HOME (/HOME)

SPECIALITY

TOPICS

SCIENTIFIC RESOURCES

PRODUCT INDEX (/PRODUCT-INDEX-LISTING)

INFOGRAPHICS (/INFOGRAPHICS)

Product Index

DUONASE Nasal Spray (Azelastine hydrochloride + Fluticasone propionate)

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DUONASE Nasal Spray (/content/duonase-nasal-spray)

Duonase nasal spray is a combination of INCS (Fluticasone propionate) and topical antihistamine (Azelastine), used in the management of allergic rhinitis in patients ≥ 12 years.

Infographic (https://ciplamedprod.blob.core.windows.net/ciplawebcast/Brand Card Duonase nasal spray vers 4-01.jpg)

Composition

Featured Content

DUONASE Nasal Spray

Each spray delivers:

Azelastine Hydrochloride BP …… 140 mcg

Fluticasone Propionate BP …… 50 mcg

Fluticasone Propionate BP ……. 0.0357% w/v

Azelastine Hydrochloride BP ….0.10% w/v

Benzalkonium Chloride NF ……0.01% w/v (as preservative)

Dosage Form

Intranasal spray

Description

DUONASE Nasal Spray is an antihistamine-corticosteroid combination available as a metered spray formulation for intranasal administration. It contains azelastine hydrochloride, which is a second generation H_1 receptor-antagonist with potent topical activity, and fluticasone propionate, a synthetic corticosteroid with anti-inflammatory properties.

Pharmacology

As **DUONASE** Nasal Spray is a combination of azelastine hydrochloride and fluticasone propionate, the pharmacological properties of both the molecules are given separately.

Pharmacodynamics

Azelastine Hydrochloride

Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H_1 receptor- antagonist activity in isolated tissues, animal models, and humans. The major metabolite, desmethylazelastine, also possesses H_1 receptor-antagonist activity.

There was no evidence of cardiac repolarization (represented as corrected QT interval) after administration of azelastine hydrochloride nasal spray (2 sprays per nostril) in 56-day placebo-controlled trial with 95 patients with

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allergic rhinitis.

Following multiple dose oral administration of azelastine 4 mg or 8 mg twice daily, the mean change in QTc was 7.2 msec and 3.6 msec, respectively.

Interaction studies investigating the cardiac repolarization effects of concomitantly administered oral azelastine hydrochloride and erythromycin or ketoconazole were conducted. These drugs had no effect on QTc based on analysis of serial electrocardiograms.

Fluticasone Propionate

Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory activity.

In pre-clinical studies, fluticasone propionate revealed progesterone-like activity similar to the natural hormone. However, the clinical significance of these findings in relation to the low plasma levels is not known.

The precise mechanism through which fluticasone propionate affects allergic 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, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

Pharmacokinetics

Absorption: After intranasal administration of two sprays per nostril (548 mcg of azelastine hydrochloride and 200 mcg of fluticasone) of azelastine hydrochloride and fluticasone propionate combination nasal spray, the mean (± standard deviation) peak plasma exposure (Cmax) was 194.5 ± 74.4 pg/mL for azelastine and 10.3±3.9 pg/mL for fluticasone propionate and the mean total exposure (AUC) was 4217 ± 2618 pg/mL*hr for azelastine and 97.7 ± 43.1 pg/mL*hr for fluticasone. The median time to peak exposure (t_{max}) from a single dose was 0.5 hours for azelastine and 1.0 hours for fluticasone.

Systemic bioavailability of azelastine from azelastine hydrochloride and fluticasone propionate combination nasal spray following intranasal administration was comparable with monotherapy azelastine hydrochloride nasal spray (i.e., approximately 40%). Systemic bioavailability of fluticasone from azelastine hydrochloride and fluticasone propionate combination nasal spray following intranasal administration was 44-61% higher than

monotherapy fluticasone propionate (bioavailability for monotherapy fluticasone nasal spray was less than 2%). Due to the low intranasal bioavailability, pharmacokinetic data for fluticasone propionate were obtained via other routes of administration. Studies using oral dosing of radiolabeled fluticasone propionate showed negligible oral bioavailability and high extraction from plasma. The majority of the circulating radioactivity was due to an inactive metabolite.

Distribution: Based on intravenous and oral administration, the steady-state volume of distribution of azelastine hydrochloride is 14.5 L/kg. In vitro studies with human plasma indicate that the plasma protein binding of azelastine hydrochloride and its metabolite, desmethylazelastine, are approximately 88% and 97%, respectively.

