For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack

Rx

Fluticasone Furoate and Azelastine Hydrochloride Nasal Spray
Allegra® nasal Duo

Each actuation delivers:
Fluticasone Furoate.……..…... 27.5 mcg
Azelastine Hydrochloride I.P. ……..140 mcg

COMPOSITION:
Fluticasone Furoate ……..….. 0.0275%w/w
Azelastine Hydrochloride I.P. …… 0.140% w/w
Benzalkonium Chloride I.P. ……0.01 % w/w
(as preservative)
Excipients ……. q.s.

DOSAGE FORM
Intranasal spray.

INDICATIONS:

Allegra® nasal Duo is indicated for the treatment of symptoms of allergic rhinitis.

Allegra® nasal Duo 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 persistent, moderate to severe symptoms in adults and adolescents above 12 years of age.

DOSAGE AND ADMINISTRATION:

Allegra® nasal Duo should be administered by the intranasal route only.

Adults and Adolescents (12 years of age and older):
One spray per nostril twice daily.
The recommended dosage should not be exceeded.

Shake the bottle well before each use.

For Intranasal use only. Do not spray in the mouth and eyes.

CONTRAINDICATIONS:

Allegra® nasal Duo is contraindicated in patients with known hypersensitivity to fluticasone furoate or azelastine hydrochloride or any of the components of this preparation.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Children and adolescents:

Do not use in children under 6 years old.

Fluticasone Furoate: Systemic Corticosteroid Effects

Systemic effects of nasal corticosteroid may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations. Potential systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and, more rarely, a range of psychological or behavioural effects, including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Treatment with higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. If there is evidence for the use of higher than recommended doses, then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery. Fluticasone furoate once daily was not associated with hypothalamic-pituitary-adrenal (HPA) axis suppression in adult, adolescent or paediatric subjects. However, the dose of this drug combination should be reduced to the lowest dose at which effective control of the symptoms of rhinitis is maintained. As with all intranasal corticosteroids, the total systemic burden of corticosteroids should be considered whenever other forms of corticosteroid treatment are prescribed concurrently.

If there is any reason to believe that adrenal function is impaired, care must be taken when transferring patients from systemic steroid treatment to fluticasone furoate nasal spray.

Visual Disturbance

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) that have been reported after use of systemic and topical corticosteroids.

Growth Retardation

Growth retardation has been reported in children receiving nasal corticosteroids at licensed doses. A reduction in growth velocity has been observed in children treated with fluticasone furoate. Therefore, children should be maintained on the lowest possible efficacious dose that delivers adequate symptom control. It is recommended that the growth of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid, if possible, to the lowest dose at which effective control of symptoms is maintained. In addition, consideration should be given to referring the patient to a paediatric specialist.

Patients on Ritonavir

Concomitant administration with ritonavir is not recommended because of the risk of increased systemic exposure of fluticasone furoate.

Azelastine Hydrochloride:
Concurrent use of this drug 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 due to azelastine hydrochloride.

In clinical trials, the occurrence of somnolence has been reported in some patients taking intranasal azelastine hydrochloride. 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 this drug combination.

Pregnancy and Lactation:

Pregnancy:

Fluticasone furoate:
There are no adequate data from the use of fluticasone furoate in pregnant women. Fluticasone furoate should be used in pregnancy only if the benefits to the mother outweigh the potential risks to the foetus or child.

Azelastine Hydrochloride:
Limited data from post marketing experience over decades of use with azelastine hydrochloride in pregnant women have not identified any drug associated risks of miscarriage, birth defects, or other adverse maternal or foetal outcomes

Lactation:

Fluticasone furoate:

It is unknown whether intranasally administered fluticasone furoate is excreted in human breast milk. Administration of fluticasone furoate to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child

Azelastine Hydrochloride:

There are no data on the presence of azelastine hydrochloride in human milk, the effects on the breastfed infant, or the effects on milk production following use of azelastine hydrochloride. Because many drugs are excreted in human milk, caution should be exercised when azelastine is administered to a nursing mother.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for azelastine and any potential adverse effects on the breastfed infant from azelastine or from the underlying maternal condition

Allegra® nasal Duo should not be used if the patient is breast feeding, unless advised by the physician.

Driving and using machines:

While using Allegra® nasal Duo nasal spray driving, operating machinery, or any other hazardous activities should be avoided.

ADVERSE REACTIONS

Fluticasone furoate:

Respiratory, thoracic and mediastinal disorders:

Nasal ulceration , dyspnoea (common)
Epistaxis (Very common)
Rhinalgia, nasal discomfort (including nasal burning, nasal irritation and nasal soreness), nasal dryness (uncommon)
Nasal septum perforation (very rare)
Bronchospasm (Not known)

Musculoskeletal and connective tissue disorder (children)

Growth retardation (known)

Immune system disorders:
Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria .

