PRODUCT MONOGRAPH

pms-FLUNISOLIDE
Nasal Mist

(Flunisolide solution U.S.P.)
0.025%

Corticosteroid for Nasal Use

Pharmascience Inc.
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Control # 061493

PRODUCT MONOGRAPH

NAME OF DRUG

pms-FLUNISOLIDE
Nasal Mist
(flunisolide solution U.S.P.)
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. When administered intranasally in therapeutic doses, it has a direct anti-inflammatory action on the nasal mucosa. The minute amount absorbed in therapeutic doses has not been shown to exert any apparent clinical systemic effects. Although the precise mechanism of action of topical flunisolide remains unclear, results of a recent study suggest that inhibition of inflammatory mediator release during the early phase of an allergic reaction may contribute to its clinical effectiveness.

A double-blind parallel group clinical study was conducted to compare the efficacy and safety of pms-FLUNISOLIDE Nasal Mist (flunisolide) and Rhinalar® (Syntex) in the treatment of allergic rhinitis. The study was conducted on 48 patients who had a history of perennial rhinitis symptoms for at least 3 months duration. Following a 2-week baseline observation period patients were randomly assigned to 4 weeks of treatment with either pms-FLUNISOLIDE or Rhinalar®.

The two drugs significantly reduced the symptoms burden and did not produce significantly different

side effects. No significant difference was observed in either the physician's assessment or the patients' assessment of the treatment. The two drugs do not differ significantly on their effect on symptoms and on rhinomanometry. Both drugs were found to be safe and effective in controlling the symptoms of perennial rhinitis.

INDICATIONS AND CLINICAL USE

pms-FLUNISOLIDE Nasal Mist (flunisolide) is indicated for treatment of perennial and seasonal allergic rhinitis when tolerance to or effectiveness of conventional treatment is unsatisfactory.

CONTRAINDICATIONS

1. Active or quiescent tuberculosis or untreated fungal, bacterial or viral infections.

2. Hypersensitivity to flunisolide or propylene and polyethylene glycols, the vehicles in the flunisolide solution.

WARNINGS

1. In patients previously on prolonged periods or high doses of systemic steroids, the replacement with a topical corticosteroid can be accompanied by symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression and, in severe cases adrenal insufficiency may occur, necessitating the temporary resumption of systemic steroid therapy.

2. Careful attention must be given to patients with asthma or other clinical conditions in whom a rapid decrease in systemic steroids may cause a severe exacerbation of their symptoms.

3. Pregnancy: See PRECAUTIONS

PRECAUTIONS

1. The replacement of a systemic steroid with flunisolide has to be gradual and carefully supervised by the physician. The guidelines under ADMINISTRATION should be followed in all such cases.

2. During long-term therapy, pituitary-adrenal function and hematological status should be assessed periodically to avoid unnecessary continued use.

3. Patients should be informed that the full effect of flunisolide therapy is not achieved until 2 to 3 days of treatment have been completed. Treatment of seasonal rhinitis should, if possible, start before exposure to allergens.

4. Treatment with flunisolide should not be stopped abruptly but tapered off gradually.

5. Corticosteroids may mask some signs of infection and new infections may appear. A decreased resistance to localized infections has been observed during corticosteroid therapy this may require treatment with appropriate therapy or stopping the administration of flunisolide.

6. The long-term effects of flunisolide are still unknown, in particular, its local effects; the possibility of atrophic rhinitis and/or pharyngeal candidiasis should be kept in mind.

7. There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis. Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypothrombinemia.

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

9. Patients should be advised to inform subsequent physicians of prior use of corticosteroids.

10. Until greater clinical experience has been gained, long-term treatment of children under age 14 is not recommended.

11. Pregnancy

The safety of flunisolide in pregnancy has not been established. If used, the expected benefits should be weighed against the potential hazard to the fetus, particularly during the first trimester of pregnancy.

Like other glucocorticosteroids, flunisolide is teratogenic to rodent species (see under TOXICOLOGY). The relevance of these findings to humans has not yet been established. Infants born of mothers who have received substantial doses of glucocorticosteroids during pregnancy should be carefully observed for hypoadrenalism.

12. Lactation

Glucocorticosteroids are secreted in human milk. It is not known whether flunisolide would be secreted in human milk, but it is suspected to be likely. The use of flunisolide in nursing mothers, requires that the possible benefits of the drug be weighed against the potential hazards to the infant.

13. Children

Flunisolide is not recommended for children younger than 6 years of age due to limited clinical data in this age group.

