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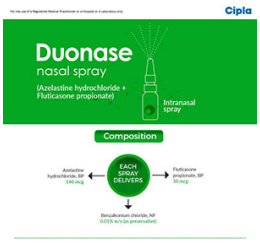
DUONASE Nasal Spray (Azelastine hydrochloride + Fluticasone propionate)



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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

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