Nervous system disorders:
Headache (common)

Eye disorders:
Transient ocular changes, vision blurred (Not known)

Azelastine Hydrochloride
Use of Azelastine Hydrochloride has been associated with somnolence.

OVERDOSAGE

Fluticasone furoate
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There are no data on the effects of acute or chronic overdosage with fluticasone furoate nasal spray. Because of low systemic bioavailability and an absence of acute drug-related systemic findings in clinical studies , overdose is unlikely to require any therapy other than observation. Chronic overdosage with any corticosteroid may result in signs or symptoms of hypercorticism.

Azelastine Hydrochloride
There have been no reported overdosages with Azelastine Hydrochloride . Acute overdosage by adults with this dosage form is unlikely to result in clinically significant adverse reactions, other than increased somnolence, since one bottle of **Allegra® nasal Duo** contains 30 mg of azelastine hydrochloride.
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 reactions. General supportive measures

should be employed if overdosage occurs. There is no known antidote to Azelastine Hydrochloride . Oral ingestion of antihistamines has the potential to cause serious adverse effects in young children. Accordingly, Azelastine Hydrochloride should be kept out of the reach of children.

PHARMACOLOGICAL PROPERTIES:

As **Allegra® nasal Duo** is a combination of fluticasone furoate and azelastine hydrochloride, the pharmacological properties of both the molecules are given separately.

- **Pharmacodynamics**

Fluticasone furoate

Fluticasone furoate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity.

Fluticasone furoate nasal spray 110 micrograms once daily significantly improved nasal symptoms (comprising rhinorrhoea, nasal congestion, sneezing and nasal itching) and ocular symptoms (comprising itching/burning, tearing/watering and redness of the eyes) in the studies. Efficacy was maintained over the full 24-hour dosing period with once-daily administration.

Onset of therapeutic benefit was observed as early as 8 hours after initial administration, with further improvement observed for several days afterwards.

Azelastine Hydrochloride

Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H_1 receptor-antagonist activity in isolated tissues, animal models, and humans. Azelastine hydrochloride is administered as a racemic mixture with no difference in pharmacologic activity noted between the enantiomers in in vitro studies. The major metabolite, desmethylazelastine, also possesses H_1 receptor-antagonist activity.

There was no evidence of an effect of azelastine hydrochloride nasal spray (two sprays per nostril twice daily for 56 days) on cardiac repolarisation as represented by the corrected QT interval (QTc) of the electrocardiogram. Following multiple-dose oral administration of azelastine 4 mg or 8 mg twice daily, the mean change in the QTc was 7.2 msec and 3.6 msec, respectively.

Interaction studies investigating the cardiac repolarisation effects of concomitantly administered oral azelastine hydrochloride and erythromycin or ketoconazole were conducted. Oral erythromycin had no effect on azelastine pharmacokinetics or QTc based on analysis of serial electrocardiograms. Ketoconazole interfered with the measurement of azelastine plasma levels; however, no effects on the QTc were observed.

- **Pharmacokinetics**

Fluticasone furoate

Absorption

Following intranasal administration of fluticasone furoate, most of the dose is eventually swallowed and undergoes incomplete absorption and extensive first-pass metabolism in the liver and gut, resulting in negligible systemic exposure.

At the highest recommended intranasal dosage of 110 mcg once daily for up to 12 months in adults and up to 12 weeks in children, plasma concentrations of fluticasone furoate are typically not quantifiable despite the use of a sensitive HPLC-MS/MS assay with a lower limit of quantification (LOQ) of 10 pg/mL. However, in a few isolated cases (<0.3%) fluticasone furoate was detected in high concentrations above 500 pg/mL, and in a single case, the concentration was as high as 1,430 pg/mL in the 52-week study. There

was no relationship between these concentrations and cortisol levels in these subjects. The reasons for these high concentrations are unknown.

Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration. Studies using oral solution and intravenous dosing of radiolabelled drug have demonstrated that at least 30% of fluticasone furoate is absorbed and then rapidly cleared from plasma. Oral bioavailability is on average 1.26%, and the majority of the circulating radioactivity is due to inactive metabolites.

Distribution

Following intravenous administration, the mean volume of distribution at steady state is 608 L. Binding of fluticasone furoate to human plasma proteins is greater than 99%.

Metabolism

In vivo studies have revealed no evidence of cleavage of the furoate moiety to form fluticasone. Fluticasone furoate is cleared (total plasma clearance of 58.7 L/h) from systemic circulation principally by hepatic metabolism via the cytochrome P450 isozyme, CYP3A4. The principal route of metabolism is hydrolysis of the S-fluoromethyl carbothioate function to form the inactive 17beta-carboxylic acid metabolite.

