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ANSONIDE NASAL SPRAY 27.5 mcg/dose

NAME AND STRENGTH OF ACTIVE SUBSTANCE:
Fluticasone Furoate 27.5 mcg/dose (Equivalent to 0.055% w/v)

PRODUCT DESCRIPTION:
An opaque off-white slight viscous suspension. Other ingredients are containing Benzalkonium Chloride, Polysorbate 80, Microcrystalline Cellulose and Carboxymethylcellulose Sodium, Dextrose Anhydrous, Disodium Edetate & Purified Water.

PHARMACODYNAMIC:
Mechanism of Action: Fluticasone furoate is a synthetic trifluorinated corticosteroid that possesses a very high affinity for the glucocorticoid receptor and has a potent anti-inflammatory action.

PHARMACOKINETICS:
Absorption: Fluticasone furoate undergoes extensive first-pass metabolism and incomplete absorption in the liver and gut resulting in negligible systemic exposure. The intranasal dosing of 110 micrograms once daily does not typically result in measurable plasma concentrations (less than 10 picograms/mL). The absolute bioavailability for fluticasone furoate administered as 880 micrograms three times per day (2640 micrograms total daily dose) is 0.50%. **Distribution:** The plasma protein binding of fluticasone furoate is greater than 99%. Fluticasone furoate is widely distributed with volume of distribution at steady-state of, on average, 608 L. **Metabolism:** Fluticasone furoate is rapidly cleared (total plasma clearance of 58.7L/h) from systemic circulation principally by hepatic metabolism to an inactive 17 beta-carboxylic metabolite (GW694301X), by the cytochrome P450 enzyme CYP3A4. The principal route of metabolism was hydrolysis of the S-fluoromethyl carbothioate function to form the 17 beta-carboxylic acid metabolite. *In vivo* studies have revealed no evidence of cleavage of the furoate moiety to form fluticasone. **Elimination:** Elimination was primarily via the faecal route following oral and intravenous administration indicative of excretion of fluticasone furoate and its metabolites via the bile. Following intravenous administration, the elimination phase half-life averaged 15.1 hours. Urinary excretion accounted for approximately 1% and 2% of the orally and intravenously administered dose, respectively.

Special Patient Populations
Elderly: Only a small number of elderly subjects (n=23/872; 2.6%) provided pharmacokinetic data. There was no evidence for a higher incidence of subjects with quantifiable fluticasone furoate concentrations in the elderly, when compared to the younger subjects. **Children:** Fluticasone furoate is typically not quantifiable (less than 10 picograms/mL) following intranasal dosing of 110 micrograms once daily. Quantifiable levels were observed in less than 16% of paediatric patients following intranasal dosing of 110 micrograms once daily and only less than 7% of paediatric patients following 55 micrograms once daily. There was no evidence for a higher incidence of quantifiable levels of fluticasone furoate in younger children (less than 6 years of age). **Renal Impairment:** Fluticasone furoate is not detectable in urine from healthy volunteers after intranasal dosing. Less than 1% of dose-related material is excreted in urine and therefore renal impairment would not be expected to affect the pharmacokinetics of fluticasone furoate. **Hepatic Impairment:** There are no data on intranasal fluticasone furoate in subjects with hepatic impairment. Data are available following inhaled administration of fluticasone furoate (as fluticasone furoate or fluticasone furoate/vilanterol) to subjects with hepatic impairment that are also applicable for intranasal dosing. A study of a single 400 microgram dose of orally inhaled fluticasone furoate in patients with moderate hepatic impairment (Child-Pugh B) resulted in increased Cmax (42%) and $AUC_{(0-\infty)}$(172%) compared to healthy subjects. Following repeat dosing of orally inhaled fluticasone furoate/vilanterol for 7 days, there was

