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

FLOMIST

(Fluticasone Propionate Aqueous Nasal Spray 50 mcg)

Each Spray Delivers:
Fluticasone Propionate BP 50mcg
Composition
Fluticasone propionate BP ..... 0.05% w/w
Benzalkonium chloride NF ..... 0.02% w/w
(As preservative)
Phenyl ethyl alcohol USP ..... 0.25% w/w
(As preservative)

Description
A white uniform, homogenous, redispersible suspension filled in White Opaque HDPE vial with crimped nasal spray assembly.

Pharmacology
PHARMACODYNAMICS
Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory activity. In vitro dose response studies on a cloned human glucocorticoid receptor system involving binding and gene expression afforded 50% responses at 1.25 and 0.17 nM concentrations, respectively. Fluticasone propionate was 3-fold to 5-fold more potent than dexamethasone in these assays. Data from the McKenzie vasoconstrictor assay in man also support its potent glucocorticoid activity.
In preclinical 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 (see Pharmacokinetics) 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. In 7 trials in adults, Flomist has decreased nasal mucosal eosinophils in 66% (35% for placebo) of patients and basophils in 39% (28% for placebo) of patients. The direct relationship of these findings to long-term symptom relief is not known.
Flomist, like other corticosteroids, is an agent that does not have an immediate effect on allergic symptoms. A decrease in nasal symptoms has been noted in some patients 12 hours after initial treatment with Nasal Spray. Maximum benefit may not be reached for several days. Similarly, when Flomist corticosteroids are discontinued, symptoms may not return for several days.

PHARMACOKINETICS
Limited data are available on the pharmacokinetics of fluticasone propionate following intranasal administration. Because of the drug's low systemic bioavailability when administered intranasally, most pharmacokinetic data for fluticasone propionate are based on studies in which the drug was administered IV or orally.

Absorption
Fluticasone propionate is poorly absorbed from the respiratory and GI tracts following nasal inhalation of the drug as an aqueous spray. Based on indirect calculations, intranasal fluticasone propionate has an absolute systemic bioavailability of less than 2%. A major portion of an intranasal dose of corticosteroids is swallowed and undergoes extensive first pass metabolism in the liver, (See pharmacokinetics: Elimination) in patients with allergic rhinitis receiving intranasal fluticasone propionate for 2-3 weeks, plasma concentrations were above the level of detection of the assay (50 pg/mL) only when recommended dosages were exceeded, and in those instances, only in occasional samples at low concentrations. Current evidence suggests that the therapeutic effects of intranasal fluticasone propionate can be attributed to the topical effects of the drug on the nasal mucosa. Limited data from studies in which radiolabeled fluticasone propionate has been administered orally indicate that the drug is poorly absorbed from the GI tract and undergoes rapid first-pass metabolism in the liver. Preliminary data from a dose-ranging study suggests that the amount of unchanged fluticasone propionate in plasma increases with dose following oral administration, but the bioavailability of the radiolabeled drug averaged about 1% or less after oral doses of 1-40 mg. Additional studies are needed to determine the oral bioavailability of fluticasone propionate.
Following oral administration of I or 16 mg of radiolabeled propionylfluticasone a few healthy individuals, peak plasma radioactivity levels (expressed as fluticasone propionate equivalents) averaging approximately 1.3 or 9.1 ng/mL, respectively, were achieved within 0.5-6 hours. Since no unchanged fluticasone propionate was detected in plasma for up to 6 hours after oral administration of unlabeled fluticasone propionate given on a separate occasion, the plasma radioactivity noted after administration of the radiolabeled drug was presumed to be fluticasone Propionate metabolites. It has been suggested that the presence of small amounts (50-70 pglmL) of fluticasone propionate in plasma from 6-24 hours after the dose in these individuals potentially may represent rectal reabsorption of unmetabolized drug. In patients with seasonal or perennial allergic or nonallergic rhinitis, the onset of symptomatic relief may occur within 12-48 hours of initiation of intranasal fluticasone propionate therapy in adults and within 36 hours in children; however, up to 2-4 days generally are required for optimum effectiveness ill most patients. Following discontinuance of intranasal fluticasone propionate therapy, symptoms of rhinitis generally do not recur for 1- 2 weeks