Elimination

Fluticasone furoate and its metabolites are eliminated primarily in the faeces, accounting for approximately 101% and 90% of the orally and intravenously administered dose, respectively. Urinary excretion accounted for approximately 1% and 2% of the orally and intravenously administered dose, respectively. The elimination phase half-life averaged 15.1 hours following intravenous administration.

Special Populations

Hepatic impairment

Since fluticasone furoate undergoes extensive first-pass metabolism by the hepatic cytochrome P450 isozyme, CYP3A4, the pharmacokinetics of fluticasone furoate may be altered in patients with hepatic impairment. The systemic exposure would be expected to be higher than that observed had the study been conducted after multiple doses and/or in patients with severe hepatic impairment. Therefore, use fluticasone furoate nasal spray with caution in patients with severe hepatic impairment.

Renal Impairment

Fluticasone furoate is not detectable in urine from healthy subjects following intranasal dosing. Less than 1% of dose related material is excreted in the urine. No dosage adjustment is required in patients with renal impairment.

Azelastine Hydrochloride

Absorption

After intranasal administration of 2 sprays per nostril (548 mcg total dose) of 137 mcg azelastine hydrochloride, the mean azelastine peak plasma concentration (C_{max}) is 200 pg/mL, the mean extent of systemic exposure (AUC) is 5122 pg•hr/mL and the median time to reach C_{max} (t_{max}) is 3 hours. The systemic bioavailability of azelastine hydrochloride is approximately 40% after intranasal administration.

Distribution

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

Metabolism

Azelastine 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.

After a single-dose, intranasal administration of 137 mcg azelastine hydrochloride (548 mcg total dose), the mean desmethylazelastine C_{max} is 23 pg/mL, the AUC is 2131 pg•hr/mL and the median t_{max} is 24 hours. After intranasal dosing of azelastine to steady-state, plasma concentrations of desmethylazelastine range from 20-50% of azelastine concentrations.

Elimination

Following intranasal administration of 137 mcg azelastine hydrochloride, the elimination half-life of azelastine is 22 hours while that of desmethylazelastine is 52 hours. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was excreted in the feces with less than 10% as unchanged azelastine.

Special Populations

Following oral administration, pharmacokinetic parameters were not influenced by age, gender, or hepatic impairment.

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

PRESENTATION:

7.0ml/ 70 Metered doses

STORAGE INSTRUCTIONS:

Store below 30°C. Protect from light. Do not freeze. Keep the medicine out of reach of children.

Manufactured in India by:

M/s Biodeal Pharmaceuticals Pvt. Ltd., Village: Saini Majra, Nalagarh –Ropar Road, Nalagarh, District: Solan-174101 (H.P), INDIA.

Marketed by:

Sanofi India Limited, Sanofi House, CT Survey No. 117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai – 400072

Created: *Feb 2022*

References:

1) Azelastine Hydrochloride: Astelin Pack Insert by Meda Pharmaceuticals (last revised in Revised: 9/2018) as accessed on 28th Feb 2022)

2) https://www.ciplamed.com/content/furamist-az-nasal-spray (As accessed on 28th Feb 2022)

Steps to use your nasal spray correctly

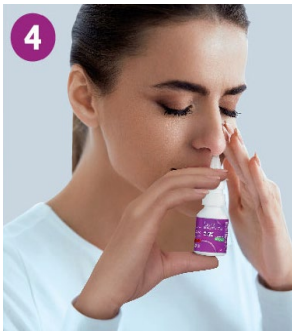
Parts of the Nasal Spray

STEP 1
Blow your nose gently.

STEP 2
Shake the bottle gently and then remove the protective dust cap.
Hold the bottle as shown with your forefinger and middle finger on either side of the nozzle and your thumb underneath the bottle.

STEP 3
If using for the first time or if you have not used it for a week or more, test the spray.
Testing of the spray: With the nozzle pointing away from you, press down a few times as shown until a fine mist comes out of the nozzle.

STEP 4
Close one nostril and hold the bottle as shown in step 2.
Tilt your head forward slightly and keeping the bottle upright, carefully insert the tip of the nozzle in the other nostril.



STEP 5
Start to breathe in through your nose and while breathing in, press down with your fingers once to release a spray.

STEP 6
Breathe out through your mouth. Repeat steps 5 and 6 to inhale a second spray.

STEP 7
Repeat steps 4,5 and 6 for the other nostril.

STEP 8
Wipe the nozzle with a clean handkerchief/ tissue and replace the protective dust cap.

IMPORTANT POINTS TO NOTE WHILE USING THE NASAL SPRAY

- DO NOT pierce the nozzle to use the nasal spray.

- DO NOT break the circular finger flange disc to use the spray.

- For effective use of the nasal spray, PRESS DOWN THE FINGER FLANGE DISC COMPLETELY.
  Incomplete or partial press will not release the medicine.