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 91% with no obvious concentration relationship. Fluticasone propionate is weakly and reversibly bound to erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism: Azelastine hydrochloride is oxidatively metabolized to the principal active metabolite, desmethylazelastine, by the cytochrome P450 enzyme system. The specific P450 isoforms responsible for the biotransformation of azelastine have not been identified. The total clearance of azelastine is approximately 0.50 L/kg/hr. For fluticasone propionate, the only circulating metabolite detected in man is the 17_-carboxylic acid derivative, which is formed through the CYP3A4 pathway. This inactive 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. The average total clearance of fluticasone propionate is relatively high (approximately 66 L/hr).

Elimination: Following intranasal administration of azelastine hydrochloride and fluticasone propionate combination nasal spray, the elimination half-life of azelastine hydrochloride is approximately 25 hours. Approximately 75% of

an oral dose of radiolabeled azelastine hydrochloride was excreted in the feces with less than 10% as unchanged azelastine.

Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. 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.

Indications

DUONASE Nasal Spray is indicated for the management of symptoms of allergic rhinitis, once the need for an antihistamine and corticosteroid has been established. It is recommended for the treatment of moderate to severe persistent symptoms in adults and adolescents above 6 years of age.

Dosage And Administration

Adults/Adolescents (Above 6 years of age)

One spray/nostril twice daily.

The recommended dosage should not be exceeded.

Contraindications

DUONASE Nasal Spray is contraindicated in patients with known hypersensitivity to azelastine hydrochloride or fluticasone propionate or any of the components of the preparation.

Warnings And Precautions

In clinical trials, the occurrence of somnolence has been reported in some patients (6 of 853 patients) taking azelastine hydrochloride and fluticasone propionate combination nasal spray. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor coordination such as operating machinery or driving a motor vehicle after administration of azelastine hydrochloride and fluticasone propionate combination nasal spray. Concurrent use of this combination with alcohol or

other central nervous system (CNS) depressants or other antihistamines should be avoided as additional reductions in alertness and additional impairment of CNS performance may occur.

In clinical trials of 2 to 52 weeks' duration, epistaxis was observed more frequently in patients treated with azelastine hydrochloride and fluticasone propionate combination nasal spray. Instances of nasal ulceration and nasal septal perforation have been reported in patients following the intranasal application of corticosteroids. There were no instances of nasal ulceration or nasal septal perforation observed in clinical trials with azelastine hydrochloride and fluticasone propionate combination nasal spray.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should not use azelastine hydrochloride and fluticasone propionate combination nasal spray until healing has occurred.

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 treatment with the combination. Patients using **DUONASE** over several months or longer should be examined periodically for evidence of Candida infection or other signs of adverse effects on the nasal mucosa.

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. Some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude, and 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 those patients who have asthma or other clinical conditions requiring long term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

When intranasal steroids 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 **DUONASE** Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral corticosteroid therapy. The concomitant use of an intranasal corticosteroid

with other corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA-axis. Therefore, such a combination should be used cautiously in patients with other pathological conditions requiring steroids.

Intranasal corticosteroids may cause a reduction in growth velocity when administered at higher dose. The recommended dosage of **DUONASE** Nasal Spray should not be exceeded.

Persons who are using drugs, such as corticosteroids, that suppress the immune system are more susceptible to infections than healthy individuals. In 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 exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex because of the potential for worsening of these infections.

During long-term therapy, monitoring of haematological and adrenal functions is advisable.

Nasal and inhaled corticosteroids may result in the development of glaucoma and/or cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

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 treatment

with **DUONASE** Nasal Spray. Patients using **DUONASE** Nasal Spray over several months or longer should be examined periodically for evidence of Candida infection or other signs of adverse effects on the nasal mucosa.

Drug Interactions

Caution should be exercised when **DUONASE** Nasal Spray is coadministered with ketoconazole and other known strong CYP3A4 inhibitors. Ritonavir and other strong cytochrome P450 3A4 (CYP3A4) inhibitors can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects. Co-treatment with other CYP 3A4 inhibitors, including cobicistat-containing products is also expected to increase the risk of systemic side effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side effects.

Concurrent use of **DUONASE** Nasal Spray with alcohol or other central nervous system depressants should be avoided because somnolence and impairment of central nervous system performance may occur.

Pregnancy

Pregnancy Category C: There are no adequate and well-controlled clinical trials of azelastine hydrochloride and fluticasone propionate combination nasal spray, azelastine hydrochloride only, or fluticasone propionate only in pregnant women. Animal reproductive studies of azelastine hydrochloride and fluticasone propionate in mice, rats, and/or rabbits revealed evidence of teratogenicity as well as other developmental toxic effects. Because animal reproduction studies are not always predictive of human response, **DUONASE** Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation

It is not known whether azelastine hydrochloride or fluticasone propionate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised while prescribing this combination to nursing mothers.

