PRODUCT MONOGRAPH

[Pr]APO-FLUNISOLIDE Nasal Spray
(Flunisolide Nasal Solution USP), 0.025%

CORTICOSTEROID FOR NASAL USE

Apotex Inc.
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DATE OF PREPARATION:
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PRODUCT MONOGRAPH

NAME OF DRUG

APO-FLUNISOLIDE Nasal Spray
(Flunisolide Nasal Solution USP), 0.025%

THERAPEUTIC CLASSIFICATION

Corticosteroid for Nasal Use

ACTIONS AND CLINICAL PHARMACOLOGY

Flunisolide has demonstrated marked anti-inflammatory and anti-allergic efficacy in classical animal test systems. It is a corticosteroid which is several hundred times more potent in animal anti-inflammatory assays than the cortisol standard. Clinical studies with flunisolide have shown a topical activity on the nasal mucous membrane with minimal associated systemic activity at the low spray doses administered. The improvement of symptoms is based on its direct local effect rather than on indirect effect through systemic absorption.

INDICATIONS AND CLINICAL USE

Flunisolide nasal solution is indicated for the treatment of perennial and seasonal allergic rhinitis when tolerance to or effectiveness of conventional treatment is unsatisfactory.

CONTRAINDICATIONS

Active or quiescent tuberculosis or untreated fungal, bacterial or viral infections. Hypersensitivity to the product. Children under 6 years of age.

WARNINGS

Glucocorticoids may mask some signs of infection, and new infections may appear during their use.

Pregnancy

Safety in pregnancy has not been established. Use of flunisolide during the first 3 months of pregnancy is not recommended. If used during the second and third trimester, weigh the expected benefits against the potential hazards to the fetus.

In patients previously on high doses of systemic corticosteroids, withdrawal of steroids may cause symptoms such as tiredness, aches and pains and depression. In severe cases, adrenal insufficiency may occur necessitating a temporary resumption of systemic corticosteroids.

Flunisolide is not recommended for those patients with a history of recurrent nasal bleeding.

PRECAUTIONS

Replacement of systemic corticosteroids with flunisolide should be gradual and carefully monitored by a physician.

Although absorption sufficient to produce systemic effects has not been shown in clinical studies with flunisolide nasal solution, the potential of adrenal suppression still exists and this must be considered as a possibility with prolonged excessive usage. Patients on long-term therapy should be reassessed periodically to avoid unnecessary continued use.

Since onset of action may be somewhat slower than that of topical or oral sympathomimetic amines or antihistamines, it should be used for several days before evaluating therapy.

If beneficial effect is not evident after approximately 7 days, re-evaluate the patient.

If hypersensitivity reactions occur, discontinue therapy and institute appropriate treatment.

Corticosteroid therapy can decrease resistance to localized infection. If nasopharyngeal infections occur during therapy, institute appropriate treatment.

Despite the very low absorption of flunisolide when administered intranasally, the following must be kept in mind: a) corticosteroid effects may be enhanced in patients with hypothyroidism and in those with cirrhosis. b) in hypoprothrombinemia, acetylsalicylic acid should be used cautiously in conjunction with corticosteroids.

Advise patients to inform subsequent physicians of the prior use of corticosteroids.

During local corticosteroid therapy, the possibility of atrophic rhinitis and/or pharyngeal candidiasis should be kept in mind.

Flunisolide should not be used during an asthmatic attack.

Because of the inhibitory effect of corticosteroids on wound healing, in patients who have had recent nasal septal ulcers, recurrent epistaxis, nasal surgery or trauma, a nasal corticosteroid should be used with caution until healing has occurred.

ADVERSE REACTIONS

Side effects noted have been consistent with what one would expect in applying a topical medication to an already inflamed membrane. The most frequent side effects observed were aftertaste and a mild, transient nasal burning and stinging. Occasionally, this was severe enough to warrant discontinuation of flunisolide therapy.

Other adverse effects seen in patients, in order of decreasing prevalence were: nasal irritation, epistaxis, runny and stuffy nose, sore throat, hoarseness, throat irritation, change or loss in the sense of smell or taste and nasal septal perforation. Exceptionally, these may require discontinuation of therapy. Rarely, a permanent loss in the sense of smell and/or taste has been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute overdosage has not been reported. When used at excessive doses, the potential of steroid effects such as hypercorticism and adrenal suppression does exist. Decreasing the dose will abolish these manifestations.

DOSAGE AND ADMINISTRATION

Flunisolide nasal solution is for administration by the intranasal route only.

Usual Starting Dose

Adults:
2 sprays (each approximately 25 μg) into each nostril twice a day. Increase to 3 times a day if needed.

