific pharmacokinetic data have been obtained.

Drug Interactions

Inhibitors of Cytochrome P450 3A4: Ritonavir: Fluticasone propionate is a substrate of CYP3A4. Coadministration of fluticasone propionate and the strong CYP3A4 inhibitor, ritonavir, is not recommended based upon a multiple-dose, crossover drug interaction trial in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable, peak levels (C_{max}) averaged 11.9 pg/mL (range: 10.8 to 14.1 pg/mL) and $AUC_{(0-\tau)}$ averaged 8.43 pg•h/mL (range: 4.2 to 18.8 pg•h/mL). Fluticasone propionate C_{max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range: 110 to 648 pg/mL) and 3,102.6 pg•h/mL (range: 1,207.1 to 5,662.0 pg•h/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Ketoconazole: Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

Erythromycin: In a multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 20 times the MRHDID in adults and approximately 10 times the MRHDID in children on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately 2 times the MRHDID in adults and approximately equivalent to the MRHDID in children on a mcg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells *in vitro*. No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in the mouse micronucleus test.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 2 times the MRHDID in adults on a mcg/m^2 basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

14 CLINICAL STUDIES

Perennial Nonallergic Rhinitis: Three randomized, double-blind, parallel-group, vehicle placebo-controlled trials were conducted in 1,191 subjects to investigate regular use of fluticasone propionate nasal spray, USP in subjects with perennial nonallergic rhinitis. These trials evaluated subject-rated total nasal symptom scores (TNSS) that included nasal obstruction, postnasal drip, rhinorrhea in subjects treated for 28 days of double-blind therapy and in 1 of the 3 trials for 6 months of open-label treatment. Two of these trials demonstrated that subjects treated with fluticasone propionate nasal spray, USP (100 mcg twice daily) exhibited statistically significant decreases in TNSS compared with subjects treated with vehicle.

16 HOW SUPPLIED/STORAGE AND HANDLING

Fluticasone Propionate Nasal Spray, USP 50 mcg is supplied in an amber glass bottle fitted with a white metering atomizing pump, white nasal adapter, in a box of 1 with FDA-approved Patient Labeling (see Patient Instructions for Use for proper actuation of the device). Fluticasone Propionate Nasal Spray, USP 50 mcg comes in two (2) sizes; a 9 gram and 16 gram. The 9 gram fill contains a net fill weight of 9 g and will provide 50 actuations and the 16 gram fill contains 16 g and will provide 120 actuations. Each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. The correct amount of medication in each spray cannot be assured after 50/120 sprays even though the bottle is not completely empty. The bottle should be discarded when the labeled number of actuations has been used.

Store between 4° and 30°C (39° and 86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Local Nasal Effects

Inform patients that treatment with fluticasone propionate nasal spray, USP may lead to adverse reactions, which include epistaxis and nasal ulceration. *Candida* infection may also occur with treatment with fluticasone propionate nasal spray, USP. In addition, fluticasone propionate nasal spray, USP has been associated with nasal septal perforation and impaired wound healing. Patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should not use fluticasone propionate nasal spray, USP until healing has occurred [*see* ***Warnings and Precautions*** *(5.1)*].

Glaucoma and Cataracts

Inform patients that glaucoma and cataracts are associated with nasal and inhaled corticosteroid use. Advise patients to notify their healthcare providers if a change in vision is noted while using fluticasone propionate nasal spray, USP [*see* ***Warnings and Precautions*** *(5.2)*].

Hypersensitivity Reactions, including Anaphylaxis

Inform patients that hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, contact dermatitis, and rash, may occur after administration of fluticasone propionate nasal spray, USP. If such reactions occur, patients should discontinue use of fluticasone propionate nasal spray, USP [*see* ***Warnings and Precautions*** *(5.3)*].

Immunosuppression

Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and if they are exposed to consult their healthcare provider without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex [*see* ***Warnings and Precautions*** *(5.4)*].

Reduced Growth Velocity

Advise parents that fluticasone propionate nasal spray, USP may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route [*see* ***Warnings and Precautions*** *(5.7),* ***Pediatric Use*** *(8.4)*].

Use Daily for Best Effect

Inform patients that they should use fluticasone propionate nasal spray, USP on a regular basis. Fluticasone propionate nasal spray, USP, like other corticosteroids, does not have an immediate effect on rhinitis symptoms. Maximum benefit may not be reached for several days. Patients should not increase the prescribed dosage but should contact their healthcare providers if symptoms do not improve or if the condition worsens.

Keep Spray Out of Eyes and Mouth

Inform patients to avoid spraying fluticasone propionate nasal spray, USP in their eyes and mouth.

Manufactured by:
Hi-Tech Pharmacal Co., Inc.
Amityville, NY 11701
Made in USA

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