an increase in fluticasone furoate systemic exposure (on average two-fold as measured by $AUC_{(0-24)}$) in subjects with moderate or severe hepatic impairment (Child-Pugh B or C) compared with healthy subjects. The increase in fluticasone furoate systemic exposure in subjects with moderate hepatic impairment (fluticasone furoate/vilanterol 200/25 micrograms) was associated with an average 34% reduction in serum cortisol compared with healthy subjects. There was no effect on serum cortisol in subjects with severe hepatic impairment (fluticasone furoate/vilanterol 100/12.5 micrograms). Based on these findings the average predicted exposure for 110 micrograms of intranasal fluticasone furoate in patients population would not be expected to result in suppression of cortisol. **Other pharmacokinetic:** Fluticasone furoate is typically not quantifiable (less than 10 picograms/mL) following intranasal dosing of 110 micrograms once daily. Quantifiable levels were only observed in less than 31% of patients aged 12 years and above and in less than 16% of paediatric patients following intranasal dosing of 110 micrograms once daily. There was no evidence for gender, age (including paediatrics), or race to be related to those subjects with quantifiable levels, when compared to those without.

INDICATIONS:
Adults and Adolescents (12 years and older): Treatment of the nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing) and ocular symptoms (itching/burning, tearing/watering, and redness of the eye) of seasonal allergic rhinitis. Treatment of the nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing) of perennial allergic rhinitis. **Children (2 to 11 years):** Treatment of the nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing) of seasonal and perennial allergic rhinitis

ROUTE OF ADMINISTRATION: For intranasal use only.

RECOMMENDED DOSAGE:
Ansonide Nasal Spray is for administration by the intranasal route only. For full therapeutic benefit, regular scheduled usage is recommended. Onset of action has been observed as early as 8 hours after initial administration. It may take several days of treatment to achieve maximum benefit. An absence of an immediate effect should be explained to the patient. **Populations:** For the treatment of seasonal allergic rhinitis and perennial allergic rhinitis: **Adults and Adolescents (12 years and older):** The recommended starting dosage is 2 sprays (27.5 micrograms per spray) in each nostril once daily (total daily dose, 110 micrograms). Once adequate control of symptoms is achieved, dose reduction to 1 spray in each nostril once daily (total daily dose, 55 micrograms) may be effective for maintenance. **Children (2 to 11 years):** The recommended starting dosage is 1 spray (27.5 micrograms per spray) in each nostril once daily (total daily dose, 55 micrograms). Patients not adequately responding to 1 spray in each nostril once daily (total daily dose, 55 micrograms) may use 2 sprays in each nostril once daily (total daily dose, 110 micrograms). Once adequate control of symptoms is achieved, dose reduction to 1 spray in each nostril once daily (total daily dose, 55 micrograms) is recommended. **Children (under 2 years of age):** There are no data to recommend use of Ansonide Nasal Spray for the treatment of seasonal or perennial allergic rhinitis in children under 2 years of age. **Elderly:** No dosage adjustment required. **Renal Impairment:** No dosage adjustment required. **Hepatic Impairment:** No dosage adjustment is required in patients with hepatic impairment.

CONTRAINDICATIONS: Fluticasone furoate nasal spray is contra-indicated in patients with hypersensitivity to any of the ingredients.

WARNINGS AND PRECAUTIONS:
Based on data with another glucocorticoid metabolised by CYP3A4, co-administration with ritonavir is not recommended because of the potential risk of increased systemic exposure to fluticasone furoate. Systemic effects with nasal corticosteroids have been reported, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur

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than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations. A reduction in growth velocity has been observed in children treated with fluticasone furoate 110 micrograms daily for one year. Therefore, children should be maintained on the lowest dose which delivers adequate symptom control. As with other intranasal corticosteroids, physicians should be alert to potential systemic steroid effects including ocular changes such as central serous chorioretinopathy.

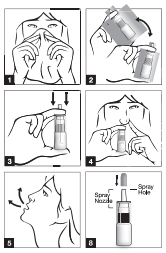
DRUG INTERACTIONS WITH OTHER MEDICAMENTS:
Fluticasone furoate is rapidly cleared by extensive first pass metabolism mediated by the cytochrome P450 3A4. In a drug interaction study of intranasal fluticasone furoate with the potent CYP3A4 inhibitor ketoconazole, there were more subjects with measurable fluticasone furoate plasma concentrations in the ketoconazole group (6 of the 20 subjects) compared to placebo (1 of the 20 subjects). This small increase in exposure did not result in a statistically significant difference in 24 hour serum cortisol levels between the two groups. The enzyme induction and inhibition data suggest that there is no theoretical basis for anticipating metabolic interactions between fluticasone furoate and the cytochrome P450 mediated metabolism of other compounds at clinically relevant intranasal doses. Therefore, no clinical studies have been conducted to investigate interactions of fluticasone furoate on other drugs.