Children:
For children 6 to 14 years of age, one spray (approximately 25 μg) into each nostril 3 times daily.

Maintenance Dose

After the desired clinical effect is obtained, the maintenance dose should be the smallest amount necessary to control the symptoms. Some patients may be maintained on as little as one spray (approximately 25 μg) to each nostril per day. Patients on long-term therapy should be reassessed periodically to avoid unnecessary continued use. There is no evidence that exceeding the

maximum recommended dosage is more effective. Therefore, maximum daily dose should not exceed 6 sprays in each nostril for adults and 3 sprays in each nostril for children 6 to 14 years of age.

The effect of flunisolide, unlike that of vasoconstrictors, is not immediate. Full therapeutic benefit requires regular usage. Explain the absence of an immediate effect to the patient in order to ensure cooperation and continuation of treatment with the regular dosage schedule.

In the presence of excessive nasal mucus secretion or edema of the nasal mucosa, the drug may fail to reach the site of action. In such cases, use the nasal vasoconstrictor for two to three days prior to flunisolide.

For full details on using the device, see INFORMATION FOR THE PATIENT.

PHARMACEUTICAL INFORMATION

Drug Substance

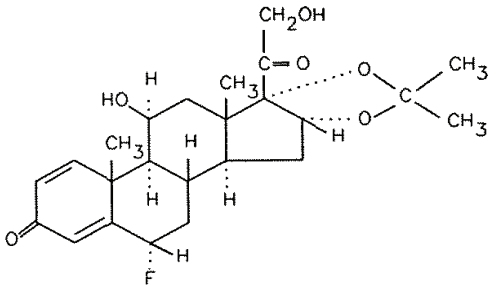
Common Name: Flunisolide (anhydrous)

Chemical Name(s):

1) Pregna-1,4-diene-3,20-dione,6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)], (6α,11β,16α)-;

2) 6α-Fluoro-11β,16α,17,21-tetrahydroxy-pregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone.

Structural Formula:



Molecular Formula: $C_{24}H_{31}FO_6$

Molecular Weight: 434.51

Description

Flunisolide is a white to creamy-white crystalline powder. Melts at about 245°C, with decomposition. Practically insoluble in water; soluble in acetone, sparingly soluble in chloroform; slightly soluble in methanol.

Composition

APO-FLUNISOLIDE (flunisolide) Nasal Spray contains the following inactive ingredients: benzalkonium chloride, butylated hydroxytoluene, citric acid (anhydrous), edetate disodium, polyethylene glycol, polysorbate 20 (Tween 20), propylene glycol, purified water, sodium citrate (hydrous) and sorbitol crystalline fines. Sodium hydroxide and/or hydrochloric acid may be used to adjust the pH.

Stability and Storage Recommendations

Store at room temperature (15-30°C).

AVAILABILITY OF DOSAGE FORMS

APO-FLUNISOLIDE (flunisolide) Nasal Spray is a 0.025% aqueous solution of flunisolide in a 25 mL plastic bottle fitted with a metered pump device which delivers approximately 25 µg of flunisolide per spray via a nozzle which is inserted into the nostril.

INFORMATION FOR THE PATIENT

INSTRUCTIONS TO THE PATIENT

APO-FLUNISOLIDE Nasal Spray
(Flunisolide Nasal Solution USP), 0.025%

CORTICOSTEROID FOR NASAL USE

- Use regularly as directed by your physician.
- Do not exceed the prescribed dose.
- APO-FLUNISOLIDE Nasal Spray is not intended to give immediate relief of your nasal symptoms and it may take a few days (and up to 2 weeks) before you notice any improvement.
- Contact your physician if:
  - no improvement occurs after 3 weeks
  - nasal irritation occurs
  - coloured (yellow or green) nasal secretions appear
  - repeated nasal bleeding occurs

DOSAGE

Usual Starting Dose:

Adults: 2 sprays (each approximately 25 µg**)** into each nostril twice a day. Increase to 3 times a day if needed.

Children: For children 6 to 14 years of age, one spray (approximately 25 µg**)** into each nostril 3 times daily.

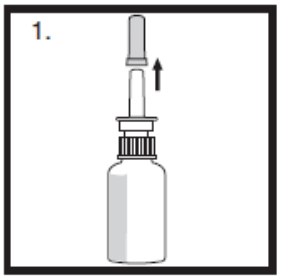
Maintenance Dose:

After the desired clinical effect is obtained, the maintenance dose should be the smallest amount necessary to control the symptoms. Some patients may be maintained on as little as one spray (approximately 25 µg) to each nostril per day. Patients on long-term therapy should be reassessed periodically to avoid unnecessary continued use. There is no evidence that exceeding the maximum recommended dosage is more effective. Therefore, maximum daily dose should not exceed 6 sprays in each nostril for adults and 3 sprays in each nostril for children 6 to 14 years of age.