14. To ensure the proper dosage and administration of the drug, the patient should be instructed by a physician or other health professionals in the use of pms-FLUNISOLIDE Nasal Mist (flunisolide). (See INSTRUCTIONS TO THE PATIENT).

ADVERSE REACTIONS

Most of the side effects noted with intranasal flunisolide have been related to the topical application of a medication to an already inflamed nasal membrane. The most frequent side effect observed was a mild transient nasal burning and stinging. Occasionally this was severe enough to warrant discontinuation of flunisolide therapy. However, recent studies have shown that a reduction in the concentration of propylene glycol, a preservative used in the vehicle, has reduced the incidence of nasal burning and stinging. Other side effects seen in patients treated with flunisolide, in order of decreasing prevalence were: nasal irritation, epistaxis, runny and stuffy nose, sore throat,

hoarseness and throat irritation. These side effects have rarely required discontinuation of therapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Like any other nasally administered corticosteroid, acute overdosing is unlikely in view of the total amount of active ingredient present. However when used chronically in excessive doses or in conjunction with other corticosteroid formulations, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes recur, the dosage of flunisolide should be discontinued slowly, consistent with accepted procedures for discontinuation of chronic steroid therapy. (see DOSAGE AND ADMINISTRATION).

The restoration of hypothalamic-pituitary-axis may be slow; during periods of pronounced physical stress (i.e. severe infections, trauma, surgery) a supplement with systemic steroids may be advisable.

DOSAGE AND ADMINISTRATION

pms-FLUNISOLIDE Nasal Mist (flunisolide) is not recommended for children under 6 years of age.

pms-FLUNISOLIDE Nasal Mist is for administration by the intranasal route only.

Careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids when transferred to flunisolide. Initially, flunisolide and the systemic corticosteroid must be given concomitantly, while the dose of the latter is gradually decreased. The usual rate

of withdrawal of the systemic steroid is the equivalent of 2.5 mg of prednisone every four days if the patient is under close supervision. If continuous supervision is not feasible, the withdrawal of the systemic steroid should be slower, approximately 2.5 mg of prednisone (or equivalent) every ten days. If withdrawal symptoms appear, the previous dose of the systemic steroid should be resumed for a week before further decrease is attempted.

The therapeutic effects of corticosteroids, unlike those of decongestants, are not immediate. Since the effect of flunisolide depends on its regular use, patients must be instructed to take the nasal inhalations at regular intervals and not as with other nasal sprays, as they feel necessary.

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, it is advisable to use a nasal vasoconstrictor for two to three days prior to pms-FLUNISOLIDE Nasal Mist.

Usual starting dose

Adults: 2 sprays (each approximately 25 mcg) 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 mcg) 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 mcg) 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.

An improvement of symptoms usually becomes apparent within a few days after the start of therapy. However, symptomatic relief may not occur in some patients for as long as two weeks. Flunisolide should not be continued beyond three weeks in the absence of significant symptomatic improvement.

INSTRUCTIONS TO THE PATIENT

pms-FLUNISOLIDE Nasal Mist

(flunisolide solution 0.025%)

Corticosteroid

Dosage

pms-FLUNISOLIDE Nasal Mist should be used regularly as directed by your physician who will determine the number of sprays per nostril you require. Do not exceed the prescribed dose. The maximum daily dose should not exceed 6 sprays (a total of 150-mcg) in each nostril for adults and 3 sprays (a total of 75 mcg) 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 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

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 press 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 in a rapid motion 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.

Administration and Maintenance of the Atomizer

1. Gently blow the nose to clear the nasal passages prior to administration of pms-FLUNISOLIDE.

2. Hold the atomizer as shown below. 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 while inspiring through the nose, with the mouth closed.

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, the atomizer should be pointed in different directions for subsequent sprays in order for the mist to cover a wider area of the nasal

passages.

If 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. After shaking off water, pump rapidly four or five times. Replace atomizer on bottle and re-prime as in step 2 of **Preparation** (above).

7. Once the bottle has been opened, it should not be used longer than three months.

PHARMACEUTICAL INFORMATION

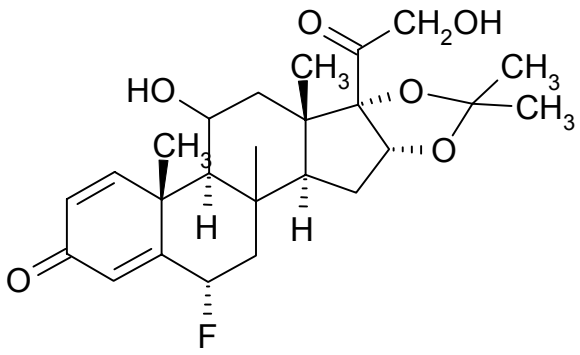
DRUG SUBSTANCE

Common Name: Flunisolide

Brand Name: pms-FLUNISOLIDE Nasal Mist

Chemical Name: 6a -Fluoro-11ß,16a,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; soluble in acetone, sparingly soluble in chloroform, slightly soluble in methanol and practically insoluble in water. It melts at about 245˚C with decomposition.

