Flutiaze™

فلوٹیئز

(Azelastine HCl+Fluticasone Propionate)

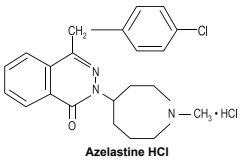
137mcg + 50mcg Nasal Spray

For Intranasal Use Only

DESCRIPTION

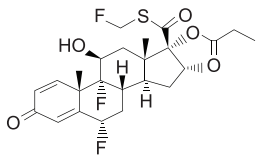
Flutiaze (Azelastine HCl + Fluticasone Propionate) nasal spray is formulated as almost white, hazy metered-spray suspension for nasal administration. It is a fixed dose combination product containing an antihistamine (H_1 receptor antagonist) and a corticosteroid as active ingredients.

The chemical name of Azelastine HCl is (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, mono HCl. Its molecular formula is $C_{22}H_{24}ClN_3O$•HCl and the structural formula is:



Azelastine HCl

The chemical name of Fluticasone Propionate is S-(fluoromethyl)-6α,9-difluoro-11 β-17-dihydroxy-16α-methyl-3-oxoandrosta1,4-diene-17β-carbothioate, 17-propionate. Its molecular formula is $C_{25}H_{31}F_3O_5S$ and the structural formula is:



Fluticasone Propionate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Flutiaze (Azelastine HCl + Fluticasone Propionate) Nasal Spray is available for administration as:

Flutiaze Nasal Spray 137mcg+50mcg
Each spray (0.14g) contains:
Azelastine HCl BP...137mcg
(Eq. to Azelastine 125mcg)
Fluticasone Propionate BP... 50mcg

CLINICAL PHARMACOLOGY

Mechanism of Action

Azelastine HCl and Fluticasone propionate have different modes of action and show synergistic effects in terms of improvement of allergic rhinitis and rhino-conjunctivitis symptoms.

Azelastine HCl

Azelastine, a phthalazinone derivative is classified as a potent long-acting anti-allergic compound with selective H_1-antagonist, mast cell stabilizing and anti-inflammatory properties. Data from in vivo (preclinical) and in vitro studies show that Azelastine inhibits the synthesis or release of the chemical mediators known to be involved in early and late stage allergic reactions, e.g. leukotrienes, histamine, platelet-activating factor (PAF) and serotonin. A relief of nasal allergic symptoms is observed within 15 minutes after administration.

Fluticasone Propionate

Fluticasone propionate is a synthetic trifluorinated corticosteroid that possesses a very high affinity for the glucocorticoid receptor and has a potent anti-inflammatory action, e.g. 3-5 fold more potent than dexamethasone in cloned human glucocorticoid receptor binding and gene expression assays.

Pharmacokinetics

Absorption

After nasal administration of two sprays per nostril (548mcg of Azelastine HCl and 200mcg of Fluticasone), the mean (± standard deviation) peak plasma exposure (C_{max}) was 194.5 ± 74.4pg/mL for Azelastine and 10.3 ± 3.9pg/mL for Fluticasone Propionate and the mean total exposure (AUC) was 4217 ± 2618pg/mL*hr for Azelastine and 97.7 ± 43.1pg/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 Propionate.

Distribution

Based on intravenous and oral administration, the steady-state volume of distribution of Azelastine HCl is 14.5L/kg. In vitro studies with human plasma indicate that the plasma protein binding of Azelastine HCl 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 4.2L/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 HCl is oxidatively metabolized to the principal active metabolite, desmethylazelastine, by the cytochrome P450 enzyme system. The total clearance of Azelastine is approximately 0.50L/kg/hr.

For Fluticasone Propionate, the only circulating metabolite detected in man is the 17β-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. The average total clearance of Fluticasone Propionate is relatively high (approximately 66L/hr).

Elimination

Following nasal administration, the elimination half-life of Azelastine HCl is approximately 25 hours. Approximately 75% of an oral dose of radiolabeled Azelastine HCl 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.

Special Population

Patients with Renal Impairment

Based on oral, single-dose studies of Azelastine HCl, renal impairment (creatinine clearance < 50mL/min) resulted in a 70-75% higher C_{max} and AUC compared to healthy subjects. Time to maximum concentration was unchanged.

THERAPEUTIC INDICATIONS

Flutiaze (Azelastine HCl + Fluticasone Propionate) is indicated for the relief of symptoms of seasonal allergic rhinitis in adult and pediatric patients 6 years of age and older.

DOSAGE & ADMINISTRATION

Recommended Dosage

The recommended dosage of Flutiaze (Azelastine HCl + Fluticasone Propionate) is single spray (137mcg of Azelastine HCl and 50mcg of Fluticasone Propionate) in each nostril twice daily.