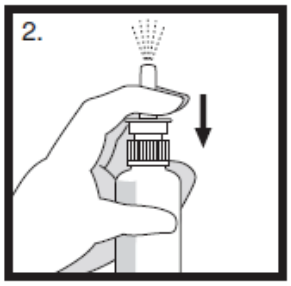
Note: Flunisolide is not intended to give immediate relief of your nasal symptoms and it may take a few days (and up to 2 weeks) before you notice any improvement.

PREPARATION

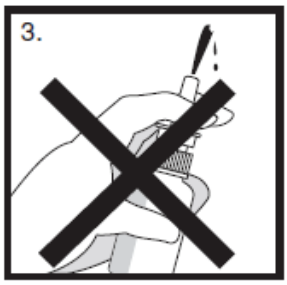
1) Remove the protective cap from the atomizer. **Do not attempt to enlarge the tiny hole in the atomizer**.



2) Hold the atomizer away from you and load the pump by rapidly and firmly pressing downwards (seven to eight times) on the white collar using your index and middle fingers while supporting the base of the bottle with your thumb as illustrated. Press down until a fine mist is produced. The atomizer is now ready for use and will not require repriming (reloading) unless used infrequently or disassembled.

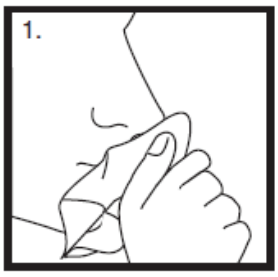


3) If the solution is delivered in a stream of liquid, it may fail to provide maximum benefit and cause some discomfort. A fine mist can only be produced by a rapid and firm pumping action.

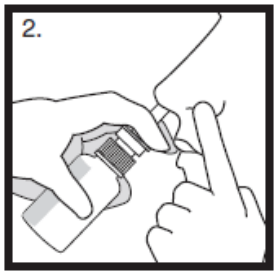


HOW TO USE - ADMINISTRATION AND MAINTENANCE

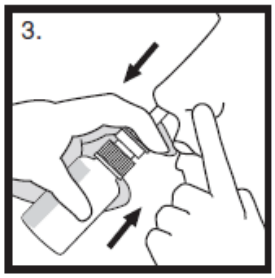
1) Gently blow the nose to clear the nostrils prior to administration of APO-FLUNISOLIDE Nasal Spray.



2) Hold the atomizer as shown. Tilt the head forward slightly, close one nostril with a finger and gently insert the tip of the atomizer into the other nostril.



3) Point the atomizer toward back of nostril and pump firmly and sharply to produce a fine mist.



4) Remove the atomizer and tilt head backwards, allowing medication to spread over back of nose. Repeat the procedure in the other nostril. Replace the protective cap.

5) If your doctor has prescribed more than one spray in each nostril, for subsequent sprays the atomizer should be pointed in different directions in order for the mist to cover a wider area of the nasal passages.

In case you experience some discomfort during the first application, prolong the interval between sprays, (two or three minutes).

6) Should a blockage occur, remove the atomizer from the bottle and soak in warm water for a few minutes. Then shake off water and pump rapidly four or five times. Replace atomizer on bottle and re-prime as in Preparation 2 above. **Never pierce the nasal adapter.**

PHARMACOLOGY

Animal Pharmacology

Flunisolide was found to have potent systemic thymolytic and anti-inflammatory activity in the adrenalectomized rat, having 320 and approximately 180 times the thymolytic and anti-granuloma potencies of cortisol, respectively, when given subcutaneously. It also demonstrated potent topical anti-inflammatory activity, having 190 times the topical anti-inflammatory potency of cortisol, and 1.3 times the potency of fluocinolone acetonide in inhibiting croton oil-induced inflammation in the rat ear. Given subcutaneously, the compound demonstrated approximately 800 times the adrenal inhibitory potency of cortisol. Flunisolide did not alter sodium excretion at doses up to 670 μg/kg, however, a dose as low as 6.7 μg/kg did cause a significant increase in urinary potassium. The test material also inhibited a delayed dermic hypersensitivity reaction in the mouse. It also inhibited both reaginic and non-reaginic passive cutaneous anaphylactic reactions in the rat. In this respect it acted synergistically when given with the β-agonist, isoproterenol.