STABILITY AND STORAGE RECOMMENDATIONS

Store pms-FLUNISOLIDE Nasal Mist at room temperature (15˚-30˚C).

AVAILABILITY OF DOSAGE FORMS

pms-FLUNISOLIDE Nasal Mist is a 0.025% (0.25mg/mL) aqueous solution of flunisolide available in plastic bottles fitted with a metered pump device which delivers approximately 25 mcg of

flunisolide per spray via a nozzle which is inserted into the nostril. Each bottle contains a total of 25 mL of flunisolide solution yielding 250 metered doses. For full information on using the device, see instructions to the patient.

PHARMACOLOGY

Pharmacodynamics

Animal Studies

Flunisolide demonstrated potent systemic thymolytic and anti-inflammatory activity in the adrenalectomized rat, having 320 and approximately 180 times the thymolytic and anti-granuloma potencies of hydrocortisone respectively when given subcutaneously. It also demonstrated potent topical anti-inflammatory activity, having 190 times the topical anti-inflammatory potency of hydrocortisone, and 1.3 times the potency of fluocinolone acetonide in inhibiting croton oil-induced inflammation in the rat ear. In mice, the order of potency for local anti-inflammatory effect observed in serotonin-induced footpad edema was: flunisolide, dexamethasone, betamethasone valerate, and beclomethas one dipropionate. Given subcutaneously, the compound demonstrated approximately 800 times the adrenal inhibitory potency of hydrocortisone. Flunisolide did not alter sodium excretion at doses up to 670 mcg/kg, however, a dose as low as 6.7 mcg/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 agonist, isoproterenol.

Human Studies

In human tolerance studies involving 20 normal volunteers, the plasma cortisol and 24-hour urinary

17-ketogenic steroids remain within the normal range. The doses varied from 500 mcg to 700 mcg a day for 10 days and 700 mcg to 2200mcg a day for 4 days (up to 5 times the maximum daily recommended therapeutic dose in the adult).

Pharmacokinetics and metabolism

Following the intravenous or oral administration of a single dose of 2 mg 14C-labeled flunisolide to man, approximately 50% of the labeled compound was recovered in urine and 40% in stool. The 6ß-OH metabolite (6ß,11ß,16a,17a,21- pentahydroxypregna-1,4-diene-3,20-dione-16,17-acetonide) represented 65 to 70% of the urinary radioactivity while unchanged flunisolide represented only 4 to 20%. Orally administered flunisolide was well absorbed but was rapidly and extensively metabolized to conjugates and to the above metabolites, all of which appear to be relatively inactive. Since a sizable 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_{50s} 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 mcg/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 the termination of the study. There was 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 aging 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 tumors 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- neoplastie 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 tumors found.

Teratology

Glucocorticoids are know 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 of 0.04 mg/kg and higher were fetotoxic and teratogenic. At subcutaneous doses greater than 0.02 mg/kg, a high incidence of cleft palate and club foot was observed in mice.

Reproduction

Flunisolide was administered to rats by 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-doses and high-doses were fetotoxic and teratogenic. At doses of 0.00 1 to 0.1 mg/kg, flunisolide was fetotoxic and teratogenic when administered during the early stages of gestation as well as during the period of organogenesis. 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.

REFERENCES

CLINICAL ARTICLES

1. Aasand G, Etholm KBO, Tronheim TMS and Norway JVR. Flunisolide nasal spray compared to beclomethasone dipropionate in the treatment of seasonal rhinitis. Rhinology 1982; 20: 205-211.

2. Backhouse CI. Intra-nasal flunisolide in the treatment of allergic rhinitis in general practice. Current Medical Research and Opinion 1979: 6 (1): 14-19.

3. Bloom FL, Cohan RH, Leifer KN, Spongier DL, Rhoades RB and Wittig HJ. Flunisolide aerosol in the treatment of perennial allergic rhinitis. Annals of Allergy 1977; 38: 408-412.

4. Brown HM, Engler C and English R. A comparative trial of flunisolide and sodium cromoglycate nasal sprays in the treatment of seasonal allergic rhinitis. Clinical Allergy 1981; 11: 169- 173.