PREGNANCY & LACTATION:
Adequate data are not available regarding the use of Ansonide Nasal Spray during pregnancy and lactation in human. Ansonide Nasal Spray should be used in pregnancy only if the benefits to the mother outweigh the potential risks to the foetus. **Fertility:** There are no data in humans. **Pregnancy:** Following intranasal administration of Ansonide Nasal Spray at the maximum recommended human dose (110 micrograms/day), plasma fluticasone furoate concentrations were typically non-quantifiable and therefore potential for reproductive toxicity is expected to be very low. **Lactation:** The excretion of fluticasone furoate into human breast milk has not been investigated.

ADVERSE EFFECTS:

System Organ Class	Common	Very Common	Uncommon	Not Known	Rare	Very Rare
Respiratory, thoracic & mediastinal disorders	Nasal ulceration	Epistaxis	Rhinalgia, nasal discomfort (including nasal burning, nasal irritation, and nasal soreness), nasal dryness			Nasal septum perforation
Musculoskeletal and connective tissue disorders				Growth retardation in children		
Immune system disorders					Hypersensitivity, reactions including anaphylaxis, angioedema, rash & urticaria	
Nervous system disorders	Headache					

DIRECTION FOR USE:



1. Blow the nose gently to clear nostrils.
2. Shake the bottle gently. Remove the cap.
3. For first time use, hold the bottle upright and fill the pump by pressing the nozzle downwards and releasing it 5 times, until a fine spray is produced.
4. Close one nostril with finger. Hold the bottle upright and insert the nozzle into the nostril as far as is comfortable. Whilst breathing in gently through the nose with the mouth closed, press the bottle upwards once to deliver one spray.
5. Breathe out through the mouth.
6. Repeat steps 4 and 5 for the other nostril.
7. For patients aged 12 years and older, steps 4, 5 and 6 should be repeated once more to achieve the recommended dosage of 2 sprays into each nostril.
8. To keep the spray nozzle clean, wipe it carefully with a clean tissue after each use and replace back the cap.

If the nasal spray has not been used for 2 weeks or more, it needs to be sprayed once into the air before use. The nozzle should be pointed away while doing this. Always shake the bottle gently before use. If the spray does not work and it may be blocked, clean it as follows. ***(See Directions for Cleaning).*** NEVER try to unblock it or enlarge the tiny spray hole with a pin or other sharp object because this will destroy the spray mechanism. The nasal spray should be cleaned at least once a week or more often if it gets blocked.

DIRECTIONS FOR CLEANING:
1. Remove the cap and pull off the spray nozzle only.
2. Soak the dust-cap and spray nozzle in warm water for a few minutes, and then rinse under cold running tap water.
3. Shake or tap off the excess water and allow to air-dry.
4. Re-fit the spray nozzles.
5. Prime the unit as necessary until a fine mist is produced and use as normal.

SYMPTOMS AND TREATMENT FOR OVERDOSE AND ANTIDOTE(S):
In a bioavailability study, intranasal doses of up to 24 times the recommended daily adult dose were studied over three days with no adverse systemic effects observed (see Pharmacokinetics).
Treatment: Acute overdose is unlikely to require any therapy other than observation.

STORAGE CONDITION: Store below 30°C. Keep out of reach of children. Jauhi daripada kanak-kanak.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE:
Based on the pharmacology of fluticasone furoate and other intranasally administered steroids, there is no reason to expect an effect on ability to drive or to operate machinery with Ansonide Nasal Spray.

PACKING: 10ml (60 doses) and 15ml (120 doses) HDPE bottle.

RECOMMENDED SHELF-LIFE:
2 years (unopened). This medicine should be used within 60 days after first opening.

MANUFACTURED BY:
HOE Pharmaceuticals Sdn Bhd
Lot 10, Jalan Sultan Mohamed 6, Bandar Sultan Suleimen, 42000 Port Klang, Selangor, Malaysia.

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