Distribution
Although fluticasone propionate is widely distributed into most tissues following IV administration, distribution of the drug following intranasal administration has not been described. Following IV administration, the volume of distribution for fluticasone propionate is 4.2 L/kg. Fluticasone propionate is approximately 91% bound to human plasma proteins; protein binding demonstrates no obvious relationship to drug concentration. Fluticasone propionate is weakly and reversibly bound to erythrocytes and equilibrates freely between erythrocytes and plasma. Fluticasone propionate is not appreciably bound to human transcortin (corticosteroid-binding globulin). Fluticasone propionate crosses the placenta in rats or rabbits following oral administration of fluticasone propionate 100 or 300 µg/kg, respectively (approximately 4 or 25 times, respectively, the maximum daily intranasal dosage in adults on a JLg/m2basis). It is not known if fluticasone propionate is distributed into human milk following intranasal administration; however, other corticosteroids are distributed into human milk. In lactating rats, subcutaneous administration of tritiated fluticasone propionate (10 µg/kg, approximately one-third the maximum recommended daily intranasal dosage in adults on a, $\mu g/m^2$ basis) resulted in measurable radioactivity in both plasma and milk.

Elimination
The apparent elimination half-life of fluticasone propionate after IV administration is approximately 3 hours. Plasma clearance of the drug ranges from 623-998 mL/minute; total blood clearance (plasma clearance adjusted for packed cell volume) of IV fluticasone propionate averages 1093 mL/minute and approximates that of liver blood flow, with renal clearance accounting for less than 0.02% of total body clearance. Fluticasone propionate is rapidly metabolized in the liver by the cytochrome P-450 isoenzyme CYP3A4; the principal metabolite is the inactive 17 β-carboxylic acid derivative. Following oral administration of radiolabeled drug, less than 5% of the dose was excreted in urine. Of the total radioactivity recovered in urine, 18% represented the fluticasone propionate, fecal recovery of unchanged drug was 9 and 20%, respectively, after a 1-mg dose and 54 and 75%, respectively, after a 16-mg dose. The increase in fecal excretion of unchanged fluticasone propionate with increased dose has been attributed to insolubility of the drug rather than to biliary elimination. The 17 β -carboxylic acid metabolite of fluticasone propionate accounted for 3-40% of fecal excretion. When a single oral 5-mg dose of fluticasone propionate was administered to patients with an ileostomy, 73% of the dose was recovered in the ileostomy effluent within 12 hours.

Indication
Flomist Aqueous Nasal Spray is indicated for the prophylaxis and treatment of seasonal allergic rhinitis including hayfever, and perennial rhinitis. Fluticasone propionate has potent anti-inflammatory activity but when used topically on the nasal mucosa has no detectable systemic activity.

Dosage and Administration
Flomist Aqueous Nasal Spray is for administration by the intranasal route only.

Adults and children over 12 years of age
For prophylaxis and treatment of seasonal allergic rhinitis and perennial rhinitis:-Two sprays into each nostril once a day, preferably in the morning . In some cases two sprays into each nostril twice daily might be required. The maximum daily dose should not exceed four sprays into each nostril.

Elderly
The normal adult dosage is applicable.

Children under 12 years of age
For prophylaxis and treatment of seasonal allergic rhinitis and perennial rhinitis in children aged 4-11 years:- One spray into each nostril once a day, preferably in the morning. In some cases one spray into each nostril twice daily may be required. The maximum daily dose should not exceed two sprays into each nostril. For full therapeutic benefit regular usage is essential. The absence of an immediate effect should be explained to the patient as maximum relief may not be obtained until after 3 to 4 days of treatment.

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Contraindications
FLOMIST is contraindicated in patients with a hypersensitivity to any of its ingredients.