5. Chaplin MD, Rooks W, Swenson EW, Cooper WC, Nerenberg C, and Chu N. Flunisolide metabolism and dynamics of a metabolite. Clinical Pharmac Ther 1980; 27 (3): 402-413.

6. Chaplin MD, Cooper WC, Segre EJ, Oren J, Jones RE and Nerenberg C. Correlation of flunisolide plasma levels to eosinopenic response in humans. J Allergy Clin Immunol 1980; 65: (6): 445-453.

7. Clayton DE, Kooistra JB, Geller M, Ouellette J, Cohen M, Reed CE and Busse W. Short-term efficacy trial and twenty-four-month follow-up of flunisolide nasal spray in the treatment of perennial rhinitis. J Allergy Clin Immunol 1981; 67 (1): 2-7.

8. Dickson DJ and Cruickshank JM. Comparison of flunisolide nasal spray and terfenadine tablets in hay fever. British J of Clinical Practice 1984; Nov/Dec: 416-422.

9. Gale AE, Harding P, and Solomon E. A communication from intrabronchial steriods in adults with both bronchial asthma and perennial rhinitis. Annal of Allergy 1981; 46: 26S-272.

10. Gale AE, Solomon E and Tan BSK. Intranasal topical flunisolide therapy in children with seasonal allergic rhinitis. Clinical Allergy 1980; 10: 527-533.

11. Greenbaum J, Leznoff A, Schulz J, Mass J, Tobe A and Miller D. Comparative tolerability of two formulations of Rhinalar (flunisolide) nasal spray in patients with seasonal allergic rhinitis. Annals of Allergy 1988; 61: 305-310.

12. Horan JD and Johnson JD. Flunisolide nasal spray in the treatment of perennial rhinitis. CMA Journal 1978; 119: 334-338.

13. Incaudo G, Schatz M, Yamamoto F, Mellon M, Crepea S and Johnson JD. Intranasal flunisolide in the treatment of perennial rhinitis: Correlation with immunologic parameters. J Allergy Clin Immunol 1980; 65(1): 41-49.

14. Kammermeyer JK, Rajtora DW, Anuras J and Richerson HB. Clinical evaluation of intranasal topical flunisolide therapy in allergic rhinitis. J Allergy Clin Immunol 1977: 59 (4): 287-293.

15. Kwaselow A, McLean J, Busse W, Bush R, Reed C, Metzger W, Richerson H, Shulan D, Koshiver J and Chaplin M. A comparison of intranasal and oral flunisolide in the therapy of allergic rhinitis. Allergy 1985; 40: 363-367.

16. McAllen MK, Portillo PR, Parr EJ, Seaton A and Engler C. Intranasal flunisolide, placebo and beclomethasone dipropionate in perennial rhinitis. Br J Dis Chest 1980; 74: 32-36.

17. Nielsen NH, Frolund L, Bindslev-Jensen C and Svendsen UG. A new formulation of flunisolide for intranasal application reduces side effects. Allergy 1989: 44: 233-234.

18. Pipkorn U, Proud D, Lightenstein LM, Kagey-Sobotka A, Norman PS and Naclerio RM. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteriods. New England J of Medicine 1987; 316 (24): 1506-1510.

19. Runkel R. Pharmacology of topical steriods. In: Allergic Rhinitis The State of the Art. Summaries and Highlights of an International Symposium. Communications Media for Education. San Francisco, California March 12, 1981. 25-28.

20. Rusnak SL. Concurrent administration of flunisolide nasal solution with beclomethasone dipropionate bronchial aerosol in patients with both rhinitis and asthma. Annals of Allergy 1981; 47: 320-324.

21. Sahay JN, Chatterjee SS and Engler C. A comparative trial of flunisolide and beclomethasone dipropionate in the treatment of perennial allergic rhinitis. Clinical Allergy 1980; 10: 65-70.

22. Sahay JN, Chatterjee and Engler C. Flunisolide--a new intranasal steroid for the treatment of allergic rhinitis. Clinical Allergy 1979; 9: 17-24.

23. Sahay JN, Ibrahim NBN, Chatterjee SS, et al. Long term study of flunisolide treatment in perennial rhinitis with special reference to nasal mucosal histology and morphology. Clinical Allergy 1980; 10: 451-457.

24. Sarfield JK and Thomson GE. Flunisolide nasal spray for perennial rhinitis in children. British Medical Journal 1979; 2: 95-97.