Pediatric Use

Safety and effectiveness of azelastine hydrochloride and fluticasone propionate combination nasal spray in pediatric patients below the age of 12 years have not been established.

Geriatric Use

Clinical trials of azelastine hydrochloride and fluticasone propionate combination nasal spray did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and 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.

Undesirable Effects

Systemic and local corticosteroid use may result in the following:

- Somnolence
- Local nasal effects, including epistaxis, nasal ulceration, nasal septal perforation, impaired wound healing, and Candida albicans infection.
- Glaucoma and cataracts
- Immunosuppression
- Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction

In placebo- controlled randomized clinical studies of two week duration with 853 adults and adolescents ≥ 12 years of age and suffering from seasonal allergic rhinitis treated with azelastine hydrochloride and fluticasone propionate combination nasal spray, the adverse reactions with ≥ 2% incidence or more frequently than placebo were: headache (2% versus 1% placebo), dysgeusia (4% versus <1% placebo) and epistaxis (2% versus 2% placebo). Somnolence was reported in <1% of patients treated with azelastine hydrochloride and fluticasone propionate combination nasal spray in these trials.

In long term open-label studies of 12-month duration with 404 patients treated with azelastine hydrochloride and fluticasone propionate combination nasal spray with perennial allergic rhinitis or vasomotor rhinitis

the most frequently (≥ 2%) reported adverse reactions were headache, pyrexia, cough, nasal congestion, rhinitis, dysgeusia, viral infection, upper respiratory tract infection, pharyngitis, pain, diarrhea, and epistaxis.

The following spontaneous adverse events have been reported during the marketing of azelastine hydrochloride nasal spray and causal relationship with the drug is unknown: anaphylactoid reaction, application site irritation, atrial fibrillation, increased heart rate, chest pain, anxiety, confusion, nervousness, dyspnea, facial edema, involuntary muscle contractions, nasal sores, palpitations, paresthesia, parosmia, pruritus, rash, disturbance or loss of sense of smell and/or taste, tolerance, urinary retention, vision abnormal and xerophthalmia.

In addition, the following events have been identified during post-approval use of fluticasone propionate nasal spray. 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: Hypersensitivity reactions, including angioedema, erythema, skin rash, edema of the face and tongue, pruritus, urticaria, bronchospasm, wheezing, dyspnea, and anaphylaxis/anaphylactoid reactions, which in rare instances were severe. Other general effects could be aches and pain, application site irritation, chest pain, edema of face and tongue, fatigue, tolerance.

Ear, Nose, and Throat: 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, dysphonia and voice changes.

Eye: Dryness and irritation, conjunctivitis, blurred vision, glaucoma, eye swelling, vision abnormal, increased intraocular pressure, and cataracts. Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Cases of growth suppression have been reported for intranasal corticosteroids, including 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.

The other adverse events could include: hypertension, dizziness, sneezing, nasal discomfort, nasal dryness, mucosal erosion, nausea, vomiting and fatigue.

In rare cases osteoporosis was observed, if nasal glucocorticoids were administered long-term.

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com (mailto:drugsafety@cipla.com). You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.

Overdosage

Azelastine Hydrochloride

There have been no reported overdosages with azelastine hydrochloride. Acute azelastine hydrochloride overdosage by adults with this dosage form is unlikely to result in clinically significant adverse events, other than increased somnolence. Clinical trials in adults with single doses of the oral formulation of azelastine hydrochloride (up to 16 mg) have not resulted in increased incidence of serious adverse events. General supportive measures should be employed if overdosage occurs. There is no known antidote to azelastine hydrochloride and fluticasone propionate combination nasal spray.

Fluticasone Propionate

Use of excessive doses of corticosteroids and/or chronic overdosage may lead to signs or symptoms of hypercorticism and/or suppression of the HPA function.

Intranasal administration of 2 mg (10 times the recommended dose) of fluticasone propionate, twice daily for 7 days, to healthy human volunteers was well tolerated. Single oral doses of up to 16 mg have been studied in human volunteers with no acute toxic effects reported. Repeat oral doses of up to 80 mg daily for 10 days in volunteers and repeat oral doses of up to 10 mg daily for 14 days in patients were also well tolerated.

Packaging Information

DUONASE Nasal Spray

Sales pack contains 70 metered doses

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Expert's Views (/expert-viewpoint-listing)
Guidelines (/guidelines-listing)
Clinical Tools (/clinical-tools-list)
Device Demos (/device-demo)
Product Index (/product-index-listing)
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