Clinical Pharmacology

In human tolerance studies involving 20 normal volunteers, the plasma cortisol and 24-hour urinary 17-ketogenic steroids remained within the normal range. The doses varied from 500 μg to 700 μg a day for 10 days and 700 μg to 2200 μg a day for 4 days (up to 5 times the maximum daily recommended therapeutic dose in the adult).

Following the intravenous or oral administration of a single dose of 2 mg ^{14}C-labelled flunisolide to man, approximately half of the labelled compound was recovered in urine and half in stool; of the material recovered in urine, 65-70% was a metabolite, 6β, 11β, 16α, 17α, 21-pentahydroxy-pregna-1, 4-diene-3, 20-dione 16,17-acetonide. Orally administered flunisolide was well absorbed but was rapidly and extensively metabolized to conjugates and to the above metabolite, all of which appear to be relatively inactive. Since a sizeable portion of an intranasally administered dose of flunisolide might be expected to be swallowed, this rapid and extensive metabolism of oral flunisolide may be responsible for the lack of systemic glucocorticoid effects noted in clinical trials. The plasma half-life of flunisolide was 1-2 hours.

TOXICOLOGY

Acute Toxicity

Flunisolide, when given intravenously to mice, rats and dogs, caused no mortalities in the 21 day observation period after administration of single doses of 4.0 mg/kg. The intravenous LD_{50}'s in these species are greater than 4.0 mg/kg.

Subacute and Chronic Toxicity

Subacute and chronic toxicity studies were carried out in a variety of species by intravenous and oral administration, inhalation (solution or powder) or nasal insufflation (solution). Systemic effects which are typical for overdosage with corticosteroids were seen in most of these studies. These included reduced body weight gains, histologic changes in the adrenal glands, liver,

lymphoid, gastric and intestinal tissues, reduced eosinophil levels, leucocytosis and increased urine volumes with corresponding decreases in specific gravity.

A 0.025% solution of flunisolide was administered twice daily for one year by nasal insufflation to dogs and rabbits. The usual systemic effects associated with overdosage of corticosteroids were evident in both species. In rabbits the upper respiratory tract was not affected. In dogs decreased numbers of mast cells and vacuolation of nasal epithelial cells were evident in the turbinates, primarily in the high dose animals. In neither species were there meaningful changes in the nasal septa.

Carcinogenicity

A two-year carcinogenicity study was conducted in male and female rats. The animals received flunisolide by gavage at dose levels of 0, 0.5, 1.0, and 2.0 µg/kg/day for two years. Each active treatment group had a corresponding control group and there were 55 males and 55 females per treatment group. The animals were subjected to thorough clinical examinations once every week during the treatment period.

Two hundred and thirty six animals (36%) survived until the termination of the study. There were no statistically significant differences in cumulative survival rates.

Clinical signs such as alopecia, body straining, pustules on the tail and swollen ears, seen in the study were those commonly observed in this strain of ageing rats.

Necropsies were carried out on all animals and a full range of tissues were examined. There was a slight increase in the numbers of females with malignant mammary tumours at the high dose relative to control and mid- and low-dose animals. The increase in the number of adenocarcinomas in high dose females is considered to be the result of chronic endocrine disturbances.

There was an increased incidence of pancreatic islet-cell adenomas in treated females albeit without evidence of an increase in islet cell hyperplasia or carcinoma. In addition, there was considerable variation in islet-cell adenomas in male control groups. However, given the biological variation in controls and the lack of increases in hyperplasia or carcinoma, the islet-cell adenoma finding is not considered biologically meaningful.

Among the high dose males, there was a small statistically significant increase in hepatocellular carcinoma. Since there were no potential pre-neoplastic changes, these findings are not considered biologically meaningful.

It is concluded that administration of flunisolide to rats, has, with the exception of mammary gland, had no influence on the numbers of tumours found.

Teratology

Glucocorticoids are known teratogens in rodent species and flunisolide is no exception. At oral doses of 1.0 mg/kg and higher, flunisolide was fetotoxic in rats and no live litters were obtained in

these groups. At lower doses cleft palates and reduction in ossification were evident. In rabbits, doses of flunisolide of0.04 mg/kg and higher were fetotoxic and teratogenic.

Reproduction

Flunisolide was administered to rats by the oral route at doses of 0.008, 0.040 and 0.200 mg/kg from 14 days before mating through weaning of pups in one experiment and from day 14 of pregnancy until weaning in a second study. The mid- and high-doses were fetotoxic and teratogenic. Results in the low dose groups were not different from the controls. Administration by inhalation of 0.52 or 2.60 mg/kg/day for 6 months to male mice did not affect fertility or reproductive capacity.

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