25. Schulz JI, Johnson JD and Freedman SO. Double-blind trial comparing flunisolide and placebo for the treatment of perennial rhinitis. Clinical Allergy 1978; 8: 313-320.

26. Siegel SC. Clinical results with flunisolide-Corticosterio as in allergic rhinitis. In Allergic Rhinitis

The State of the Art. Summaries and Highlights of an International Symposium. San Francisco, California March 12, 1981. 33-37.

27. Soderberg-Warner ML. Nasal septal perforation associated with topical corticosteriod therapy. J of Pediatrics 1984; 105 (5): 840-84 1.

28. Spector SL, Wangaard C and Bardana EJ. The use of cultures and immunologic procedures to predict oropharyngeal candidiasis in patients on steriod aerosols. Clinical Allergy 1982; 12: 269-278.

29. Standard Minimal Prescribing Information For The Product Monograph Of Nasal Corticosteroid Formulations. Canadian Health Protection Branch.

30. Strem EL, Austrian S, Geller GR, Johnson JD and Crepea S. Flunisolide nasal spray for the treatment of children with seasonal allergic rhinitis. Annals of Allergy 1978; 41: 145- 149.

31. Sy RK. Flunisolide intranasal spray in the treatment of perennial rhinitis. Arch Otolaryngol 1979; 105: 649-653.

32. Syntex Laboratories, Nasalide (flunisolide) Nasal solution 0.025%. Assessment and Review, 1981, p. 25-27

33. Toogood JH, Jennings B, Crepeea SB and Johnson JD. Efficacy and safety of concurrent use of intranasal flunisolide and oral beclomethasone aerosols in the treatment of asthmatics with rhinitis.

34. Turkeltaub PC, Norman PS, Johnson JD and Crepea S. Treatment of seasonal and perennial rhinitis with intranasal lunisolide. Allergy 1982; 37: 303-311.

35. Turkeltaub PC, Norman PS, and Crepea S. Treatment of ragweed hay fever with an intranasal spray containing flunisolide (RS3999)--A new synthetic corticosteriod. [Abstract]. J Allergy Clin Immunol 1975; 55(2): 120-121.

36. Warland A. Evaluation of flunisolide nasal solution in the symptomatic treatment of perennial rhinitis. Allergy 2982; 37: 417-420.

PRECLINICAL ARTICLES

37. Chu NI, Amos BA, Tokes L, Maddox ML, Matin SB, Hama KM, Patterson JW, Wagner PJ, Bell JP and Chaplin MD. Disposition of flunisolide in the rat, mouse, dog, Rhesus monkey, and Cynomolgus monkey. Drug Metabolism and Disposition 1979; 7: 81-89.

38. Itabashi M, Yamazaki M, Watanabe H, Takehara K and Tajima M. Flunisolide: Reproduction studies on flunisolide in rats (1) Oral administration prior to mating and in early stage of gestation. 1982; 24 (5): 631-641.

39. Itabashi M, Inoue T, Yokota M, Takehara K and Tajima M. Flunisolide: Reproduction studies in rats (2). Oral administration during the period of organogenesis 1982; 24 (5): 643-659.

40. Itabashi M, Yokota M, Inoue T Takehara K and Tajima M. Flunisolide: Reproduction studies on flunisolide in rats (3). Oral administration in the perinatal and lactating periods.

4 1. Magata K, Sakamoto T, Takai M, Umezato M, Ohsaka T, Asakuni T and Honma M. Flunisolide: Anti-inflammatory effect of flunisolide. 1982; 23 (3): 365-378.

42. Mygrind N and Vesterhauge S. Aerosol distribution in the nose. Rhinology 1978; XVI: 79-88.

43. Stafanger G. In vitro effect of beclomethasone dipropionate and flunisolide on the mobility of human nasal cilia. Allergy 1987; 42: 507-511.

44. Syntex Inc. Product Mongraph-Rhinalar (flunisolide) corticosteriod. August 17, 1987.

45. Takai M, Sugio K and Tsurufuji S. The predominance of lunisolide in the topical use of anti-inflammatory steroids. J Pharm Dyn 1982; 5: 200-207.

46. Tamagawa M, Hatori M, Ooi A, Nishioeda R and Tanaka N. Flunisolide: Comarative teratological study of flunisolide in mice. 1982; 24 (6): 741-750.

UNPUBLISHED CLINICAL ARTICLE

47. Pharmascience Inc.. A comparative study of Pharmascience (Rhinaris-F) and Syntex (Rhinalar) flunisolide metered-dose nasal sprays in allergic rhinitis. Unpublished data on file at Pharmascience Inc.1990.