Important Administration Instructions

- Administer Flutiaze (Azelastine HCl + Fluticasone Propionate) by the nasal route only.
- Shake the bottle well before each use.
- Avoid spraying Flutiaze (Azelastine HCl + Fluticasone Propionate) into the eyes. If sprayed in the eyes, flush eyes with water for at least 10 minutes.

Priming

Prime Flutiaze (Azelastine HCl + Fluticasone Propionate) Nasal Spray before initial use by releasing 6 sprays or until a fine mist appears.

Repriming (as needed)

When Flutiaze (Azelastine HCl + Fluticasone Propionate) Nasal Spray has not been used for 7 or more days, reprime with 1 spray or until a fine mist appears.

ADVERSE REACTIONS

Very common: Epitaxis.

Common: Headache, dysgeusia (unpleasant taste) and unpleasant smell.

Uncommon: Nasal discomfort (including nasal irritation, stinging, itching), sneezing, nasal dryness, cough, dry throat and throat irritation.

Rare: Dry mouth.

Very Rare: Hypersensitivity including anaphylactic reactions, angioedema (oedema of the face or tongue and skin rash), bronchospasm, dizziness, somnolence (drowsiness, sleepiness), glaucoma, increased intraocular pressure, cataract, nasal septal perforation, mucosal erosion, nausea, rash, pruritus, urticaria, fatigue (weariness, exhaustion) and weakness.

Not known: Blurred vision and nasal ulcers.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS

Azelastine HCl + Fluticasone Propionate is contraindicated in patients with hypersensitivity to the active substances or to any of the excipient of the product.

PRECAUTIONS

Somnolence

Somnolence has been reported in some patients. 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 HCl + Fluticasone Propionate.

Local Nasal Effects

Instances of nasal ulceration and nasal septal perforation have been reported in patients following the nasal application of corticosteroids. Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should avoid use of Azelastine HCl + Fluticasone Propionate until healing has occurred.

When Fluticasone Propionate administered nasally, 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 Azelastine HCl + Fluticasone Propionate. Patients using Azelastine HCl + Fluticasone Propionate over several months or longer should be examined periodically for evidence of Candida infection or other signs of adverse effects on the nasal mucosa.

Glaucoma and Cataracts

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.

Immunosuppression and Risk of Infections

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. More serious or even fatal course of chickenpox or measles in susceptible patients. Use caution in these patients.

Hypercorticism and Adrenal Suppression

When nasal 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 Azelastine HCl + Fluticasone Propionate should be discontinued slowly, consistent with accepted procedures for discontinuing oral corticosteroid therapy. The concomitant use of nasal corticosteroids with other inhaled corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis.

Severe Liver Disease

Azelastine HCl + Fluticasone Propionate undergoes extensive first-pass metabolism, therefore the systemic exposure of intranasal Fluticasone Propionate in patients with severe liver disease is likely to be increased. This may result in a higher frequency of systemic adverse events. Caution is advised when treating these patients.

Effect on Growth

Corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth routinely of pediatric patients receiving Azelastine HCl + Fluticasone Propionate.

Effects on ability to drive and use machines

Azelastine HCl + Fluticasone Propionate has minor influence on the ability to drive and use machines. In isolated cases fatigue, weariness, exhaustion, dizziness or weakness that may also be caused by the disease itself, may occur when using Azelastine HCl + Fluticasone Propionate. In these cases, the ability to drive and use machines may be impaired. Alcohol may enhance this effect.

Excipient

Azelastine HCl + Fluticasone Propionate contains benzalkonium chloride. Long term use may cause oedema of the nasal mucosa.

Pregnancy

There are no or limited amount of data from the use of Azelastine HCl + Fluticasone Propionate in pregnant women. Therefore, Azelastine HCl + Fluticasone Propionate Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is unknown whether nasally administered Azelastine HCl + Fluticasone Propionate metabolites are excreted in human breast milk. Azelastine HCl + Fluticasone Propionate Nasal Spray should be used during lactation only if the potential benefit justifies the potential risk to the newborns/infant.

DRUG INTERACTIONS

Central Nervous System Depressants

Concurrent use of Azelastine HCl + Fluticasone Propionate with alcohol or other central nervous system depressants should be avoided because somnolence and impairment of central nervous system performance may occur.

Cytochrome P450 3A4 Inhibitors

Ritonavir and other strong cytochrome P450 3A4 (CYP3A4) inhibitors can significantly increase plasma Fluticasone Propionate exposure, resulting in significantly reduced serum cortisol concentrations, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of Azelastine HCl + Fluticasone Propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Use caution with the coadministration of Azelastine HCl + Fluticasone Propionate and other potent CYP3A4 inhibitors, such as ketoconazole.