Warning & Precautions
Local infections: infections of the nasal airways should be appropriately treated but do not constitute a specific contra-indication to treatment with Flomist Aqueous Nasal Spray.
The full benefit of Flomist Aqueous Nasal Spray may not be achieved until treatment has been administered for several days.
Care must be taken while transferring patients from systemic steroid treatment to Flomist Aqueous Nasal Spray if there is any reason to suppose that their adrenal function is impaired.
Although Flomist Aqueous Nasal Spray will control seasonal allergic rhinitis in most cases, an abnormally heavy challenge of summer allergens may in certain instances necessitate appropriate additional therapy.
Systemic effects of nasal corticosteroids may occur particularly at high doses prescribed for prolonged periods. These effects vary between patients and different corticosteroids (please refer to pharmacokinetic and pharmacodynamic information).
Growth retardation has been reported in children receiving some nasal corticosteroids at licensed doses. It is recommended that the height 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.
Treatment with higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. If there is evidence for higher than recommended doses being used then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.
Ritonavir can greatly increase the concentration of fluticasone propionate in plasma. Therefore, concomitant use should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. There is also an increased risk of systemic side effects when combining fluticasone propionate with other potent CYP3A inhibitors

Drug Interactions
Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.
In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome P450 3A4 inhibitor) 100 mg b.i.d. increased the fluticasone propionate plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol concentrations. Information about this interaction is lacking for inhaled fluticasone propionate, but a marked increase in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side-effects.

Pregnancy
There is inadequate evidence of safety in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development, including cleft palate and intra-uterine growth retardation. There may therefore be a very small risk of such effects in the human foetus. It should be noted, however, that the foetal changes in animals occur after relatively high systemic exposure; direct intranasal application ensures minimal systemic exposure.
As with other drugs the use of Flomist Aqueous Nasal Spray during human pregnancy requires that the possible benefits of the drug be weighed against the possible hazards.

Lactation
The secretion of fluticasone propionate in human breast milk has not been investigated. Subcutaneous administration of fluticasone propionate to lactating laboratory rats produced measurable plasma levels and evidence of fluticasone propionate in the milk. However, following intranasal administration to primates, no drug was detected in the plasma, and it is therefore unlikely that the drug would be detectable in milk. When Flomist Aqueous Nasal Spray is used in breast feeding mothers the therapeutic benefits must be weighed against the potential hazards to mother and baby

Side effect
Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. Rare and very rare events were generally determined from spontaneous data. In assigning adverse event frequencies, the background rates in placebo groups were not taken into account.

System Organ Class	Adverse Event	Frequency
Immune system disorders	Hypersensitivity reactions with the following manifestations:	
	Cutaneous hypersensitivity reactions	Very rare
	Angioedema (mainly facial and oropharyngeal oedema)	Very rare
	Respiratory symptoms (bronchospasm)	Very rare
	Anaphylactic reactions	Very rare
Nervous system disorders	Headache, unpleasant taste, unpleasant smell.	Common
Eye disorders	Glaucoma, raised intraocular pressure, cataract These events have been identified from spontaneous reports following prolonged treatment.	Very rare
Respiratory, Thoracic & Mediastinal disorders	Epistaxis	Very common
	Nasal dryness, nasal irritation, throat dryness, throat irritation.	Common
	Nasal septal perforation.	Very rare

As with other nasal sprays, unpleasant taste and smell and headache have been reported.
As with other nasal sprays, dryness and irritation of the nose and throat, and epistaxis have been reported.
Nasal septal perforation has also been reported following the use of intranasal corticosteroids.
Systemic effects of some nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods.

Overdosage
There are no data available on the effects of acute or chronic overdosage with Flomist Aqueous Nasal Spray.
Intranasal administration of 2 mg fluticasone propionate twice daily for seven days to healthy human volunteers has no effect on hypothalamo-pituitary-adrenal (HPA) axis function.
Inhalation or oral administration of high doses of corticosteroids over a long period may lead to suppression of HPA axis function.

Storage
Store below 30°C.

Shelf life
24 Months

Presentation:
White Opaque HDPE vial of 100 metered Doses.

Registration Holder in Malaysia
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NASAL SPRAY

SAP Code: XXXXXXXX (Ver. 01)
Leaflet size: 200 x 160 mm
Size after folding: 25 x 160 mm
Colours:

Black

Reference / Supersedes: 460LU
Ph_code :
Country : Malaysia
Date: 02-03-2023

Path: PC: F:\Users\vaibhav.sawant1\OneDrive - Cipla Limited\Vaibhav\Vinod\Malaysia\xxxxxxxx Asthalin Respules Leaflet Malaysia.ai