OVERDOSAGE

Azelastine HCl

There have been no reported overdosages with Azelastine HCl. Acute Azelastine HCl overdosage by adults with this dosage form is unlikely to result in clinically significant adverse reactions, other than increased somnolence.

Fluticasone Propionate

Chronic Fluticasone Propionate overdosage may result in signs/symptoms of hypercorticism.

Treatment

General supportive measures should be employed if overdosage occurs. There is no known antidote to Azelastine HCl + Fluticasone Propionate.

STORAGE

Do not store above 30°C.
Do not refrigerate or freeze.
Protect from light.

Do not use longer than 3 months after first use.

HOW SUPPLIED

Flutiaze (Azelastine HCl + Fluticasone Propionate) Nasal Spray 137mcg + 50mcg is supplied in a bottle fitted with a metered-dose, manual spray pump and a cap in a pack size of 120 sprays.

Keep out of reach of children.

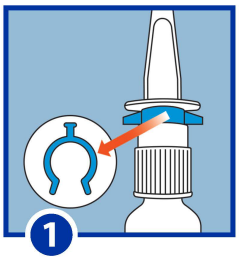
To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

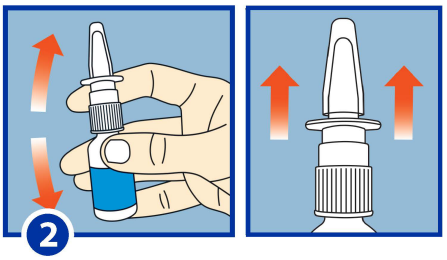
Manufactured by:
Saffron Pharmaceuticals (Pvt.) Ltd.
19km, Sheikhupura Road, Faisalabad, Pakistan

Manufactured for:
Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan

Flutiaze™ | INSTRUCTIONS FOR USE



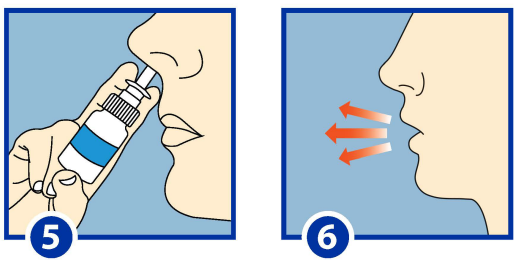
Remove the blue ring.



Shake the bottle well and remove the transparent protective cap.

When the spray is used for the first time, prime the pump by pressing downward on the right and left sides of the white nasal applicator using your index and middle fingers while holding the base of the bottle with your thumb. DO NOT pierce the nasal applicator. Press down and release the pump few times until a fine spray appears.

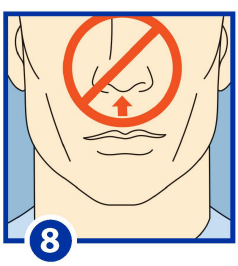
Gently blow your nose to clear the nostrils. Close one nostril. Tilt your head forward slightly, keep the bottle upright. Carefully insert the nasal applicator into the other nostril. Do not spray directly onto Nasal Septum.



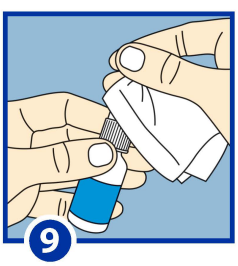
For each spray, hold the spray bottle upright and press firmly downward one time on the shoulder of the nasal applicator using your index and middle fingers while supporting the base of the bottle with your thumb. Breathe gently inward through the nostril.

Then breathe out through the mouth.

Repeat in the other nostril.



Do not tilt your head back after dosing. This will stop the medicine going into your throat and causing an unpleasant taste.



After each use, wipe the nasal applicator with a clean tissue or cloth and replace the transparent protective cap.

APPLICATOR CLEANING INSTRUCTIONS

1. To clean the nasal applicator, remove the transparent protective cap.
2. Pull gently upward on the white nasal applicator to remove.
3. Soak the nasal applicator in cold tap water and/or rinse both ends of the nasal applicator under cold tap water and dry. Do not try to unblock the nasal applicator by inserting a pin or other sharp object as this will damage the applicator and cause you not to get the right dose of medicine.
4. Rinse the plastic cap under cold water and dry.
5. Put the nasal applicator back together making sure the pump stem is reinserted into the applicator's center hole.
6. Reprime the pump by pressing downward on the shoulders of the white nasal applicator using your index and middle fingers while holding the base of the bottle with your thumb. Press down and release the pump two times or until a fine spray appears. DO NOT spray into eyes. The pump is now ready to use. The pump may be stored unused for up to one week without repriming. If unused for more than one week, reprime by spraying two times or until a fine spray appears.
7. Replace the transparent protective cap.

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